SPECIAL INQUIRY

THE HONOURABLE THOMAS BATHURST AC KC

FIFTH DAY: WEDNESDAY 15 FEBRUARY 2023

INQUIRY INTO THE CONVICTIONS OF KATHLEEN MEGAN FOLBIGG

JUDICIAL OFFICER: Yes, Ms Wootton?

WOOTTON: Your Honour, before we recommence with the evidence of Professor Vinuesa there are just a few procedural matters to deal with.

JUDICIAL OFFICER: Yes?

WOOTTON: Your Honour made a non-publication order on 13 February 2023, and I would seek a variation of that non-publication order. If your Honour doesn't have it available, I have a copy.

JUDICIAL OFFICER: I have a copy here, I think, yes.

WOOTTON: It is a variation to 1 (i), to add in the words after "Tracy Chapman", "Craig Folbigg, Caleb Folbigg, Patrick Folbigg, Sarah Folbigg and Laura Folbigg".

JUDICIAL OFFICER: Yes.

WOOTTON: The parties have been provided with a version of that yesterday, and I understand there is no objection.

JUDICIAL OFFICER: Is there any objection to that?

I will vary the order made by me on 13 February 2023 in relation to certain non-publication orders, the parts of certain letters written by Ms Folbigg. The terms of the variation are contained in a document headed "Non-Publication Order - 15 February 2023", signed by me.

WOOTTON: The second matter, your Honour, is to replace two pages in the tender bundle, which contained an inadvertent error. The first page is in tab 1807 at p 203 of that tab. Does your Honour have the corrected version available?

JUDICIAL OFFICER: Yes, I do.

WOOTTON: I understand that has been added to the tender bundle. It was circulated on the parties and there has been no objection notified. That will just replace the old version of p 203 with this new version; removing the words "(December) December" from item 320.

JUDICIAL OFFICER: Thank you.

WOOTTON: The second matter is in tab 1808 at p 229. In effect, it is the same correction: To change "December" to "November" in item 320. There has been no objection notified of that either.

JUDICIAL OFFICER: Yes, I have it. There's no objection to that? Those two replacement pages will be placed in the tender bundle.

WOOTTON: May it please your Honour, we are otherwise ready to commence.

CALLAN: Your Honour, yesterday during the evidence of Professor Vinuesa I referred her to an article in "WIRED" by journalist, Oscar Schwartz of 9 December 2021; could that be marked for identification?

JUDICIAL OFFICER: Yes.

MFI #6 ARTICLE EXTRACTED FROM "WIRED" MAGAZINE WRITTEN BY OSCAR SCHWARTZ DATED 09/12/21

<MARIA CAROLA GARCIA DE VINUESA DE LA CONCHA, CONTINUING(10.14AM)

<EXAMINATION BY MS CALLAN

Q. Professor Vinuesa, yesterday you explained your work at the ANU, which you described as using "next generation sequencing to diagnose patients with immunological disorders for a research purpose to discover novel genetic causes of death and their mechanism through functional validation".
A. Yes.

Q. You recall giving that evidence?
A. Yes.

Q. I asked if you draw on clinical experience and your answer was that you say, "I think it's useful to put variants in context of clinical disease. I consider I have a general understanding but of course, I am not a specialist in any one area of medicine". Do you recall giving that evidence?
A. Yes.

Q. Have you undertaken clinical practice in relation to genetics?
A. No.

Q. Subsequently in some questions I asked you yesterday, by reference to the specific topic of functional assays, you indicated, as I understood your evidence, that you did not disagree with Professor Schwartz's observation that the clinical reality may be much more complex than what is apparent on the results of functional assays.
A. Yes.

Q. I suggested "the complexity and the potential for unexpected clinical consequences mean that functional assays, whilst of value, have their limits".
A. Yes.

Q. And you said yesterday, yes, and then you went on to point out in this instance every single assay has pointed to the pathogenicity and none to benign?
A. Yes.

Q. Then when I asked you about the task of translating functional assays into the clinical picture, you said that is beyond your expertise, do you recall giving that evidence?
A. I probably did yes.

Q. That is your position?
A. Yes.

Q. Do you accept that when it comes to arriving at an ultimate view or conclusion about the pathogenicity of a variant it's important that in vitro data is concordant with clinical findings?

A. I think that has to be nuanced because for genes for which we know very little, sometimes it is sufficient to know that this is a novel variant in a gene that crosses a spectrum of disease compatible with the presentation. So, I form part of panels where we discuss this as a team and the information provided by scientists is equally important.

Q. When you say you form part of panels, what panels are you speaking of?
A. So, for example, when I was in Canberra I was part of Canberra Clinical Genomics, I was one of the genomicists that helped interpret rare variants in paediatric disease. Currently I am member of a ClinGen panel, it's a gene curation expert panel in rheumatologic disease where I also provide my expertise in curating genes that may be import causative of human disease.

Q. As I heard your evidence you made particular reference to a situation of a novel genetic variant - I wanted to just understand your perspective on how that affects the conclusions reached about pathogenicity. Can I start with this proposition? Are you of the view, and this is at a general level, that when it comes to arriving at a conclusion about pathogenicity there is a need to robustly link genetic findings with a concordant phenotype to infer causality?

A. Look, I'm glad you asked me that question, because the field has moved very rapidly. I provided a paper to the Inquiry, French et al., 2019, where they took a large cohort of children that had presented to neonatal intensive care unit, so very sick children, together with a cohort of children with very severe paediatric disease. They performed agnostic whole exome sequencing to see if they could find the cause of death and their conclusion was that in 90% of the cases the phenotype was a poor predictor of the gene identified, which means that only in 10% of the cases the phenotype led to the causative gene that would have been predicted. Now, in 65 of these children, 65% of the children, after diagnosis a treatment was implemented based on the gene that they identified, which means that today we're reaching diagnosis first by looking at the whole exome sequencing, then finding genes that look at very - as very hot VUSs and then trying to understand why the phenotype didn't match as well. So phenotype is not a good predictor in very sick children of the causative gene.

CALLAN: For the record, your Honour, that article is included in the tender bundle at Exhibit 15, tab 38.

Q. What you've described as I understand it, would that accord with the evidence Professor Nyegaard gave on Monday as to the genotype first approach as distinct from a phenotype first approach?
A. Well not entirely, because she was talking about doing whole exome sequencing on cohorts of people that could be healthy.

Q. Yes?
A. This is having exactly the opposite situation, you start with children that have extreme phenotypes, they are very sick, this could be, you know, these are children that present to hospital and are admitted to intensive care unit because they are very sick, but then you undertake whole exome sequencing

with an unbiased idea of which genes you are going to find, and in 90% of those cases the genes they found could not have been predicted due to prior knowledge of what those genes did or of known phenotypes of those genes. So it means that in severe paediatric disease the phenotypes are not helpful because very often these children arrive sick, you could have sudden unexpected presentations and the genes do much more than what we think they do, and the clinical spectrums are continuously expanding.

Q. I think it may be that part that you've just referred to as to the clinical spectrum which I'm keen to try and have you address. Do you accept that when you are arriving at conclusions about the pathogenicity of a gene that it is necessary to identify a concordant phenotype in order to infer that causality? What else are you looking at?
A. Yes, but I've just explained to you that in 90% of the cases there is no concordance. Having said that, in the case we are talking about, sudden unexpected death is a phenotype, and in some cases and some diseases that are intimately related with calmodulinopathy that is the only presentation, and in fact stress tests are negative, ECGs are negative, so this is an absolutely accepted presentation of some cardiac arrhythmias.

JUDICIAL OFFICER

Q. Can I just try and understand it, and I'm sorry, Professor, it's me, not you I should add. You say that with those very sick children 90% of the phenotype wasn't concordant with the genotype, is that right?
A. Yes.

Q. Well, how do you know then that the variant in the gene had anything to do with the presentation? That's what I'm having difficulty with.
A. Well, if you look at the paper, eventually they established causality by understanding why those presentations could have come about. Think that if a child has been unwell or, for example, has a cardiac arrhythmia, it might have led to some type of syncope, the child might have not been eating or drinking properly, so the child might present dehydrated, in a state of lethargy, perhaps with some other symptomology that nobody would have linked to a cardiac arrhythmia. Once they found, for example, that the gene was let's say in this case a calmodulinopathy, they might have thought, actually that fits the picture retrospectively, because in children, children don't speak, they don't tell you what they feel. In a little child you don't know if they've fainted or they just are asleep in their cot because they are most of the time lying in their cot. So, it is very difficult in a child that doesn't verbalise, that simply looks poorly, that arrives dehydrated to make a proper diagnosis, and in the case of sudden unexpected death, very often there is absolutely no electrocardiographic manifestation and that is the case of IVF, and for example in the case of this Calcium Release Deficiency Syndrome, that we've been alerted to thanks to one of the experts that provided a report to the Inquiry, there are syndromes like this that - and these are - in proteins that interact with calmodulin. In this case was ryanodine receptor nicely described syndrome, absolutely no trace. Sudden unexpected death, first presentation.
Q. You're addressing the particular topic as you said it, absolutely no trace,

that is the absence of investigative or other information that suggests a particular phenotype?
A. Not just investigative. In some cases even when there are the investigations, the investigations are negative. So in this Calcium Release Deficiency Syndrome, the sudden unexpected deaths cannot be associated with any ECG trace, even if you perform stress tests in these individuals. So, eventually, I think it was in this - only last year Professor Hugh Watkins from what we've just recently learnt devised a new diagnostic method by induction with a particular cocktail of drugs, and I don't understand that field so don't ask me which drugs or how. Just implying that, there are presentations with no trace, and even IVF, Idiopathic Ventricular Fibrillation, which is a common manifestation of a few cardiac arrhythmias including calmodulinopathy, unless the individual is being monitored with a halter tracing, you would not have found an ECG abnormality before or after the event. After the event most of them die. So, even IVF can only be in the absence of any prior warning that that child might have a mutation, you would never have found a trace in the ECG that would have told you this child is susceptible to sudden cardiac death.

CALLAN

Q. In that scenario, and you've already indicated as much, in respect of IVF, there may be no trace in terms of evidence or information to confirm or exclude the presence of IVF. That is a feature of that condition and taking that into account the task, isn't it, is one of inferring causality - can this variant be confidently inferred to have caused that outcome?
A. Well, for example, the G114W caused IVF in one of the two children. So by extension this variant could have caused IVF, it's G114 is the same residue.

Q. The task in that instance was one of inferring causality and it was done, can I suggest, by linking the genetic finding with that phenotype of IVF?
A. That child had an ECG monitoring, because he had been implanted with a cardioverter defibrillator. In the Folbigg family no child--

Q. I understand, and can I take a step back--
A. Yes.

Q. --to address aspects of the approach which has been taken, and the way in which you've undertaken the exercise. As I understand your evidence, what you are doing is you are inferring causality?
A. I am saying that another variant in the same residue caused IVF, so there is that possibility. I'm not saying in the Folbigg child he died of IVF or she died of IVF, I'm saying that another child with a mutation in G114 died from IVF and I'm saying when we have a gene that we understand very little of, that we are only each day understanding new interactions with new channels and that this particular residue is in fact interacting with these channels. We shouldn't be speculating because we can't even start even functionally testing the interaction between these channels. So we've got so much information already, a novel variant in a gene that can cause all of these spectrums of diseases including sudden death. In the clinic these would be diagnostic.

Q. I'll pause you there. You've said, we shouldn't be speculating. You've just given that evidence.
A. About where--

Q. Do you accept there is a degree of speculation in the views that you are expressing? We do not know.
A. I'm just saying that--

Q. Can you answer the question?
A. I do not want to speculate, yes.

JUDICIAL OFFICER

Q. Is this what it boils down to, that it's really what we - what lawyers describe I suppose as a process of inference? You've seen a number of people die who have that variant, and I the absence of any other explanation you infer that the particular patient or child in question died after having a similar or associated variant, and ultimately evidence might show that that inference was right or firms up and evidence might show that it was wrong. Is that a fair way of putting it?
A. It is, but if I may say, normally you would wait potentially for a second case with the identical same variant, that might happen in ten years or never, and that's why we have ACMG criteria, and that's why we say, well once you arrive at a likelihood of pathogenicity of 90 to 99%, that's why we say well, then we can apply this criteria and say it's very likely that it caused--

Q. But that criteria helps you draw the inference; again going back into terms lawyers use?
A. You can call it, I mean, that's why we have the criteria: to help us make a clinical decision.

CALLAN

Q. That rounds out the particular topic I wanted to address with you in relation to functional assays and the task of drawing inferences as to causality. You mentioned right at the end of your evidence yesterday that you had prepared a presentation?
A. Yes.

Q. And I apologise; I hadn't appreciated when you commenced your evidence yesterday that that was something that you had done. I think the slides were conveyed to those assisting on Sunday, and I didn't--
A. No, I sent them last week, Friday.

Q. I apologise. Would you like to take the time now to present that slideshow?
A. Yes, thank you.

Q. Certainly, and please take your time.
A. Thank you.

Q. Thank you. We are just setting up the tech; do you have notes or anything else that you need to refer to?
A. No.

Q. All right.

JUDICIAL OFFICER

Q. Professor, please when you're giving the presentation, bear in mind that we are all novices in this field so don't rush.
A. Thank you. You wouldn't have a pointer, would you? Thank you, because it is easier to point to the key part of the slide.

CALLAN

Q. We will organise, I think - for instance, when Professor Toft Overgaard was giving his evidence there was a mouse that he was able to take control of.
A. That would be great, thank you.

Q. We will organise that.
A. Thank you very much.

JUDICIAL OFFICER: It is not one of the experimental mice, I hope?

CALLAN

Q. Professor, it may be from time to time I interrupt to just point out what slide number we are at, so you just flow with your presentation, but if I say for the record--
A. Yes.

Q. It will just be about slide numbers.
A. Thank you. Okay, shall I start?

JUDICIAL OFFICER

Q. Yes.
A. I will try to not be quick.

Here, I wanted to show a graph from OMIM. OMIM is the online database of Mendelian diseases in humans, and we can see here in the purple lines - well, in the yellow lines, the increasing number of genetic diseases that we have been discovering and how this increase has been made substantial, particularly after the year 2000, which is when the whole - the first draft of the whole genome sequence was provided.

In blue, instead of genes we have phenotypes which, in this case, we can also call "diseases", " Mendelian diseases". We can see that before the human sequence draft was available we had more or less one disease per gene. As time has passed, and thanks to being able to use these agnostic ways of

identifying diseases, whole exome sequencing, so this next-generation sequencing capability that makes - helps us look at the entire genome, we have now got to a point where there are many genes that cause more than one disease. In fact, there are about 800 genes that cause two diseases or two phenotypes, and we have over 200 genes where we have more than four phenotypes.

Now, why is this? Because each gene has a few different parts. Some parts can be regulatory; others can interact with a number of proteins. Also, because within each gene, each variant can do something different. Some can have a gain of function; others can have a loss of function. And the third main reason is because genes act in a universe of thousands of other genes that modify their function. So we're not talking about one genetic modifier; thousands of genetic modifiers.

Now, in cardiology in the year 2011, Ackerman started testing for cardiac diseases with panels. So genes that were known to cause cardiac disease. It was actually the Australian, Chris Semsarian, that first applied next-generation sequencing to molecular autopsies. So autopsy-negative individuals sudden death in children that otherwise did not have a known cause of death underwent whole exome sequencing, and this led to the beginning of a period in which we've been able to increase the number of genes that cause disease because of this more agnostic approach.

Next slide, please.

So with this, I wanted to take you - what it takes from the discovery process to understanding or being able to apply ACMG criteria.

CALLAN

Q. For the record, we are at slide 2.
A. Slide 2, yes. This is where our activity is involved, so all of these ticks is where my team, for example, works with. So we discover new genes; we discover new gene functions; new gene domains; new genetic causes of disease in mice and in humans; new phenotypes for known genes; and, new causal variants. Here is a list of some of the genes that my group has either been the primary lead of these discoveries or contributed to these discoveries, and just for your information, to understand the way we work, we do phenotype-to-gene but in an agnostic manner. So up to the time where next-generation sequencing was available, I participated in these forward-genetics approach, which was taking a phenotype in mice that we didn't understand and again, in an agnostic way, try and find the causal gene.

When next-generation sequencing became available, we would do the same but with humans. We would take patients with phenotypes that were severe, extreme and poorly-characterised, and without any preconceived idea of what the causal gene would be, we would make educated guesses and develop algorithms that could take us to the most promising gene.

Now, imagine the bets and the risks. Each of these projects would be one PhD student, so we have developed ways of an intuition and algorithms that can point in the 20,000 genes in a genome, which gene we thought would be the causal one, and we would eventually demonstrate this with functional studies.

So, the next one please, slide 3.

These are two examples where we had what you could have called "surprises" but for us, they weren't surprises. We also were the first ones in Australia and in the world to use whole exome sequencing to identify causes of immune genetic disease, and this is a nice case because for us, it was just proof of principle. We took a young child with an extreme presentation of Lupus. She had had a stroke. We found that the causal variant was in a gene called "TREX1". Others might have been surprised because TREX1 in children had only been associated with a different disease called "Aicardi-Goutières", but in adults, it had been associated with Lupus. I remember calling the clinicians and asking them "are you sure this child doesn't have the features of Aicardi-Goutières? Have you looked for calcifications in the brain? Have you looked for liver function test results?" And they assured us this child had Lupus.

So we did the functional validation. We published this. We were not surprised that we had found a phenotype in children that were 30 years younger than the known phenotype, but eventually, history proved us right. Now, it is known that 2% of monogenic Lupus is caused by TREX1 variants. And TREX1 had been first identified in mice for causing myocarditis and autoimmunity.

Only last year we published this paper. We found a little child, again, with severe Lupus, and we published that the cause was a mutation in TLR7; a mutation that had never been caused - or, a gene that had never been shown to cause Lupus in humans. In fact, only the year before, mutations in TLR7 had been found to cause or to explain a fraction of males developing severe COVID. And it turns out that when we try to understand why this was the case - we did all the functional validation - we found out that loss of function variants in TLR7 cause severe COVID, but gain of function variants in TLR7 cause Lupus. And this is because TLR7 is in the X chromosome; males have one dose of the X chromosome, they are more susceptible to viral infections; women have two copies - they are more susceptible to Lupus. Completely different phenotypes, but we were not surprised - we do the functional validation, we prove it.

Next slide, please. Thank you.

Slide 4 relates to cardiac genes and again, I will only talk from a genetic perspective. Here, this is a slide from an article published last year, which - it has been tendered, Anderson et al.

In this graph we see the 25 genes that are best understood to cause cardiac arrhythmias. Among them you can see CALM1, CALM2 and CALM3.

On the X-axis is the number of known variants per each of these genes. You can see that for a gene like Ryanodine receptor, which interacts with calmodulin, there is over 5,000 variants known. For a gene like SCN5A that also interacts with calmodulin, there is over 3,000 variants that are known. But for the CALM genes, we know very few variants.

Now, for the three CALM genes there has been a total of 23 missense variants identified: six for CALM1, eight for CALM2 and the rest, I think it might be 11, for CALM3. Nine, sorry, for CALM3.

Now, I think it is important for us to know that none of this has been classified as benign. This is one of the few genes in the genome that has not a single benign or likely benign variant identified either in ClinVar or in gnomAD, which is significant. Now the other thing I want to point to your attention is that the number of variants identified tends to be proportional to the size of the gene. So Ryanodine receptor 2 is 34 times bigger than the calmodulin genes, so there will be 34 more chances in a cohort looking for SIDS, for example, to find a variant in Ryanodine receptor. SCN5A is 14 times bigger than calmodulin.

Now there have been comments made that in the SIDS study that contained 427 individuals there were no findings in calmodulin, where there were only 12 variants found in Ryanodine receptor, there were only four variants found in SCN5A. By these numbers we would need a cohort that is three times larger, so over 1200 patients to be able to detect a single variant in calmodulin. So the fact that we haven't found more cases is just a question of numbers and time will tell, these are very small genes.

So, coming back to here, why are there so few CALM variants identified yet? They're very small genes. On top of that, they do not tolerate substitution, Professor Nyegaard has gone through that, I'm not going to repeat. They're highly constrained and they're often lethal in children, so we are not going to find them very easily in cohorts of live individuals. So what is the problems of having so few variants? I have mentioned the first one, it would be very difficult to find them in usual cohort analysis. It would also take longer, sometimes decades, to find the same variant twice. So if that is a criterion that something is useful for pathogenicity, I mean ClinVar and tends to wait until there are several cases with the same exact substitution to call a variant pathogenic, this is never going to happen or very rarely going to happen for the CALM genes. And also, it will take longer to understand the full phenotypic spectrum, so we have to keep our minds open because there is a lot yet to know about this.

Can I have the next slide please?

No, sorry, can I go back, one moment? I also wanted to highlight something. Even in this rare 2-gene that has had more than 5,000 variants known, only a year ago a new syndrome was identified in a gene that we should have known everything about for a long time. So up to very recently we only knew about gain-of-function variants causing CPVT. Actually the first

study was published by Arthur Wilde himself in 2007, even though at the time it wasn't recognised as a different syndrome. So these are two then that now present with sudden cardiac death and no electrocardiographic manifestations, and after a few different studies with these children only last year a new name and a new arrhythmic disorder was coined called Calcium Release Deficiency Syndrome. This is now due to loss-of-function mutations instead of gain-of-function. But still it's within the same spectrum, children die from sudden unexpected death. Same thing happened for CACNA1C, the Cav1.2 cardiac channel. It was supposed to call this Tim Syndrome or Timothy Syndrome and only in 2015 the spectrum was expanded, and these are genes that are large, many variants known. So a word of caution, that we shouldn't make too many interpretations yet until we understand the full spectrum of calmodulinopathies, but to say that because there hasn't been a single benign or a likely benign variant identified, the likelihood is that there are many or most will turn out to be pathogenic. Can we come to the next slide please?

Q. So this is slide 5?
A. Slide 5. So this is a figure also taken from the Anderson review and this is showing you what's at the moment is known by Michael Toft Overgaard, he's shown us that G114 of calmodulin interacts and affects this calcium, this ryanodine channel, this calcium channel. Now we also know it affects the sodium channel, and as of a couple of days ago before I printed these, or before - I mean I gave you this presentation last week, I didn't even know that yet - G114 now also affects this potassium channel. Now, if you do this exercise, just for those of you that might not be aware, calmodulin binds to 300 proteins in our body, 300 proteins. So it's not trivial, it's one of the most highly networked proteins. In this diagram all I did was use an algorithm and ask out of this gene list of genes that cause cardiac arrhythmias, which of these proteins interacts with calmodulin. And this program is called String, and I did this analysis on the 8th February. In this figure, every protein, when it is linked to another protein by a pink line, it means that this interaction is proven. It is experimentally determined. You can see here that CALM1, CALM2 and CALM3 physically not only interact with SCN5A and RyR2, and CACNA1C, it also shows it interacts with KCNQ1, with KCNE1, with ANK2, with MYH6 and with other channels that are known to be the causes of cardiac arrhythmias. So we are only at the very beginning of understanding the consequences of these interactions. And where I have put question marks I was saying, well, very soon we might find out that G114 also affects this potassium channel, actually within two days of me drawing this presentation a paper came out that not only it interacts, it severely diminishes the affinity for binding to potassium. Can I have the next slide please?

CALLAN: Before we move on, I see actually both slides 4, 5 and I think at least 6 refer to the publication from Anderson and others of this year. Your Honour, for the record that's at - sorry, 2022 - that's at Exhibit 15, tab 186.

JUDICIAL OFFICER: Thank you.

CALLAN

Q. Yes.
A. So if I can go to the next slide please. So here I have highlighted in red the known interactions of G114 and in blue the potential interactions, interactions that we know that calmodulin interacts with these proteins but we still have to know whether G114 will exert an effect on these interactions, and I should not have made these red, because as I have just mentioned, we know that G114 also alters interaction with KCNQ1. Here I've got a graph of a syndrome that has been called Sudden Unexplained Nocturnal Death Syndrome with a very arbitrary criteria based on age. So everything that is sudden death while asleep before 12 months of age has been called SIDS, everything that is above 12 months of age is more or less this kind of vague umbrella of syndromes called Sudden Unexpected Nocturnal Death Syndrome. Now we know that the genes that cause SIDS include the interactors with calmodulin that we've described: Ryanodine receptor, CACNA1C which is the Cav1.2 channel, or sorry SCN5A, which is the cause of Brugada Syndrome. Surprise, surprise when whole exome sequencing entered the clinical space, and when they started finding the genetic causes of these Sudden Uexpected Nocturnal Death Syndrome the same genes start to pop up. All of the genes that I've just told you that interact with calmodulin, KCNQ1, KCNH2, KCNE1, RyR2, CACNA1C, SCN5A, which again tells us there is nothing about age. It is arbitrary to say that a disease can cause a syndrome before 12 months, after 12 months, at 35 years, at birth. It is the same genetic mutations and we just need time to find these very rare ones a bit more represented. But we've already found calmodulin mutations that kill children before birth, cause foetal bradycardia immediately after birth, weeks after birth, years after birth. Can I have the next slide please?

Q. Slide 7.
A. So here I want to make the point that we don't know too much about G114R but from the little we know it's proven to be one of the most intriguing and unique amino acids in calmodulin. G114 is not only conserved in all vertebrates, it's conserved in all plants, it's conserved in yeast, and as Professor Nyegaard pointed, this points to it being a critical amino acid for the function, it cannot be substituted. In this map from Weile, et al, 2017 where they used this mutational screen to see which variants in calmodulin enabled or permitted survival and growth of yeast, they found that only two variants could not be substituted by any amino acid. Losing 106 and glycine 114, and you know this because in blue we have variants that behave like an empty vector control, behave - so this is when you give yeast a calmodulin variant that is equivalent to having no variant. A complete loss of function is the darkest blue. So glycine 114 is only one of two amino acids that does not tolerate that glycine being substituted by any of the other 19 amino acids. That tells us that this is a very unique residue. To date, G114 and the substitution specific to the Folbigg mutation R - has shown a problem in function with the five tests performed to date. It also appears to act differently from the variants that have been tested alongside, so it's slightly different to G114 for example to G114W because it has a profound effect on - sorry, it is different to N98S at least because it has a profound decrease in its ability to bind a sodium channel. It's slightly different also to some other variants because I mean each of them as you see shows something quite unique, but according to Professor

Toft Overgaard, G114R is the only one that he has tested to date that completely abolishes binding to sodium in – at low concentrations of calcium, and we also know that at substitution in the same codon causes, sudden unexpected death and IVF. Can I have the next one please?

So in this, CALM2 is one of the few genes associated with sudden death below two years old. It has been found both *de novo* and now we know that 40% of the cases are inherited, not *de novo*. It has been already shown to cause a spectrum of arrhythmias including Long QT Syndrome, IVF, CPVT, mixture of defence syndromes and now perhaps Brugada Syndrome, but that hasn't been show formally yet. It can cause sudden death while asleep or while awake. The clinical spectrum is expanding but there are such small numbers, only 132 cases in the world, that we need probably hundreds if not thousands of more cases to understand the full spectrum. We know that as for other calmodulin genes the penetrance is incomplete. We know that this mutation is novel, CALM2-G114R has not been found in another individual. It's intolerant to substitution and causes a unique alteration in function. Not just now SCN5A if I could add, these now also KCNQ1. It impairs protein function with five different readouts and is classified as likely pathogenic. With this information six cardiologists have said that they would have considered these as the likely cause of Sarah. That was Professor Peter Schwartz and Lia Crotti, and Hari Raju, and Chris Semsarian, Reza Razavi and more recently, Hugh Watkins.

I think this is my last slide; is there any other slides? Four more? Okay, can I have the next one. Right, so this now coming in to try and tell you why discoveries in mice make a difference and most times, not all the time, are translated into human disease. These are two examples drawn from our own discoveries.

In 2005 I discovered a new gene. It hadn't been annotated yet in the genome, so I had the fortune of being able to give it a name; I named it "Roquin". This gene in mice caused an autoimmune disease with autoinflammation. It took 14 years to find the first human that had a roquin mutation and this discovery was made by a group in the Netherlands; my group contributed to part of this effort. Again, this showing that discoveries in mice eventually, but after quite a lot of years, translated into discoveries in humans.

I have talked about TLR7. In 2006, there were mice shown to have a translocation of a small fragment of the chromosome X containing TLR7 into the Y chromosome. So two copies of TLR7. The mice developed a Lupus-like disease. It took 16 years for us to publish last year, the first human mutations causing Lupus in humans. Now, this was a *de novo* mutation, so it was easy to validate.

Since we have published this - I mean, we have published three different kindreds with mutations that turned out to be gain-of-function. We have now had numerous investigators telling us about mutations in their patients.

Also to tell you how this process works, still if a pathologist wants to use ACMG criteria, they won't be able to use ACMG criteria for these diagnoses

because it follows a process. So we publish this in 2022; a few months later, it appeared onto OMIM, the online catalogue of genome variation, that TLR7 causes Lupus in humans; and now, it is being considered in ClinGen as a gene for Lupus. Until it goes through all of these steps, pathologists cannot diagnose children formally, but they can do informally, because these children are now being offered treatments that target this mutation.

Can I go to the next slide, slide 10, please?

We have developed, as I say, very good prediction algorithms for finding which mutations in mice and possibly in humans might be responsible for human disease. In the progress paper, we mentioned that the two boys carried biallelic variants in a gene called BSN, Bassoon. For us, it was a very significant finding because after the novel variants, there are only two types of variants that are highly suspicious. Those are homozygous, exactly the same, ultra-rare variant found in both chromosomes; or biallelic. Two rare variants occurring in the same gene but on different chromosomes, so that means one inherited from the mother and one inherited from the father, or presumed to be inherited from the father on this occasion.

We felt we had to mention this because in 2003 there had been a paper published showing that mice with deficiencies in Bassoon developed spontaneous epileptic seizures and problems with the retina that could cause blindness and we thought this finding is significant. We yet have little information, as we said, an autosomal-recessive form of this disease has not yet been described. So we were cautious. We flagged it; this looks interesting, but we don't know enough about it yet.

Well, within a year of publishing of that, there was the first GWAS (Genome-Wide Association Study) reporting an association between BSN variants and febrile seizures and as of six weeks ago - and I didn't pick that up, I just read this from a report that Professor Watkins submitted to this Inquiry - he alerted us to a publication only in December 2022 in which, for the first time, variants in Bassoon have been found associated with human epilepsy.

I will have the next slide, Slide 11, please.

In this slide they show eight kindreds; four of them are biallelic; two rare missense variants in Bassoon. All of these kindreds developed epilepsy. In some families, they only need one but they find that both - there has been an affected mother and an affected child, or an affected father and an affected child. They find that the ones that have only got one variant tend to respond to one anti-epileptic drug; the ones that have two variants required a combination therapy with two anti-epileptic drugs to control the epilepsy. This is preliminary. There is no functional validation performed.

But while this has been published, I put in my report that I had consulted with Professor Leanne Dibbens when I first submitted the 10 October report, and she had told me they had exactly the same findings. They had found four

biallelic cases of children with epilepsy; one *de novo* mutation and one homozygous variant. So they have been scooped in their publication but they had the same findings. They were trying to perform some - or some of their colleagues were trying to perform some functional validation.

All we are saying is we need to wait. We know too little, but there is something intriguing here.

In the experiments we have performed - and I didn't want to submit them to the Inquiry because they were far too preliminary; when I was asked to submit them, I said, "We have not repeated these. We just don't know too much about this", but I was still asked to submit everything we had done. I won't go into those results because I still think they are preliminary, but the one thing that we now know - and I have talked to Dr Nathalie Dehorter, who is doing these experiments - is that mice with the two variants that are found in the Folbigg children are not born in the normal Mendelian ratios, which means there is prenatal lethality. When I submitted my report, we only had had very few double-heads and I couldn't do the statistics on that one; I had done statistics of the single head and I said those were born on the Mendelian ratios.

So now we know that this particular combination, at least in mice, there is something unusual in that the compound heterozygous mice are not being born at the normal variant. It might have nothing to do with epilepsy or with what the Folbigg children have, but it is intriguing.

Can I have the last slide, please? This is slide 12.

With these, I want to show these are the BSN variants in the two Folbigg boys. One has been inherited from the mother. The second one is presumed to be inherited from the father, but we couldn't sequence the father. Now, on top of these two variants, only last year there has been a new gene associated with epilepsy: CELSR3. The four Folbigg children have an ultra-rare variant in this gene. There's only one other individual in the world found to carry this variant. It has been shown to be intolerant by MetaDome, although it is borderline-intolerant by other metrics, and it has been shown in a large project as a probable cause of febrile seizures and epilepsy with antecedent febrile seizures.

But actually, the variant that I think, to me, looks more interesting is this other variant called - inner gene called SEH1L. Only Patrick has this variant. It is a variant that has not been inherited from the mother, so it is presumed to be inherited from the father, or it might not be inherited from the father because it is novel, there has been not a single individual found with this variant, so for all we know, it could be *de novo*.

In mice when it is absent, the mice die. They are not even born; they die in utero. But when the variant is only absent in the brain, the mice developed seizures two weeks after birth and died in the third week after birth. This might mean nothing; it might be completely irrelevant. But, as a geneticist, if I was a

neuroscientist, I would be following this up because to me, it looks sufficiently intriguing - but I would only follow it up if we sequenced the paternal DNA and we found it was *de novo*. *De novo* would be a very important indicator that this would be significant.

Now, this is an example but an example that unless we do this analysis seriously and we have a chance to sequence paternal DNA, it is going to be very difficult to establish whether there is a genetic cause of death for the children, and with this, I finish.

JUDICIAL OFFICER

Q. Thank you very much, Professor.

CALLAN

Q. Thank you, Professor.

CALLAN: Your Honour, I will tender the slides; we will just work out the most convenient location for them by way of exhibit number.

Q. Can I clarify - could I ask that we go back to slide 8? By reference to slide 8, you referred to a number of experts and I missed what you said about what they had concluded as to the variant; as to what it was likely to cause.
A. Yes, so Professor Lia Crotti, Professor Peter Schwartz and Professor Hari Raju were co-authors of the Brohus et al paper. The three of them are cardiologists and as co-authors, they agreed with the conclusion of the paper that CALM2-G114R was the likely cause of the death of Sarah and Laura Folbigg. In terms of Chris Semsarian and Reza Razavi, who is a Professor of Cardiology and a Cardiologist in Kings College, London; they both signed a petition concluding that because of the Brohus article, the - this was the likely cause of the death of the children and in a report we've recently been sent, Professor Hugh Watkins from the University of Oxford said that he would find these - I can't remember the words but he would conclude if it was presented to him in the clinic that this was absolutely the plausible cause of death of children in these circumstances.

Q. I think we will defer to Professor Watkins' written report in terms of the way he expresses the view that he holds.
A. Yes, absolutely.

Q. You have invoked those who signed the petition as an indication of a view held by those two cardiologists on the question, by reference to what appears in the Brohus article.
A. Yep.

Q. And you've referred to three of the co-authors of the Brohus article itself. The article's conclusion is that the variant presents as a reasonable explanation for the death?
A. Yes.

Q. That is different from a likely cause of death; you accept the distinction?
A. It's also written in those wordings in other parts of the article. I'm pretty sure that even in the conclusions at the end of the article that sentence can be found - or somewhere, I mean, if you search for "likely" you can find it, I'm pretty sure.

Q. The article will speak for itself in any event, thank you, Professor.
A. Yeah.

Q. The evidence you gave towards the end of your presentation in relation to the position as it relates to the two Folbigg boys, do you accept the proposition that as things presently stand no genetic variant presents as a plausible cause of their death?
A. I think that there is the possibility that these variants may contribute, we just need to test them functionally and have access to paternal DNA, so plausibility is there.

Q. Plausible in the sense that it's possible--
A. Yes.

Q. --but there's too little known at this present time?
A. Yes.

Q. The Brohus article makes reference to the BSN L1898M variant?
A. Yes.

Q. After it was published - sorry, actually I just want to clarify the timing. The report that you prepared for this Inquiry of 10 October of 2022 refers amongst other things to steps that had been taken in relation to functional testing of the BSN variant?
A. Yes.

CALLAN: Your Honour, the report is at Exhibit 5, tab 4 and it's in part 4 of that report.

Q. Could I ask that you turn that up or we'll have it turned up for you?
A. Yeah, I can. Yeah, which page, sorry?

Q. Part 4, page 15 of your report, it's red page 77, your Honour.
A. Yeah. Yeah. Yeah.

Q. Paragraph 4.5 you refer to after the Europace publication a GWAS study, which had appeared--
A. Yes.

Q. Paragraph 4.6 you go on to say to investigate a possible link between the Folbigg BSN variants and sudden death, epilepsy, et cetera?
A. Yes.

Q. A team undertook some functional testing?

A. Yes.

Q. In terms of timing, did that functional testing commence first of all after the Europace publication?
A. It would have been started, our - perhaps the CRISPR oligos might have started before the Europace publication but it takes about three or four years to perform these types of functional assays with mice.

Q. So when did it start?
A. I'm not sure, I can't remember an exact date, but when we found these variants, it might have been some time 2020, I'm not - can't tell you a precise date.

Q. Can I ask why you included reference to this variant in the Brohus - first of all, did you cause the reference to this BSN variant to be included in the Brohus publication?
A. I consulted with my co-authors, and we reached the opinion that it was sufficiently intriguing and a very hot VUS, that we should mention it.

Q. You knew at the time that there was a functional testing that was being undertaken?
A. We hadn't - not when we - I mean we knew it would take four years at least to know the outcome, but when you have *de novos*, homozygous or biallelic ultra-rare variants, they are worth reporting in a publication and we would have done that, it would have found a *de novo*, a homozygous or another biallelic variant in a plausible pathway. This was the only one, there was no other homozygous, we couldn't have *de novos* and this was the only biallelic one significant, and in fact reviewers asked us if there was any other thing worth reporting. So, you - it's the norm to report these things. Can I have some water please?

Q. Yes.
A. Thank you.

Q. Over the page at paragraph 4.10, you indicate since the Brohus paper was published more individuals have been identified in the gnomAD with the Folbigg variant?
A. Yes.

Q. You say the numbers suggest the Folbigg BSN variant is unlikely to cause sudden death in humans at least in the absence of other genetic or environmental factors?
A. So this was before I found out that there is neo or pre-natal lethality with a compound heterozygous variants. This information was only given to me by Nathalie Dehorter last week when I showed her the paper about the human causality or the human publication showing BSN can't cause epilepsy in humans. So I asked Nathalie “do you have an update, look at this paper, I wasn't awareof it”, and the only update that she could give me, so Nathalie Dehorter has moved to Brisbane, she left Canberra in December, so she hasn't really done any more functional experiments, but she told me that what

she could tell me is that they were not born at the normal Mendelian frequencies. So this changes things because what we have here from ClinVar are individual frequencies of individual alleles. ClinVar cannot evaluate the outcome of the association of two variants and I now know from Nathalie that they are not being born at the normal Mendelian ratios. Plus this new paper has been published which suggests it's not definitive because there is no functional validation, but they found eight pedigrees, four of them with biallelic variants in BSN that have epilepsy. So there is a strong proposition that these actually might be relevant after all.

Q. I see, but to use your words, we presently know too little?
A. Yes. Definitely.

Q. You said in relation to this topic of the BSN variant in the two boys that it was worth reporting?
A. Yes.

Q. You used the words you felt you had to mention it in the Brohus article?
A. Yes.

Q. What did it have to do at all with the G114R variant?
A. Well, when you study a pedigree, reviewers asked us, “have you found any relevant VUSs or variants in the other members of the family?”. There were four deaths being reported in that pedigree. So you have to say what you found. I mean this is a normal thing to do and obviously part of the issue here is that we have four deaths and one mutation referring to two of them. So it is absolutely normal to explain, and actually we wrote in part of our results which variants were found in which children.

Q. Yes?
A. So it is an absolutely normal thing to do.

Q. Is it relevant by reference to whether the presence of another variant affects the G114R variant, that was the focus of the functional studies and the focus of the Brohus article?
A. You know, in an article you can have more than one focus, and in this article we were doing a genetic study in the Folbigg family, and we start by saying we were asked to identify a genetic cause of death in this family. So, it wasn't about G114R, it was about the genetic study that led to these conclusions.

JUDICIAL OFFICER

Q. When you said you were asked, who asked you?
A. Well, officially we were asked by a lawyer in 2018 after we had made the first CALM-G114R discovery.

Q. That's what I wanted to understand. The article was prepared, wasn't it, or originated from the request of Ms Folbigg's legal advisors, is that right?
A. In my case it was. In the case of Professor Cook, he was approached by

the Crown, and he's a co-author of the paper.

CALLAN

Q. I just want to be clear that we're using the right terminology. The article, we're talking about the Brohus article, who asked you to write that article?
A. We were told we were free to publish the results of our genetic study. So we decided to publish the results of the genetic study.

JUDICIAL OFFICER

Q. So no one external to the article asked you to do so? No one specifically requested you or any of the other authors to write the Brohus article?
A. No.

CALLAN

Q. The article, can I suggest, doesn't report generally on what you found in terms of the genomic sequencing analysis you undertook in relation to the four children?
A. It does. We mention quite a few variants in the article. We mentioned NLRP1, dup(1), KCNAB2, there is a section where we report all the variants that were considered significant in the four children.

Q. The title of the article is "Infanticide vs inherited cardiac arrhythmias". That was the - it was inherited cardiac arrhythmias which was the focus of the article, wasn't it?
A. You can't have a title that encompasses every single finding in a paper. So normally - and actually you are limited by the number of characters in a title, so it's always a compromise what title - I mean we could have gone through a number of titles but we couldn't mention every possible gene in the title. Eventually you give the focus of the most definitive finding and the most definitive finding was the G114R. But, you have to be comprehensive in your description, and in fact reviewers asked us for the findings, and you can't select your findings, you can't put ones and leave others out.

Q. In the first page of the article it describes the aim, amongst other things, "In 2019 we were asked to investigate if a genetic cause could explain the children's death as part of an inquiry into the mother's convictions"?
A. Yes.

Q. There's then reference to method and result, and with a particular description of the functional analysis that had been undertaken in relation to the CALM2-G114R variant. Then a conclusion is reached as to a prediction based on the functional assays performed on that G114R variant and reads, "calmodulinopathy emerges as a reasonable explanation for a natural cause of their deaths", that is the two children, yes?
A. Yes.

Q. Do you recall that part of the article?

A. Yes. Yes.

Q. That, can I suggest to you, plainly reflects the focus of the article? That is the particular findings that were made through the functional testing in relation to the G114R variant?
A. They're the positive findings, yes.

Q. Yes. Insofar as you have made reference in that article to the BSN variant can I suggest that that - sorry. Was that done to strengthen an act of advocacy on behalf of Ms Folbigg in terms of her innocence?
A. Absolutely not. We report positive and negative findings. If you notice we performed a very extensive study on the KCNAB2 variant that is present in three children that is predicted to cause Brugada Syndrome. So the only child that doesn't have a KCNAB2 variant is Patrick, who had epilepsy. Now, we could have hidden those results or we could have left them out, but it is good practice when we publish a paper to publish positive and negative findings, and I insisted that we publish the KCNAB2 as a negative finding. It's a very interesting variant, if I may say, because it's an LN11 - residue and the two residues immediately next to LN11 have been found to be pathogenic in Brugada Syndrome. Now, by putting the negative data we are doing what we always do in papers, we put the positive and the negative, and the other only worth mentioning reporting here was the very hot VUS of the BSN which, as I've just shown you, has now just proven or published to cause epilepsy in humans, possibly. So this is what we do: we publish negative; we publish positive. If we were being selective, we would only be telling part of the truth.

Q. But the truth in relation to BSN is that it was too early to tell whether this was relevant or not?
A. We work in the field of genetic discovery. When you make a finding that looks very suspicious, you report it because it is the only way our other colleague scientists can pick things up and follow those trails. So we do it routinely. We've done it - I mean, in every paper I publish, I also mention other VUS's that could have done something or might not have done something, and reviewers always ask "but was there anything else in those genomes? Have you checked for all possible causes?". It is standard practice. It would be, I think, not professional not to mention if there was one other hot VUS and this was the only other hot VUS we had at the time. If I was writing this paper now, I would mention SEH1L and I would say it is remarkable, it causes epilepsy in mice, it has never been found before, it could have been *de novo*. At the time, I hadn't been - I hadn't identified SEH1L, nor this CSLR3. This variant that has now been published to cause epilepsy, if I had known when we wrote the paper that it was present in the four children, of course I would have mentioned it. It's another very hot VUS. This is what we do. You don't select some parts and leave others out.

Q. Just to be clear, the work that was done in relation to the functional assay provided a contribution to the state of knowledge about that variant and about the CALM gene; do you agree with that?
A. Yes.

Q. What contribution do you make to the state of knowledge about the BSN variant in this paper?
A. Well, we might have been the people that alerted this Chinese group to look for it in their GWAS study or in the next study, you know, the--

Q. I'll just pause you there. You are not reporting on any contribution as to the state of knowledge.
A. Yes, we have discovered the first biallelic variant in BSN that - a gene that has been associated with epilepsy in humans and has now been found in mice. All that this recent paper points out, the one I've just showed you--

Q. No, I'm just talking about the Brohus article.
A. It is--

Q. What is that contributing to the state of knowledge about the BSN variant?
A. Yes.

Q. What is it contributing to the state of knowledge?
A. That you might find a biallelic variant that is a very hot VUS in a child with epilepsy and in fact, the recent paper published only recently has not done anything else. They have just done the same thing but within eight pedigrees instead of one. They haven't done functional validation, but they have found it in eight pedigrees. So we were the first ones to find it in the first one.

Q. Could I take to your report of 25 October, which is Exhibit 5-06? Do you have that report?
A. Yes.

Q. It is report page 38, red pagination 153.
A. Yes.

Q. There you set out some clinical information.
A. Yes.

Q. Obtained from the evidence in this matter in relation to Caleb Folbigg.
A. Yes.

Q. Insofar as this sets out consideration of a possible cause of death of Caleb Folbigg, do you accept that other than matters pertaining to genetics, this is beyond your areas of specialised expertise?
A. Yes.

Q. Does the same apply to the content and description of clinical information concerning Patrick Folbigg?
A. Yes.

Q. Can I come back to the task that you have undertaken in relation to the G114R variant? Would it be correct to describe the phenotypic data as incomplete?
A. Of what?

Q. The phenotypic data is incomplete in this case?
A. In the mother was incomplete, in the children, yes, we would have liked to have ECGs.

Q. 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 deaths of Caleb or Patrick Folbigg?
A. No.

Q. As it appears from the evidence, nobody has suggested a candidate variant which is shared by all four children as to cause of death?
A. Well, I mean, as I said, the study is incomplete.

Q. Yes, but--
A. From what we have--

Q. From what we have?
A. Yes, there is not a genetic variant that explains the four deaths.

Q. You observe in your report of 25 October, Exhibit 5-06, it is unreasonable to assume “a single unifying cause of death in relation to the four children"?
A. In - yes, I did write that, yeah.

Q. Can I take you to what you then go on to write, it's at page 16 of the report which is red page 131. It's the final sentence on that page that begins "It is also unreasonable to assume". Do you see that sentence?
A. Yes.

Q. Which goes onto the top of the next page.
A. I do, I do see it, yes.

Q. Were you here when Professor Arsov was asked about that portion of the report?
A. Yes.

Q. He was asked, "You're in effect saying you don't know at the present time whether there was a genetic cause for the boys' death but one day in the future, you might find out?"
A. Yes.

Q. That is your position?
A. Yes.

Q. In the 2019 Inquiry, the letter that you furnished to the Inquiry after giving your evidence included an observation that "the starting point is that the phenotype which caused death in each child remains ambiguous". Does that continue to be your view as to the "starting point on phenotype"?
A. Well, we don't have ECGs from the children. Other than that, we'd have a phenotype which is sudden unexpected death.

Q. Sudden unexpected death is a diagnosis of exclusion?
A. No, it is a phenotype, as I have just described, for example, in the Calcium Release Deficiency Syndrome, it is the only phenotype. In the case of IVF, it is the only phenotype unless you are monitoring the child at the time of death.

JUDICIAL OFFICER

Q. I just want to try and understand this, Professor, it's a phenotype, in effect, because you haven't got any other further basis for investigation; is that right?
A. Look, you're right in saying that in some cases that could be the case. We might not have enough - more information. In other--

Q. You know there's the variant and that's all you know, basically?
A. But I'm saying that in the context of calmodulinopathy, sudden unexpected death can be the only presentation, especially with IVF, for example, and in syndromes of proteins that interact with calmodulinopathy, we now know that sudden unexpected death is the only presentation. There won't be ECG findings, even if you look for them. There won't be prior warnings. So we know now it is a phenotype of cardiac arrhythmias. Whether that was the phenotype in this case, whether there might have been else that we might have missed, it is possible.

CALLAN: One further question and then if it is convenient for morning tea, your Honour?

Q. Professor Abrams in his report expresses the view that "sudden death alone in the absence of other clinical findings cannot be considered a phenotype because it is non-specific". Do you disagree?
A. I do, for the reasons I have just expressed.

SHORT ADJOURNMENT

Q. Professor Vinuesa, yesterday during the evidence of Professor Arsov, you said, "the phenotype in this family includes sudden cardiac death"; for the record, that is at transcript 241. Is that how you conceive of the phenotype?
A. Yes.

Q. Is that based on the views that you've formed about the G114R variant?
A. It is one of the probable phenotypes, yes.

Q. In assessing the pathogenicity of the G114R variant, have you taken into account the fact of the two girls' deaths?
A. That was what we were looking for; that was our starting phenotype, yes, sudden cardiac death.

Q. Your starting phenotype--
A. Yes, because in most--

Q. You would say was sudden cardiac death?
A. When we - just to bring it back to when we started, we were asked to

investigate a possible genetic cause for the deaths of two children. In the literature, if you search what are the more common causes of SIDS or sudden death in infancy and childhood, they are cardiac, and it is sudden cardiac death what you look for generally. That's in every literature review, in most papers and that's what molecular autopsies mainly look for: causes of sudden cardiac death. So it wasn't a big jump or a big - it was before even finding the CALM1 variant, we put a gene list together and the gene list was the causes of SIDS and sudden cardiac death - and sudden death in infancy and childhood that happened to be mainly sudden cardiac death, and I would say it is a phenotype because even today, every - most genetic sequencing companies, our Canberra Clinical Genome service, we have a panel for sudden unexpected death or sudden cardiac death because death can occur suddenly and in children, it is a very common cause of sudden death - sudden cardiac death.

Q. You don't suggest that that is the phenotype for the two boys, do you?
A. Look, we know very little about the two boys. All we were told is that Patrick had intractable epilepsy and that Caleb had had problems with breathing from birth and had been clinically diagnosed with laryngomalacia, so I can't say anything else. I'm not an expert and I won't comment on their deaths, but we had been given information about those two pieces of the phenotypes of the boys.

Q. Can you answer my question, you didn't approach the phenotype of the boys as being sudden cardiac death?
A. We looked for - I mean, we first - remember, we sequenced Ms Folbigg, and we heard a history of recurrent syncope and we found a calmodulin variant, so obviously we were thinking that either it had been a cause of death. One of the possibilities would include sudden cardiac death. We hadn't formed an opinion, but you could argue that the children had somewhat different phenotypes.

Q. Do you accept a criticism that it is not appropriate to take into account the death of the girls in assessing the pathogenicity of the variant?
A. No because I consider that sudden expected death is a phenotype.

Q. Sorry, sudden unexpected cardiac death?
A. Sudden unexpected death, SUD, is a phenotype and is within the spectrum of calmogenopathies. I mean, we were asked to undertake an exercise to investigate a possible genetic cause and the presenting feature was sudden unexplained death and that is a phenotype, and it is a phenotype that is common in molecular autopsies. It is children dying suddenly with no other explanation and most of the times, it is cardiac. So it wasn't a big leap. We weren't making a big speculation. I hadn't been asked to interrogate, I mean, anything else except if there is a possible cause of death, we are looking at what are the most common causes of sudden unexplained death? It is cardiac, so our gene list and the terms that we put together, the geneticists in the first Inquiry, both teams, included channelopathies, Brugada Syndrome, Long QTS. You can see in the reports that these terms were agreed on by both teams and the speculation even before we started the genetic testing,

Sydney and Canberra teams, was that we were specifically going to look for genes that had these terms associated in the literature, and it wasn't our list; it was a genes - a list that was put together by Sydney and Canberra teams. So even before we undertook a sequencing of the children, in a small list of terms, we had Long QTS, and it's in one of our first reports, I have to say, EAF or AG, as I say, all those terms were cardiac because that was the most expected cause of death in young children that is unexplained.

Q. We may be at slightly cross-purposes, Professor Vinuesa. I understand you've now said several times about the breadth and the particular path that you followed and the rationale for that. I want to ask you about the slightly different topic, which is invoking or using the fact of the girls' death in the process by which you classify the variant. There is a criticism in taking such an approach in the report of Professors Kirk and Skinner - for the record, it is at Exhibit 7-03, red page 50 - that that includes circular reasoning. Do you accept that criticism?
A. No.

Q. What is your answer to that criticism?
A. That we had a - we had a starting phenotype because first of all we had talked to Ms Folbigg, as you heard yesterday, she detailed a recurrent history of syncope, which is within the spectrum of sudden unexpected death, and if we had to have any hypothesis from which to perform a genetic exercise, we had to come up with the most plausible phenotype. You can't do a genetic exercise without having a starting phenotype and we agreed and actually, it was Dr Buckley that put together the first gene list that we should all consider from two reviews, one of them was Ackerman's reviews--

Q. I think we're getting a little off topic, Professor, could you answer my question? You say you reject the proposition that you're engaging in circular reasoning when you are using the fact of the girls' deaths in your assessment of the pathogenicity of the G114R variant. That's all I'm asking you about.
A. I absolutely reject that proposition. We started off from assuming--

Q. I'm not talking about where you started; I'm talking about what you take into account to arrive at the view that you do as to the pathogenicity of the variant.
A. There was no circular thinking in our approach.

JUDICIAL OFFICER

Q. Professor, this Inquiry has received a lot of evidence from forensic pathologists and they, I think, almost universally say that SIDS is a diagnosis of exclusion. In other words, in certain criteria, that would be diagnosed as the cause of death where there is no other explanation. Now, what is - I think the criticism that is levelled against your approach is that you assume the cause of death is the genetic variant because the children have the genetic variant. That's the circle they are talking about. I'd be interested in your view on that.
A. I entirely understand where you're coming from. We were asked to undertake a genetic exercise. When you undertake a genetic exercise, it's

because you are considering there may be a genetic cause for these deaths, and the most common cause of sudden unexpected death is cardiac. And I tell you, my father died from sudden unexpected death at 55 and the only--

Q. So did mine at 96.
A. Yeah, anyway, the most common cause of sudden unexpected death is cardiac followed by epilepsy. So we had to assume there had been a genetic cause. We had to call a phenotype.

Q. In other words, you assumed - this is what I'm interested in - you assumed the death was a cardiac cause, if I can use that very generally?
A. We assumed that it was one of the two-most common causes, so we included it in our panel. Sudden unexpected cardiac death genes and sudden unexpected epilepsy genes, SUDEP.

Q. So because you were able to - or you did include sudden unexpected cardiac genes there, that proceeds on the assumption that the girls died from a cardiac failure, because otherwise there would be no use looking for those genes?
A. We also included sudden unexpected epileptic death.

Q. I understand that, just focusing on the cardiac for the moment. Now, it is, in one sense, is it, and I may be wrong about this, critical to your conclusion as to the pathogenicity of these genes that the girls died from a cardiac failure?
A. I mean, you can - your Honour, if you start a genetic exercise, you have to say what are the most possible causes for this presentation.

Q. Leave aside epilepsy for the moment; you concluded one of the most plausible causes was cardiac failure?
A. It's the top - the top cause of sudden unexpected death in infancy or childhood - is cardiac.

Q. So the phenotype was cardiac failure?
A. It was sudden unexpected death, possibly from a cardiac arrhythmia or from epilepsy.

CALLAN

Q. Insofar as you took into account the fact of the girls' death in assessing the pathogenicity of the variant, is that accommodated within the ACMG criteria?
A. Yes.

Q. In what way?
A. In that you have a phenotype or you have a condition, and--

Q. Just pausing there, what was the condition, to be clear?
A. Well, I mean, to be sudden unexpected death and the Sydney team performed that exercise for the 2019 Inquiry and they never questioned that they were arbitrarily using the ACMG criteria. So this was a proposition we had all reached together in the first meeting of the Inquiry where we put

together--

Q. We are aware of the history, Professor--
A. Yes--

Q. I'll move on.
A. Yep.

Q. Can I speak to you about Laura's myocarditis?
A. Yes.

Q. In your report of 25 October - which is at Exhibit 5-06 of the Inquiry, red page 136, your page 21 - you set out some answers to the question which was question number 1.4, and you do so by reference to a number of propositions which emerge from the literature about myocarditis?
A. Yes.

Q. Can I ask, on the topic of any relevant interplay between myocarditis and the CALM-G114R variant, do you defer to the views of a cardiogeneticist?
A. Well I would like to say that this is very well reported in the literature, 70% of cases of myocarditis cause a prolongation of the QT interval.

Q. You do not defer, is that your position?
A. I've read the literature, there are many papers on this.

Q. In your report from 23 January 2023, Exhibit 5-07, you recall you include some observations and comments about the video footage of Laura Folbigg?
A. Of what, sorry?

Q. Laura Folbigg?
A. Yes.

Q. You weren't asked any questions by the Inquiry about that footage, were you?
A. Yes. We were asked to comment on the video.

Q. Your comments, you've confined yourself to relevant genetic-related observations, have you?
A. Well it was difficult for us to know why they wanted us to look at the video, we thought they might be asking us to respond, is this compatible, with either CALM-G114R or with a possibility that she had myocarditis.

Q. You recognised that you're not paediatricians and you say you provide your view based on the evidence provided by experts in the Inquiry and the available literature?
A. Yes.

Q. Can I turn to the position in terms of Ms Folbigg's phenotype?
A. Yes.

Q. Just trying to understand the landscape of information available to you in order for you to - and in terms of the position and the views that you've formed about her phenotype?
A. Yeah.

Q. So first there are the cardiac investigations which have been conducted including some ECGs?
A. Yes.

Q. You've had regard to that?
A. I think there has been three very interesting observations in the ECGs that point there could be something cardiac.

Q. Those observations, are they observation that have been made by a cardiologist interpreting those ECGs?
A. Yes.

Q. You also in considering the position as to Ms Folbigg's phenotype have regard to the history that Ms Folbigg has provided?
A. Yes. That's, Dr Hari Raju has detailed - and the history from the health records, both before and during prison.

Q. And the information she has told you?
A. Yes. Well, that one, as I say, my memory wasn't absolutely clear, so I will not refer to the - that one.

Q. Your report of 10 October which details relevant phenotypic information - your Honour, for the record it's Exhibit 5, tab 04 - so it's what you say you're doing is providing a summary of relevant phenotypic information and within that you include reference to syncope, so page 6, red page 68, paragraph 2.3, syncopes you understand have been witnessed or documented in health records?
A. Yes.

Q. There's a reference to, and I won't cover the ground again, what you report about the fainting while at the swimming carnival?
A. Yes.

Q. The final sentence refers to her friend Billy Jo--
A. Yes.

Q. --and what her recollection is, and then do you see the next paragraph there is a reference to a syncope at age 17?
A. Yes.

Q. By reference to an interchange between Ms Folbigg and her friend Billy Jo?
A. Yes.

Q. Did you speak to friends of Ms Folbigg about her early years?

A. I spoke to Tracy Chapman, her next of kin, asking her about her cardiac history.

Q. When did you do that?
A. Probably when I visited Ms Folbigg in prison.

Q. Around the same time or at that location?
A. At that location.

Q. She was also at the prison at the time?
A. She facilitated entry to the prison. I didn't go to the - in the prison with Ms Chapman.

Q. Why were you asking Ms Chapman about matters relevant to Ms Folbigg's cardiac history?
A. Just to understand the full picture, because there were still lots of gaps in our understanding.

Q. Still on this topic of the sources of information that you have had reference to in relation to Ms Folbigg's phenotype, you've already referenced health records and that encompasses Justice Health records that have become available in relation to Ms Folbigg in custody and other, I might describe them as primary medical documents. You also had regard to the views which have been expressed, for instance, by Professor Schwartz and Professor Wilde about Ms Folbigg's possible phenotype?
A. I suppose, I don't know what you're asking me there, sorry.

Q. I'm trying to understand the sources of information which have informed what your view is about her phenotype?
A. Look, I - I am not qualified about talking about the significance of her syncope. I leave that to the cardiologists. I'm just detailing a recurrent history of syncope which appears quite common in the literature, and for there to be a patient in the International Calmodulinopathy Registry, a single syncope qualifies for that patient entering in the Registry. So we know there's been a recurrence in history of syncopes including one detailed in the prison health records when she was going to be transferred to another prison where the nurse asks her if this was due to anxiety - she expresses that it was and in fact that she had taken her Seroquel that morning because of anxiety. I'm not saying those are significant, they might be completely insignificant, I'm detailing the history of syncope and I leave it to the cardiologists to say if there's anything there or not.

Q. Just as you would defer to a cardiologist as to the significance or otherwise of that history of syncope, you also deferred to a cardiologist as to whether Ms Folbigg is symptomatic of a calmodulinopathy?
A. Absolutely.

Q. In any event, as I read it, for instance in your report of 25 October, in your view Ms Folbigg's symptomology has little bearing on whether the G114R variant is pathogenic?

A. Yes.

Q. You say that by reference to concepts including variable expressivity and incomplete penetrance?
A. Yes.

Q. You go so far as to observe that it's been demonstrated that lethal calmodulinopathy causing CALM variants can be present in an asymptomatic and healthy carrier?
A. Yes, there's a few papers showing that.

Q. That accords with the broader proposition that carrying a variant classified as pathogenic does not automatically mean it has or will cause a clinically manifest disease?
A. Yes.

Q. That's the position in relation to Kathleen Folbigg?
A. Yes.

Q. And that's the position in relation to Sarah and Laura Folbigg, isn't it?
A. It would be, yes.

Q. During the 2019 Inquiry hearing when you gave oral evidence you recommended further investigative cardiac testing be undertaken to determine - to seek more answers about Ms Folbigg's phenotype?
A. Yes.

Q. When this Inquiry commenced in 2022, did you maintain that recommendation?
A. Well, the testing had been performed.

Q. Beyond the testing which had been performed in the interim, did you take a position as to any other cardiac tests which might provide further investigative tools in relation to a cardiac position?
A. I'm not sure what you're asking, I don't think I recommended any. I remember you asking us would you perform an adrenaline test and I was saying I'm not sure that would exclude necessarily anything. So I didn't see the value, but again we also referred you to Peter Schwartz or other cardiologists to give their opinion, given that I'm not a cardiologist.

Q. In circumstances where whilst you were not a cardiologist, in 2019 in that Inquiry you recommended further investigative cardiac testing. Could I just be clear as to your position, sitting here today do you consider that further investigative cardiac testing should be undertaken to determine if Ms Folbigg has a phenotype?
A. Today I will - I cannot comment because all I needed to say is that in order to exclude Long QT Syndrome we needed a stress test, and that hadn't been performed when we were asked to classify the genes before the hearings of the 2019 Inquiry. That is the essential basic test. Further tests, I cannot comment on, that's beyond my area of expertise.

Q. Ultimately it's a matter for Ms Folbigg on the advice of a cardiologist?
A. Absolutely.

Q. In your report of 25 October, amongst other things you were asked to comment on the relevance, if any, of potential triggers and you commence your answer to that question noting that the study of triggers in genetic conditions is a relatively nascent field?
A. Yes.

Q. Professor Wilde has suggested the relevance, if any, of potential triggers is highly speculative, do you agree with that statement?
A. Yes, it's becoming less and less since the recent finding of Professor Toft Overgaard because if G114 completely impairs binding to the sodium channel than fever, it becomes less speculative.

Q. Less speculative but nevertheless as things presently stand we're in speculative territory?
A. Yes.

Q. Continuing with that theme of speculative territory, can I take you to your report of 1 February 2023 that you co-authored with Professor Cook? Your Honour, for the record it's Exhibit 5-08. This is on the potential role of a modifier gene. In your concluding remarks which are under the heading "Implications" at red page 214, report page 5, you recommend that the Inquiry engage experts with specialised knowledge in cardiac arrhythmia modifying variants such as Professors Schwartz, George Junior and Isabelle Deschênes to provide their opinion as to what effect that REM2 variant may have had in modifying the phenotype caused by the G114R variant. As I understand it, what you do is present a potential relationship and nothing more than that?
A. Yes.

Q. Whether the REM2 variant has any relevant modifying effect on G114R would have to be studied before any conclusions could be drawn?
A. I cannot comment, it's not my area.

Q. The 2018 paper that is referenced in your report concerned the potential modifying effect of the REM2 variant for variants in KCNH2. The authors of that paper don't suggest that the REM2 variant has an aggravating, modifying effect for sudden cardiac death in any general sense; they confine it, don't they?
A. Actually, they - because they say that it affects the potassium, Cav1.2 channel - sorry, the calcium flux and the calcium flux that is L-voltage-gated, which is relevant to Cav1.2, it is suggestive that it could affect any other protein that is influenced by this channel.

Q. You looked on, for instance, gnomAD, as to the numbers who carry this REM2 variant?
A. Yes, the mineral frequency is 0.09, which would - means that 18% of the population would carry it. Now, this is typical for modifier genes; alone, might be present in a large number of individuals but when present with some of

these ultra-rare variants, it could cause a phenotype, and that is the beauty and mystery of modifier genes.

Q. In terms of a view you have expressed which goes beyond the pathogenicity of G114R, to the question of whether there is a reasonable possibility it caused the death of Sarah and Laura Folbigg, you have accepted, as I understand it, the classification of that variant as pathogenic doesn't automatically mean it will cause a clinically manifest disease?
A. It doesn't, but if this variant was to present in the clinic, I'm sure nearly every cardiologist would report it and ascribe it as a "high probability" that that was the cause of death.

Q. I am just asking you about the general proposition. I'm trying to work through your thinking process to arrive at the position you do as to the reasonable possibility. In circumstances where you accept that classifying a variant as "pathogenic" does not mean it has or will cause a clinically manifest disease, and you point that out when you're dealing with Ms Folbigg's phenotype, what is it that causes you to arrive at the conclusion that there is a reasonable possibility it caused the death in Sarah and Laura Folbigg?
A. So when we are determining a variant is pathogenic, we are saying it has more than 99 probability of causing that particular phenotype. If a child or a family was to arrive in a clinic with two or one sudden unexpected deaths and a pathogenic mutation in CALM1 was identified, the logical conclusion would be that that would be the cause of the sudden unexpected death, particularly if it's a novel variant in calmodulin.

Q. The functional tests which were reported in the Brohus article predicted, by reference to those functional tests, the carrier of this variant would be prone to cardiac arrhythmias of IVF or CPVT-like phenotypes, with a potential component of mild Long QT Syndrome. You are well aware that Professor Wilde, but also, Professor Abrams and Professor - and I think largely, if I confine myself to their views - point to what Professor Wilde describes as a "mismatch between the phenotype presumed for the Folbigg family", which he describes as the "death of two infants at ten and 18 months while asleep", and what the functional assays report in the Brohus article as predicting - that is, CPVT or possibly mild Long QT Syndrome. It is for that reason, as I understand the views expressed, that they articulate doubt that this variant caused the death of Sarah and Laura Folbigg. Pausing there, what is your response to - first, do you consider that you have sufficient qualification or expertise to comment on that question?
A. My expertise would be to say that we know very little about the spectrum. After this paper was published, it was shown that G114 alters binding to sodium, calcium. Three days ago it was shown that it alters binding to potassium. I think it would be a big mistake to draw a conclusion from a single functional assay, but these functional assays are informative. They are only used to say that this protein is damaging and to attempt to draw a conclusion, the full breadth of the phenotype from a single-channel experiment, I don't think anybody would do it and I think to speculate that from this assay, we can precisely call the phenotype. But the phenotype is well within the spectrum of calmodulinopathy. I mean, we are talking about a

difference in, you know, perhaps two or three years of age to find an IVF versus a mixed phenotype. So I do think it's a mistake to speculate based on one assay. I think there is sufficient information that the mutation is damaging; it causes a phenotype within the spectrum of calmodulinopathy and from thereon, I mean, I think it is - it is not reasonable to either infer from this channel functions what the precise phenotype is going to be. We need to look at the interaction between the channels. But in the clinic, all you need to know is, is this within the spectrum, is this a novel mutation, is it in a gene that is so constrained it doesn't tolerate substitution? And most reasonable cardiologists would put it as a VUS and would tell the family you probably don't want to have another child with this mutation and would recommend PGD, pre-implantation genetic diagnosis. I mean, this is the way these things operate. The functional assays are not meant to be done to just tell you the precise phenotype. Are meant to tell you is this variant damaging to protein function? And it will be years until we understand exactly the final function. I mean, we've shown calmodulin interacts with 300 proteins including nearly every channel that causes a cardiac arrhythmia. So the functionality, it's just the first introspection as to does this variant cause a damage to the protein? We do this in most diseases. We don't understand how variants cause disease in nearly every disease; all we do is have that first insight as to does it damage the protein?

Q. You used the word "speculate" in part of that lengthy answer. Could you agree that what Professor Wilde and Professor Abrams have done is place particular weight on what the functional assays have shown?
A. Perhaps - look, I'm not going to be too critical. I'm just saying that, you know, you've got another six cardiologists that think that's very reasonable--

Q. Can I just ask you to come back to the question, Professor?
A. Yep.

Q. You accept that what they've done is, they have pointed to what the functional assay results are as reported in Brohus; step one?
A. Yes.

Q. Step two: They've pointed to what is the current state of knowledge about the phenotypes that fall within the broad umbrella of calmodulinopathy: LQTS, IVF and CPVT. That's what they have done; you accept that?
A. Yes, yes, yes.

Q. And what they have identified is a mismatch between the functional tests and the current state of knowledge about those phenotypes; having regard to the circumstances of the girls' death. Do you accept that's what they have done?
A. I think they have also speculated, I'm sorry.

Q. In what way do you say they have speculated?
A. Because without knowing the interactions, without being able to test the interactions between the channels, one cannot draw a conclusion about what that mutation can do.

Q. So that is the area of speculation, yes?
A. To draw an inference of the phenotype from those two assays is impossible.

Q. Do you accept that we are in speculative territory? Whether it's them or what your--
A. Or Peter Schwartz or Toft Overgaard, I agree.

Q. Yes.
A. That's why you just have to say this variant is damaging to protein function, and time will tell what is the final phenotype.

JUDICIAL OFFICER

Q. Is this right, you say it is impossible to draw any inference as to what caused the death, and you reason from that because the children had this variant, there is a possibility that in some way, their death resulted from that variant? Is that fair?
A. I'm saying it's partially fair. I'm saying that there has never been a benign calmodulin mutation found to date, and this one has been shown to be damaging by five assays. So the possibility is quite large that it crosses a phenotype in the spectrum of calmodulinopathies, which we yet know very little about it but includes sudden death.

Q. We are talking in a region of both possibility and uncertainty; is that also fair?
A. I'm sorry I didn't--

Q. We are dealing with an area--
A. Yes.

Q. --that is both - where there's possibilities, but it is entirely uncertain?
A. I agree with that, your Honour.

CALLAN

Q. Given that we are in that terrain, do you recall in the report furnished by Professor Watkins that he suggests the task that is being undertaken by himself, Professor Schwartz, Professor Wilde, Professor Abrams, to name a few, involves matters of judgment rather than interpretation?
A. Yes.

Q. He says, "there is not enough data to confirm the variant is pathogenic"; do you agree with that?
A. Yes.

Q. His view is "it is plausible but not provable that the variant was responsible for the sudden deaths of Laura and Sarah Folbigg"; do you agree with that?
A. Yes, but he also adds "in a routine clinical setting, I would absolutely conclude that a variant in this gene with these characteristics was the likely

explanation following a young sudden death with a negative autopsy".

Q. Yes, we have that report.
A. (No verbal reply).

Q. Yesterday, I asked you a series of questions as to the basis for your description in a number of reports that Ms Folbigg had fainted whilst swimming which necessitated being dragged from the pool. You have referred to the honest mistake you made in recalling your conversation with Ms Folbigg in that telephone call in January of 2019. Within that evidence, you also refer to Professor Raju's description in his report as to what Ms Folbigg told him, and I think the words used were that his impression was that she had been "helped out of the pool". Do you recall that part of his report and that part of the evidence?
A. Yes.

Q. For the record, this is at transcript 285, you say, "in the Brohus article, Dr Raju read and edited the part of Ms Folbigg's cardiac history", and I ask, "are you saying you relied solely on Dr Raju for that description of being dragged out of the pool?", and your answer was "he edited the section of the cardiac history of Ms Folbigg". I just want to be clear that we're not at cross-purposes; I can't identify any statement in the Brohus article that describes Ms Folbigg as having been dragged out of the pool. So when you were talking about him editing the section of the cardiac history--
A. It's in the supplementary data.

Q. Okay, we'll look there, thank you. You were asked some questions yesterday by Mr Bathurst about whether you participated in the preparation of material which led to the petition going to the Attorney General, which formed the base for this Inquiry and your answer was, you didn't prepare that material. I asked if you participated in any way in the preparation of the material and you referred to providing the Brohus article. You signed the petition, didn't you, Professor Vinuesa?
A. Yes.

Q. You urged others to sign it?
A. I didn't urge others to sign it, I probably mentioned it or asked the opinions of a couple of the other people, yes.

Q. What do you mean you asked the opinions?
A. Well, I approached a few people and asked them if they thought this was a reasonable article and if they thought this was a reasonable proposition.

Q. Did you make any public statements urging people to sign the petition?
A. No.

Q. Aside from signing the petition, have you made any public statements or other communications urging the Attorney General to bring about the pardon of Ms Folbigg?
A. I have spoken to media about my opinion and I'm not sure I would

remember exactly the wording, but because I signed the petition I would have somehow or other implied that I was expecting a pardon.

Q. So only by implication, not in square terms that you were seeking a pardon--
A. I did--

Q. --or you were urging a pardon?
A. I did seek a pardon, I can't tell you the wording or how, but I did seek a pardon.

Q. I asked you yesterday about articles and speaking to the media and whether you'd expressed your personal view about Ms Folbigg's innocence and you said, I've expressed a view that was an extension of my professional work?
A. Yes.

Q. I asked whether you'd then done so as a form of advocacy for Ms Folbigg and you said, as advocacy for the science?
A. Yes.

Q. Do you deny that you've spoken out publicly as an advocate for Ms Folbigg's course?
A. I have. I think I am entitled to have my opinion, my opinion is an extension of my science, and I think if asked by the media about my opinion I am free to give my opinion, but it's predominantly because I believe in our science.

Q. You've in public statement expressed affinity for the view that Kathleen Folbigg did not kill her children?
A. Yes. I think our conclusions, if we are concluding in the Brohus article that we think this is a reasonable explanation for their deaths--

Q. Of two children?
A. --that would be an extension.

Q. I see. Professor Vinuesa, can I show you an extracted series of tweets which I understand are under your hand that span a period from August 2021 to September 2022?
A. Yes.

Q. Do you see they're paginated in the bottom right-hand corner, there's 36 pages?
A. Yes.

MFI #7 TWEETS BY PROFESSOR VINUESA DATED AUGUST 2021 TO SEPTEMBER 2022

WOODS: We would appreciate having a copy of that.

CALLAN: Of course.

JUDICIAL OFFICER: I think you now have it, Dr Woods.

CALLAN: Yes.

Q. On page number 1 is a tweet under your handle dated 29 August 2021?
A. Yes.

Q. Commences, "Can you please sign and share our petition for Kathleen Folbigg"?
A. Yes, I had--

Q. Did you post that tweet?
A. Well I must have, yes, it says - I had forgotten about this but I must have, yes.

Q. Do you accept that that's an instance of urging people to sign the petition?
A. Yes.

Q. Could we go to page 3?
A. Yes.

Q. See that, two days later, 31 August 2021, it appears that you have re-tweeted?
A. Yes.

Q. A tweet by Ms Rego, who is Ms Folbigg's lawyer, in which she, that is Ms Rego, had said:

> "If you haven't already, please sign and share the petition to call upon Attorney General Mark Speakman to recommend pardoning Kathleen Folbigg. Every day that goes by she remains in prison is a day of shame for this country."

What was your purpose in re-tweeting that tweet?
A. Well I imagine that I shared the view that the petition was important and I was re-tweeting signing the petition, yeah.

Q. Do you accept that was an instance of urging, a public expression urging people to sign the petition?
A. You could say that, yes.

Q. I'll take you to page 9, one tweet of 1 September 2021.
A. Yes.

Q. Your tweet reads, "Sign the petition to have science listened to by our legal system and a terrible miscarriage of justice corrected"?
A. Yes.

Q. Do you accept that was an instance of you urging others to sign the petition?

A. Yes.

Q. You're expressing a view as to a miscarriage of justice?
A. Yes.

Q. What is that miscarriage of justice that you were asserting?
A. Yes.

Q. What is it that you are suggesting is a miscarriage of justice?
A. Well, we were asking for a petition for a pardon because we - as an extension of our scientific findings we thought there were natural causes of death for the children.

Q. When you say we, who do you mean?
A. Well, the petition signatories.

Q. You've in your professional capacity arrived at a position as to a reasonable natural cause for the death of the two girls?
A. Yes.

Q. And you say you also formed a view as to a natural cause of death of the two boys?
A. Well I had read numerous reports from the forensic pathologists.

Q. This is not in your professional capacity, you've - it's you're informed by the experts of others?
A. Yes.

Q. Can you turn over the page, page 10? This is a tweet posted at 8.25pm on 24 December 2021?
A. Yes.

Q. Expressing, "It's very sad that Kathleen will spend another Christmas in prison despite", you say, "the overwhelming evidence that all her children died of natural causes"?
A. Yes.

Q. Do you see that there's handles above that of Ms Rego and also the Attorney General of New South Wales, Mark Speakman?
A. Yes.

Q. Was that an instance of you seeking to communicate to Mark Speakman, the Attorney General, what he should do in relation to Ms Folbigg's case?
A. Probably, yes.

Q. Urging that she be pardoned?
A. Yes.

Q. Over the page, page 11, 5 March 2022, refers to Ms Folbigg languishing in jail, do you see that there?

A. Yes.

Q. That reflects your personal view that she is innocent of murder and manslaughter?
A. My personal view?

Q. Yes?
A. Yes.

Q. Could you turn to page 29? This is a tweet from 7 News Australia that you have re-tweeted, so the 7 News tweet refers to you, Professor Vinuesa, and refers to you having described Ms Folbigg's imprisonment as heartbreaking and cruel. That's your view?
A. Yes.

Q. Why have you re-tweeted this tweet?
A. Well, I suppose because that's my view.

Q. And you wanted to share that view with anyone following you on Twitter?
A. Yes.

Q. Could I ask you finally to turn to page 33? You're on Twitter communicating with another individual and you're--

JUDICIAL OFFICER: I think Ms Rodriguez is a person who interviewed Professor Vinuesa.

CALLAN

Q. This is the person who interviewed you?
A. An interview? No, I think it was a communication from Patricia.

JUDICIAL OFFICER

Q. If you go back to page 32, that's why I thought it might be an interview.
A. Yeah, it must have been, it must have been an interview, yes.

CALLAN: Yes.

Q. So it was an interview that you'd undertaken with the media?
A. Yes.

Q. And which the journalist Patricia, her tweet reads, "It was a pleasure talking to @carovinuesa", that's your Twitter handle, "about her genetic findings", and then you respond to that in a tweet which amongst other things says, "it is important that articles like yours change the public perception of Kathleen so that she gets out of jail with dignity". Professor Vinuesa, why are you interested in changing or improving the public perception of Kathleen Folbigg?
A. Look, I am allowed to feel empathy. If I am convinced of my science, then the logical thinking about this is that she shouldn't be in prison, that's - what

can I say, I have to be honest, this is the conclusions that we have reached. When you appointed me to this Inquiry you were aware of me having expressed these views.

JUDICIAL OFFICER

Q. Let me just ask you this, those tweets, I would suggest to you show that you have a fairly strong view that the work that you and your colleagues have done demonstrates that Ms Folbigg may well have been innocent of these crimes. Would you agree with that?
A. I would agree with that, yes, your Honour.

Q. And, in those circumstances, you feel some degree of sympathy or considerable sympathy for Ms Folbigg in the position she finds herself?
A. I do, yes.

Q. Now, is it possible that that sympathy and your conviction has, not necessarily consciously, but unconsciously influenced you in dealing with those experts, to use the general term, who have come to either a contrary or a more nuanced view than you have come to?
A. All I have contributed to this Inquiry is an initial finding of the calmodulin mutation and the negative finding that she is a mosaic. Everything else comes from the expertise of people in their fields. The evidence that I have provided cannot be manipulated. You can test it; you can find this mutation.

Q. When I come to consider your evidence in the context of the Inquiry, I should limit it to those two matters you just referred to?
A. You can indeed.

<EXAMINATION BY DR WOODS

Q. On that last point, in response to his Honour's question, it's been suggested to you that you may have perhaps an unconscious sympathy which has influenced you in dealing with the experts. Now, when you responded to that, you said firstly that the evidence can't be manipulated. Do you mean by that that much of the material that's been presented is objective material?
A. Yes, the genetic testing is there. It can be sequenced, and re-sequenced and the experts that we reached out were the experts in calmodulin and I have not done anything to influence - in fact, you know, every time I might have raised the syncopes, most times, Peter Schwartz himself said, "I don't care about the syncopes. I don't care if she's healthy or unhealthy". So in a way, there is nothing I can do to influence. Our evidence is objective. I think the mosaicism could be re-tested, I don't think we have finished what we have finished. It's all a little bit - a bit inconclusive, but there's nothing that we've provided in terms of the science that cannot be tested.

Q. You presented a number of reports; do you wish all of those reports to be considered by his Honour?
A. I do but I don't think we say anything that is terribly new with respect to our original findings, which is the fundamental finding that there is this particular

variant and that the mother is perhaps unlikely to be a mosaic. We have been asked many questions and we've provided answers as best as we could, but in the end, I think your Honour can consider any evidence, but of all the evidence, ours--

Q. What I'm asking is you're not limiting the material that you provided so that only a small part of it will be considered by his Honour, are you?
A. I'm not, no.

Q. The first of the tweets that you were taken to a moment ago occurred after the termination of the previous Inquiry.
A. Yes.

Q. At that stage you were living in Australia, were you?
A. I was still living in Australia, yes. In 2020 - I moved in August 2021. I can't remember the date - actually, this was when I was already in the UK, 29 August 2021.

Q. You were taken to your involvement or the suggested involvement with a petition which you signed as somehow possibly casting some doubt on your independence. Do you understand that that was the suggestion?
A. Yes.

Q. Were you aware at the time that you were involved with the petition and signed it that the right to petition the King about a perceived injustice is one of the foundational rights that Australian people have?
A. I'm very glad you tell me. I understood from the lawyers it was a right, and I think, as a scientist, I have to make sure that the science is heard. I was not involved in any Inquiry when I was expressing these opinions, and I think I am entitled to express my opinion.

Q. The move to the UK came about because you'd been offered a position in England at the Francis Crick Institute; is that right?
A. Well, I was seeking an opportunity to move to Europe, and I looked at a few different options. I'm European and I had decided that it was the right time to come back to Europe, so it wasn't a position that took me to Europe; I actually actively moved for positions to look to Europe, to move to Europe. I interviewed at a few places; got a few different offers.

Q. Was that before or after you were appointed as a Fellow of the Royal Society?
A. That was before I was appointed as a Fellow of the Royal Society.

Q. Indeed, you were elected as a Fellow of the Royal Society?
A. I was, yes.

Q. You are thereby entitled to put after the initials after your name, the famous initials, "FRS"?
A. Yes.

Q. Thereby joining Charles Darwin, Einstein and Francis Crick himself as members of that--

JUDICIAL OFFICER: And quite a number of other people, Dr Woods. I don't really quite see the relevance of this.

WOODS: Your Honour, it's this:

Q. You have become the group leader of a laboratory in the Francis Crick Institute?
A. Yes.

Q. Under you, you have how many scientists working?
A. Well, my group is starting but I have about ten at the moment working with me there.

Q. In the course of that work, do you insist on standards of scientific propriety?
A. Yes.

Q. Does that include matters such as insisting on accurate measurement, truthfulness?
A. Yes.

Q. Repetition of experiments?
A. Yes.

Q. Consultation with colleagues?
A. Yes.

Q. In relation to the reports which you presented to this Inquiry, do you say that you have been independent and objective in preparing those reports?
A. Yes.

Q. Did the fact that you were a mother and Kathleen Folbigg was a mother cause you to abandon your scientific objectivity in considering her case?
A. No.

Q. Did you exaggerate an account by Kathleen Folbigg about an incident at a swimming pool when she was about 12?
A. No, not consciously.

Q. Did you distort any report or any other aspect of the case?
A. No.

LUNCHEON ADJOURNMENT

CALLAN: Your Honour, just one matter for everyone's understanding in terms of the schedule for the afternoon. As your Honour is aware, Professor Schwartz is to give his evidence. It's proposed he commence giving evidence at 5pm, which is outside ordinary sitting hours, to accommodate his location in

South Africa and the time difference. Per the witness schedule, it's anticipated that we would spend two hours in relation to his evidence, finishing at 7pm. If at 7pm we have not finished with Professor Schwartz's evidence, in my submission, we should nevertheless adjourn and we can identify a suitable additional window for him to resume if that be necessary.

JUDICIAL OFFICER: Does anyone want to say anything in opposition to that? Very well. I do hope we can finish Professor Schwartz, but let's see how we go.

WOODS

Q. Professor, can I just clarify something which you said earlier. I can't quite be certain I got the gist of it, but you were being asked about the ACMG criteria and you said something like, if I heard you correctly, "I'm sure all cardiologists would agree that it was a VUS", or did I mishear that?
A. VUS in which variant are we talking about?

Q. G114R.

JUDICIAL OFFICER: I don't think anyone said--

WOODS: That wasn't the context?

WITNESS: No.

JUDICIAL OFFICER: That was a variant of uncertain significance.

WOODS: I thought I must have made a mistake and I apparently have.

WITNESS: No.

WOODS

Q. I'll withdraw that. You were taken by my learned friend to a short summary of something that was concluded by Professors Abrams and Wilde as to what they both regard as a mismatch between the phenotypes and the--

JUDICIAL OFFICER: Can I just interrupt you, Dr Woods. I'm not going to stop you answering the question, but as I understood at the conclusion of Counsel's Assisting evidence, Professor Vinuesa suggested that my consideration of her evidence should be limited to the question of the variant and whether there was any mosaicism. If that's right, this really goes outside the area which she wants me to have regard to her--

WOODS: The variant and the what, your Honour? Mosaicism. I--

JUDICIAL OFFICER: I don't know if you've got the last part of that transcript.

CALLAN: Yes, your Honour. I'm instructed from the transcript at the end of

my examination, Professor Vinuesa stated, "All I have contributed to this Inquiry is the initial finding of the calmodulin mutation and the negative finding that she is a mosaic. Everything else comes from the expertise of people in their fields". Your Honour said, "When I come to consider your evidence in the context of the Inquiry, I should limit it to those two matters that you just referred to". And Professor Vinuesa says, "You can indeed."

WITNESS: If I may clarify. That's in terms of the results of our investigation, but our reports encompass also our expertise in the analysis of the variants and in the interpretation of the variants.

WOODS: Yes, I thought that was what you intended. Your Honour, we would, in due course, press that that more extended version of it be taken into account.

JUDICIAL OFFICER: You ask the question.

WOODS

Q. You mentioned in response to one of the questions that you're on a ClinGen panel in relation to Lupus; is that correct?
A. Yes.

Q. Is that because of your special expertise in relation to that disease?
A. Yes.

Q. Are there similar panels in relation to a number of diseases for ClinGen?
A. Yes. There is a panel for most diseases that are sufficiently frequent in the population. In the case of diseases that are extremely rare, sometimes they are lumped together in panels with a broader remit.

Q. How does the work of those panels relate to clinical medicine?
A. Well, in order for pathologists in laboratories to be able to interpret variants, there needs to be a panel that curates the genes that are relevant for that particular disease, and another panel that curates the individual variants for each gene. So, when a new gene is discovered, for example, that could be a cause of disease, then a ClinGen panel gets together and discusses whether that gene should or should not be considered as disease causing.

So, in the panel, they normally are the biocurators who use some criteria to be able to classify, and then the experts, and the experts are both clinicians and scientists that, by definition, have spent many years in the focus disease or area.

Q. You were taken, shortly before lunch, to a series of tweets which you had either written yourself or sent onwards. I think re-tweeted is the technical term. You were taken to some of those in what is MFI 7, I understand, your Honour. It is correct, is it not, that none of those tweets were from the period of the earlier Inquiry, but they commenced after that.
A. Correct.

Q. Was it after the first Inquiry that you formed a view that an unfairness in relation to the presentation of the science had occurred?
A. Yes.

Q. Similarly, that you formed a view that unfairness in relation to Kathleen Folbigg had occurred.
A. Yes.

Q. Page 2 of that MFI 7 is dated 30 August 2021. Do you have that?
A. Yes.

Q. Is that something which you re-tweeted?
A. Yes.

Q. Does that show you outside the Australian Academy of Science building in Canberra?
A. Yes.

Q. Quoting Nobel Laureate Professor Elizabeth Blackburn.
A. Yes.

Q. Turning to page 5 of the document, MFI 7.
A. Yes.

Q. That's a tweet re-tweeted by you, is it not?
A. Yes.

Q. Was that written by you, or were you just--
A. No, Cosmos Magazine tweeted that, and I re-tweeted it.

Q. Did this take place at a point in time when the first Inquiry had been completed, and a number of people, including yourself, were making efforts to have a further Inquiry conducted?
A. When we were making efforts to have the science evaluated rigorously.

Q. You say in that tweet that the Cosmos Magazine says, which you re-tweeted, "Nearly six months after petitioning the New South Wales Governor for a pardon based on scientific evidence, Kathleen Folbigg remains in prison"; correct?
A. Yes.

Q. If you turn to page 11. Before I deal with page 11, is it to your knowledge that the Academy offered a meeting to the learned Attorney General?
A. Yes.

Q. In due course, there was, indeed, this second Inquiry.
A. Yes.

JUDICIAL OFFICER: I'm not quite sure of the relevance of this, Dr Woods.

WOODS: Yes, your Honour.

JUDICIAL OFFICER: Do you mind explaining the relevance of it to me?

WOODS: Of 11?

JUDICIAL OFFICER: Of this line of questioning.

WOODS: Your Honour, she's been cross-examined to suggest that there's some adverse effect to her credit on issues in this Inquiry, mainly because she'd express certain views in the tweets.

JUDICIAL OFFICER: I don't know what submission is going to be made. The proposition which I put, I put it fairly carefully, was that because of what appears to be her self-evident support of Ms Folbigg, she may have been unconsciously biased against those who had a different or more nuanced report. That's my recollection of it. The response led to what she said to me at the end of the examination, namely that the areas I should consider are her conclusions as to the genetic variant and as to whether or not Ms Folbigg was in that mosaic. Now, you have, I think, asked her to expand or widen the scope of which I should consider, that's fine, but - let me put it to you this way. I'm not saying there is anything wrong with Professor Vinuesa supporting Ms Folbigg or expressing her views publicly. All I asked her was whether the firm view she held may have some influence - may be some influence on her approach to people that are of a contrary view. Nothing particularly controversial about it.

WOODS: Very well, your Honour, I won't take--

JUDICIAL OFFICER: You take your own course but all you seem to be doing is reinforcing the fact that she was expressing these views publicly.

WOODS: Yes, she certainly has, yes. I understand, your Honour.

Q. Finally, Professor, do you stand by the integrity of all the reports and evidence that you have provided?
A. Absolutely, and as I said yesterday, when I work and I do science, I separate my personal opinions from my scientific work.

<EXAMINATION BY MR JORDAN

Q. Professor Vinuesa, have you read any of Ms Folbigg's diaries?
A. Some brief excerpts, not in - I haven't read them in full, no.

Q. When did you do that?
A. Well, they've been - there's been a few things on and off been mentioned. In the first Inquiry we were offered a full or a transcript that wasn't in its entirety the diaries, but we read quite a few pages that were given to us. So, probably I would have read most of what I've read during that first Inquiry.

Q. Right, and I'm really just seeking to understand, so when you say we read, who are you referring to?
A. I read, sorry. I read what we were given and I'm not sure in full because part of the writing I couldn't understand very well, and I'm not an expert in diaries, but I did read fragments of - or sections of what I was given during the first Inquiry.

Q. Who gave you those fragments of the diaries?
A. The legal team, the Crown gave us a folder including an exhibit that contained diary entries.

Q. I think I know what happened, let me put something to you and ask you if this is a fair summary as to how this occurred. You were already there as a witness in the 2019 Inquiry for scientific purposes?
A. Yes.

Q. Correct, and in the course of that participation the people assisting the Inquiry made available to you other evidence in the Inquiry which included the diaries?
A. Yes.

Q. And is it your evidence that it was in that context that you read some fragments of the diaries?
A. Look, it would have been in that context, some probably in other contexts too, because the diaries have been referred to on multiple occasions, so that probably was my first encounter with the diaries. I've probably read excerpts at other times and I'm not sure I can remember every time.

JUDICIAL OFFICER

Q. Professor, did you read Mr Blanch's report?
A. I read - I don't think I read the full report, I think I read the sections that were probably relevant to the genetics, but I did read - I tried to read most of it.

Q. The only reason I ask that is because he'd made some quite extensive reference to the diaries?
A. To the diaries. Yes, I think I remembered some references to lies and to something like that, yeah.

JORDAN

Q. Did anybody specifically ask you to read those diary entries or is that something that you chose to do?
A. We were asked to read the information that we were given for the first Inquiry, so I read as much as I could. We were given three very large folders full of exhibits and I can't say I read them all in full because it would have been probably impossible but I read as much as I could.

Q. Is it the case that you did not read the diaries in full because those diaries really had no relevance directly to your scientific issues for consideration?

A. Yes.

Q. I'm not at all being critical by putting this to you, and it follows upon some questions from his Honour, you do feel some sense of sympathy for Ms Folbigg, correct?
A. Look, I'm human, I - I do, yes.

Q. Is it your position that there is a clear difference between your personal views and the scientific opinions that you express as a witness called to assist this Inquiry?
A. Well, there is, because I try to very consciously separate what I do in my science and I've provided evidence with some of the evidence that was not clear-cut and, as I say, as I've explained with a case of mosaicism, with a case of KCNAB2 putting forward negative data, and then I separate that from my opinion, but of course my opinion is an extension of our professional work, and it's always going to be there.

Q. But they are different, aren't they?
A. They are different.

Q. Could I just take you to one of the tweets, please.
A. Yes.

Q. In MFI 7, it's on page 10.
A. Yes.

Q. For the record, this is something that you tweeted.
A. Yes. Yes.

Q. It's not a re-tweet. On 24 December 2021, you tweeted: "It is very very sad that Kathleen will spend another Christmas in prison despite the overwhelming evidence that all her children died of natural causes"
A. Yes.

Q. Is that still how you feel today?
A. I do think it's sad, yes. That with the evidence from the genetics and the pathology that she is in prison, yes.

Q. That is your personal view, as distinct from the scientific opinion that you expressed as a witness called to assist this Inquiry?
A. Yes.

<EXAMINATION BY MS HORVATH

Q. Doctor, I appear for Dr Cala--
A. Yes.

Q. --in this Inquiry. I just have one matter I wanted to ask about, and it's to do with the Brohus article.

EXHIBIT 15-02 SHOWN TO WITNESS

Q. Could you go over to the next page, please. I wanted to ask, in the second column of that entry, towards the bottom of the first paragraph, there is reference to child four, and it says, "child four died at 18-months old; two days after being treated with paracetamol and pseudoephedrine for a respiratory infection." I'm not going to ask you about that bit. I'm just trying to make sure you are in the right spot.

JUDICIAL OFFICER: Which page is this, Ms Horvath, I'm sorry?

HORVATH: I'm sorry, your Honour?

JUDICIAL OFFICER: Which page?

HORVATH: I'm sorry, the second page. On p 12--

JUDICIAL OFFICER: Yeah.

HORVATH: --so, the part of the screen that's open now, the second column--

JUDICIAL OFFICER: I have it, sorry, yeah.

HORVATH: --towards the bottom of the first paragraph.

JUDICIAL OFFICER: Yep.

HORVATH

Q. There's then a reference, the next sentence: "At autopsy, she was found to have florid myocarditis." Do you see that?
A. Yes.

Q. This part of the journal article and the reference to the fact that she had florid myocarditis at autopsy, was this part of the article that you were involved in or somebody else?
A. Professor Cordner provided the photomicrographs and described the pathology, and then he reviewed the article because we are not expert forensic pathologists. So, this was the opinion of Professor Stephen Cordner. We acknowledged him for this, and as I say, he critically reviewed this section.

Q. But you acknowledged him for the provision of the micrographs, yes?
A. Yes.

Q. And it was his opinion, was it, that it was florid myocarditis?
A. Yes.

Q. Did anyone check the autopsy report?
A. We checked that there were profusely emphysitic infiltrates in sections of the--

Q. Could you answer my question--
A. Yes.

Q. --which was did anyone check the autopsy reports?
A. Yes.

Q. And so, the statement that "at autopsy", florid myocarditis was found is wrong, isn't it?
A. No. If you have profusely emphysitic infiltrates in different sections of the heart, that can be described as "florid", and if the pathologist that has reviewed the article and is an expert in that describes it as that, he would know much better than us.

Q. So, it's not something that you can comment on, I take it?
A. I will take the opinion of Professor Cordner on this.

NO EXAMINATION BY MS LOVE, MR HASTINGS AND DR WATERHOUSE

<EXAMINATION BY MS CALLAN

Q. I read out a few minutes ago the exchange between yourself and Mr Bathurst at the end of your evidence-in-chief in response to the question he asked of you about whether you considered - I'll put it this way, the considerable sympathy you feel for Ms Folbigg has interfered with your ability to objectively consider the evidence of other experts who've expressed a different or more nuanced view to you. In answer to his question at that stage, you made your statement as to the fact that you - so, you said all you contributed to this Inquiry is the initial finding of the mutation and the negative finding that she's mosaic.
A. In terms of scientific results.

Q. Yes.
A. But there is - we have contributed to the interpretation, to the analysis and to the other areas of understanding that we are qualified to comment on, and I've said many times that I separate my personal opinion from what we put in writing. And we've been extremely careful to write things that are accurate, that are backed up by the scientific literature, that are referenced and that are shared by my co-authors in what we've written.

Q. Does the effect of that position, that you do not consider your considerable sympathy for Ms Folbigg, has in any way interfered with your ability to objectively consider the views that other experts have expressed which might be different to yours?
A. I do not, and as you realise, there is quite a lot of other experts, and at least five other cardiologies that I've mentioned that also have different views.

Q. The circumstance in which you came to read Ms Folbigg's diaries, I just want to make sure I understand. Could the witness be shown the Exhibit 2-AF which was the original report you furnished to the 2019 Inquiry on 29 March 2019? It may be the hardcopy report.

EXHIBIT 2-AF SHOWN TO WITNESS

A. Thank you.

Q. Professor, you see this is a copy of the report that you furnished?
A. Yes.

Q. If you turn, using the red pagination, to page 5629.
A. Yes.

Q. Do you see that's a letter of instruction that was sent to Professor Cook by the Inquiry, by way of a letter of engagement?
A. Yes.

Q. If you turn back a few pages, do you see at 5623--
A. Yes.

Q. --there's a letter from those assisting the Inquiry to you noting you'd been instructed by the solicitor for Ms Folbigg to prepare a report?
A. Yes.

Q. Then there it goes on to say, in order “to ensure consistency in the form of reports prepared", and there's a request that you comply with certain matters?
A. Yes.

Q. That's been included at the end of your report, if you keep going a few pages, do you see page 5632?
A. Yes.

Q. That's described as an index to briefing material?
A. Yes.

Q. That's briefing material which accompanied the brief to or engagement of Professor Cook?
A. Okay.

Q. Did you have access to that briefing material when you prepared your report jointly with him?
A. Look, I can't go through all of this in detail. We were - we received three folders like this one full of briefing material in print.

Q. That was before you prepared your report?
A. I would imagine so, yes.

Q. The list here of this annexure index of briefing material, just work your way through it--
A. Yes.

Q. --did not include copies of Ms Folbigg's diaries?
A. I don't know, but I definitely received copies in one of these three big

folders.

Q. You say you received that before you prepared your report?
A. Yes. I don't think I would have received anything after the report, and it was sent to me by the Crown, the three folders.

Q. In hard copy?
A. In hard copy, yes. Three white folders exactly like this. I didn't have to print out anything.

Q. Did you receive any documents from Ms Folbigg's solicitor?
A. No.

Q. The only material you received was from the Inquiry?
A. Yes.

Q. You say before you prepared your report, amongst the documents supplied to you was a copy of Ms Folbigg's diaries?
A. There were a few pages, yes.

Q. I think I understand the effect of your evidence is you regarded those diaries had no relevance to your work in terms of the whole genome sequence analysis?
A. Yes.

Q. You've read more than what you saw in that original briefing material by way of her diaries, have you?
A. I don't think so. It's just I'm unsure to say whether I might have encountered them. You might just show me something now saying that I've seen them somewhere else, but my recollection is that most of what I've seen, if not all, was at least in that initial bundle that we received with photocopies of Ms Folbigg's diaries.

Q. In MFI6, which is the article by Mr Schwartz, the journalist, of 9 December 2021 published in WIRED, indicates at page 22 of that printout:

> "When she read Folbigg's diaries, she didn't see ciphers of a criminal mind. She saw another woman grappling with occasional despair of motherhood. This, she knew on some level, was why for the past year she had spent almost all her free time thinking about Folbigg."

Did you tell the journalist, Mr Schwartz, anything about reading Ms Folbigg's diaries?
A. Yes, and if - I'm starting to remember, as well. I did listen to the 2021 appeal, which was in February 2021, and I listened only through probably the first day and half of the second day, and a long time of that appeal was spent going through sentences of Ms Folbigg's diaries, and through that, I think, I learned quite a lot more about that information.

Q. You remember speaking to the journalist, Mr Schwartz, about having read Ms Folbigg's diaries?
A. I would never have said in their entirety. I had read extracts.

Q. What you have read--
A. Or I would have--

Q. --from what--
A. --listened to extracts.

Q. From what you have read or listened to, your personal view is that you didn't see ciphers of a criminal mind?
A. I'm not an expert in that. I just thought that I could have said some of those things in those diaries during motherhood.

Q. Did you reading those diaries affect the approach you've taken to your work to this Inquiry?
A. No.

<THE WITNESS WITHDREW

<MATTHEW CAVANAUGH COOK, AFFIRMED(2.36PM)

<EXAMINATION BY MS CALLAN

Q. Sir, could you tell the Inquiry your full name?
A. Matthew Cavanaugh Cook.

Q. The Inquiry has received several reports of which you're a co-author, including a report of 25 October 2022, which includes a copy of your curriculum vitae. I take you to that document. It's Exhibit 5, tab 06, report of 25 October 2022. If you use the red pagination, Professor, at page 164.
A. Yes.

JUDICIAL OFFICER: Can that be made available to Professor Cook, please.

CALLAN

Q. That records your qualifications, current and previous appointments and positions?
A. Yes.

Q. And other items that we generally expect to find on a curriculum vitae. Is there anything that you wish to add to your curriculum vitae, for instance, that's occurred since October 2022?
A. No.

Q. Can I ask you, to assist the Inquiry, in terms of the areas of expertise or specialisation that you've drawn upon--
A. Yes.

Q. --in expressing the views that you have in the reports that this Inquiry's received?
A. Certainly. So I'm a Physician Scientist. I'm professionally qualified as a Physician Specialist in Clinical Immunology and also a Specialist in Pathology. I have a PhD in immunogenetics, and during the course of my career, in addition to my clinical practice my research activities have been directed at understanding the genetic and cellular basis of immune diseases. Since approximately 2009, those activities have been concentrated on the analysis of human genome sequences and variants detected through human genome sequencing that have enabled us to formulate and explore hypotheses for mechanisms of immune-mediated disease, and during the course of those investigations, we've performed many functional studies and, as a result, have described new syndromes, for example, based on the identification and characterisation of new genetic variants. Also on the strength of that activity and because of the nature of the referrals that we were receiving, we proposed and were funded to implement a diagnostic sequencing service, which became known as Canberra Clinical Genomics. I was the inaugural Director of that service and remained the Director until my relatively recent move to the University of Cambridge. So that was a diagnostic service publicly funded. We provided and, in fact, Canberra Clinical

Genomics, or CCG, continues to be the primary provider of diagnostic whole exome sequencing for patients in the ACT and surrounding regions.

Q. Across those years working in this field in relation to genetics, have you undertaken research or other work in the field of calmodulin or calmodulinopathies?
A. No.

Q. Can I broaden things a bit more widely, in terms of the field of cardiac genetics?
A. My research has not directly involved cardiac genetics.

Q. Having regard to your qualifications and experience, would you regard yourself as being in a position to express views in the field of electrophysiology?
A. No.

Q. As I understand, you may have been in Court yesterday and today? Is that the case?
A. Yes.

Q. I've asked both Professor Arsov and Professor Vinuesa about their position having regard to the collection of, if I can describe them, experts in calmodulin and cardiogenetics?
A. Yes.

Q. That have furnished reports to the Inquiry being Professor Schwartz, Toft Overgaard, Nyegaard, Guicheney, Wilde, Abrams, MacRae and Watkins?
A. Yes.

Q. On matters specific to calmodulin or calmodulinopathy, do you defer to the more specialised expertise that exists within that group of experts?
A. I do, but if I may I'd like to--

Q. Yes?
A. --clarify the nature of that deferral. I think that it's useful when considering that sort of expertise to think about three layers of expertise. First layer is cardiology, any qualified cardiologist has specialised area of knowledge of course in the diagnosis and treatment of diseases of the heart and vascular system. The second layer concerns specific diseases that may be relevant to the cardiac system and increasingly specific diseases can be defined according to the underlying genes, so in this case we might consider calmodulinopathies as a specific example. The reason for this distinction is that when questions arise for clinicians such as myself who are not in that area, then the expertise that we're seeking is that which only comes from knowledge of the aggregated experience of all cases, all known cases of that rare disease. Because, as we've heard, that expertise goes to understanding unusual presentations, possible phenotypic extensions, and that really only comes from having access to the largest possible cohorts of that specific disorder.

Q. Does Professor Schwartz fall in that category?
A. Yes.

Q. Where do you put Professors Toft Overgaard and Nyegaard?
A. Well that brings me to my third layer, and that is when we get down to not just the specific disorder but a specific allele, and I think that they're in that category, but to draw this out, sometimes I am in that category for specific alleles of immune mediated disease. There may be a condition which my group has been involved in describing and a colleague from elsewhere might approach us to say that they've recently identified a patient with a novel allele of that particular gene, what do we think about that, is it likely to be pathogenic. Now, under those circumstances, even though we have described the condition, if the allele is novel, the reason that they approach us is not because we can necessarily provide any additional insight to those that, you know, the referring doctor can gather from the available evidence from existing databases. What they're seeking is our technical expertise and the possibility that we might be able to perform functional analysis, and because we have described the condition, it's likely that we will be able to apply those functional analyses to the next novel allele that comes along. Of course Professors Toft Overgaard and Nyegaard fall into that category when we come back to the field of calmodulinopathies.

Q. The position in relation to Professor Guicheney, do you regard anything about her qualifications or experience that distinguishes her from what you can say, for instance on the topic of cardiogenetics?
A. Well I think she has knowledge of and has contributed to the understanding and description of the spectrum of calmodulin-related disorders.

Q. What about Professor Wilde?
A. The same applies.

Q. Professor Abrams?
A. I think Professor Abrams has understanding of channelopathies, has published experience of channelopathies and perhaps would be more in my first category than in the second category of expertise.

Q. In terms of cardiology?
A. Yes.

Q. From your perspective, does the same go for Professors MacRae and Watkins?
A. Yes.

Q. Insofar as what they bring to bear draws on the aggregated experience they have as cardiologists?
A. Yes.

Q. Not in cardiac genetics?
A. Cardiac genetics, they have expertise in. My distinction was between that general expertise and the specific expertise that comes from understanding

the current phenotypic spectrum of calmodulinopathies which only comes from a detailed knowledge of the largest possible cohort of those disorders.

Q. I understand your position on that. As to the circumstance that you have not undertaken research or aggregated specialised experience in the field of cardiac genetics, does it follow that where views have been expressed that draw on such aggregated experience you would defer to the views, for instance, of Professors Abrams, MacRae and Watkins?
A. Yes, certainly, within the constraints that I have explained.

Q. Yes, thank you. You first became involved in relation to, if I can put it, this case, when you were briefed or engaged by the 2019 Inquiry--
A. Yes.

Q. --and you recall producing a report - you might not recall the precise date but 29 March 2019, it's marked Exhibit 2-AF in this Inquiry. Have you ever spoken directly with Ms Folbigg?
A. No.

Q. You did not give oral evidence in the 2019 Inquiry?
A. I did not.

Q. You are a co-author of the Brohus article?
A. That's true.

Q. What was your contribution to that article?
A. Well, I contributed to the genetic findings and I contributed to discussions about the significance of those findings and the overall direction of the article and I reviewed the final manuscript.

Q. Insofar as that article arrived at some particular conclusions referable to the functional assays in terms of impairing calmodulin's ability to bind calcium and regulate those two calcium channels, you'd had your own, you've described, professional aspect of your work has included undertaking such functional studies?
A. Yes.

Q. Is this the case, drawing inferences and arriving at conclusions about the implication for such functional studies for a variant that's under consideration?
A. Yes.

Q. The article - the passage predicts that "the variant is pathogenic and carriers were prone to cardiac arrhythmias of IVF for CPVT-like phenotypes with a potential component of mild long QT syndrome". Do you recall that prediction in the article?
A. Yes.

Q. As an author of that article you considered that that was a prediction that was available having regard to the results of the functional assays?
A. Yes.

Q. The particular reference to IVF, CPVT-like phenotypes and a potential component of mild Long QT Syndrome, the way that the position as to those calmodulinopathies was directly informed by the results of the functional assays?
A. That's my understanding.

Q. You're aware, as I understand it, but please correct me if I'm wrong, from reports which had been furnished to this Inquiry by Professor Wilde and Professor Abrams, for instance that that prediction does not accord with, there's a mismatch between that, so they say, and the phenotype when it comes to the death of Sarah and Laura Folbigg, and that is, as I and you might address it, but as I read their criticism it's by reference to the fact that the age of the two girls and the fact that they were asleep and known presentations of CPVT not having been observed in children so young or asleep. What is your - do you regard that as a valid criticism?
A. Well, I think it follows from my description of my particular expertise that, you know, it's difficult for me to say with any authority whether that view is valid or not, but it also follows that I would also take careful regard of the opinion of Professor Schwartz based on the importance of considering the full extent of phenotypic possibilities of calmodulinopathies and the best evidence that we have for that at the moment is from the assembled cohort of calmodulinopathies.

Q. So we have in terms of the best evidence that's available, the results of functional testing which has occurred in relation to this variant?
A. Yes.

Q. We have the clinical information, incomplete as it is, when in terms of the phenotype of relevantly Kathleen Folbigg, Sarah Folbigg and Laura Folbigg. There are the other considerations that are brought to bear, if I can for convenience refer to them as the ACMG criteria, that being identified as relevant to the assessment of pathogenicity, and there is the assembled information in the Calmodulinopathy Register?
A. Yes.

Q. Professor Watkins, and I've raised this with some of your colleagues, I think you've been in Court for that, in his report observes that this question as to the role or potential role of the G114R variant in the death of Laura and Sarah Folbigg is one of judgment rather than interpretation. You recall he's expressed the position in that way?
A. Yes.

Q. He says he regards it as plausible, but not provable, that the variant was responsible for the sudden death of the two girls?
A. Yes.

Q. In terms of his reference to the need for judgment, rather than interpretation, that's the judgment of individuals who bring relevant aggregated experience, in terms of calmodulin and cardiac genetics. Do you agree with that?

A. I may need to get you to restate it. I'm sure - I thought you were making a distinction between judgment and interpretation, which isn't clear to me.

Q. I realised I've put a number of propositions. It's not fair to you. The report of Professor Watkins - this is at, your Honour, tab 14-10 - the top of - it's red page 322, page 2 of his report. By reference to the reports of Professor Schwartz, Professor Wilde and Professor MacRae it says:

> "What I see is that reasonable, thoughtful, authoritative experts are looking at the same data but drawing different inferences. This is because there are substantial uncertainty, and so judgment rather than interpretation of disputable fact is needed to reach a conclusion."

Do you concur with his description of the task required in terms of the question whether the variant was responsible for the sudden death of Laura and Sarah Folbigg?
A. Well, I do, because I think that this neatly summarises where we stand with genomics overall for many cases at the moment. And that's why so much effort is currently going in to try and resolve how to deal with uncertainty in this field.

Q. Where there's reference there to "judgment", you agree that - I think a term you used, the aggregated experience of people in a specialised field is essential to judgment being brought to bear?
A. Well, I think expertise is important. Yes, if that's - if I understand your question correctly. It's important that we draw on all expertise, but I refer back to my earlier answer that there are differences in the nature of that expertise and so it depends on which particular aspect of uncertainty we're attempting to resolve, where we might turn for the relevant expertise.

Q. A few minutes ago when I was asking you about the relevance of the functional data information, as reported in the Brohus article, to the question of whether the variant is - there's a reasonable possibility it caused the death of Sarah and Laura Folbigg, I drew your attention to the criticisms that Professor Wilde and Professor Abrams have made, and you urged careful regard also to the view of Professor Schwartz. I take it from that answer that you regard those experts as, and you, as it were, defer to their specialised expertise on that question?
A. I think what I was getting at is that there are aspects of speculation or, perhaps, extrapolation in some of the reports that have been provided, and then there are other aspects of the assessment of this variant where we can be - you know, where the results are much more conclusive, and it's important that we don't conflate those. So there are functional studies which have been performed, which assess the impact of this amino acid substitution on the normal function of the protein. Then there are questions about the specific presentation, age, for example, of the - as a clinical manifestation of this particular version of calmodulinopathy. So those are two separate areas of uncertainty, and I think it's important we deal with those separately.

Q. So in terms of those two separate areas of uncertainty, do you disagree with the criticisms or concerns raised by Professor Wilde and Professor Abrams?
A. I don't - disagree, but I think that because it's very difficult to disagree with the areas of speculation and areas of agreed uncertainty. I think it's more productive to concentrate on the positive evidence.

Q. Professor Schwartz has commented on, notwithstanding the utility of functional tests, the limitations which come by a physical knowledge. He says it fails to fully explain sometimes dramatic clinical consequences in a variant. Do you have a similar view as to the limitations of functional tests, when it comes to the clinical setting?
A. Yes. I mean I think it's useful again to frame the objectives of functional analyses of specific alleles. I remember in gene encodes a protein and most functional assays aim to determine whether any of the known functions of that encoded protein are perturbed by the amino acid substitution if we're dealing with a missense variant. Now, that's often a long way down stream of the cellular consequences, the consequences for the organ function and the consequences for the individual. That in no way diminishes the significance of the functional assay for that altered protein. All it says is that biology is complicated and to understand the complete pathogenesis of a disorder and by implication phenotypic variation that might arise in two individuals who carry precisely the same variant is the challenging problem. It's not just a challenging problem for calmodulinopathies, it's a challenging problem for the field.

Q. Yesterday in her evidence, Professor Vinuesa, when I asked about whether her current view was that the variant satisfies the ACMG criteria for pathogenic, said she would be flexible, she'd be happy between likely pathogenic and pathogenic, referring to there being a bit of grey area with PS3, and PS3 is in relation to functional assays?
A. Yes.

Q. Do you take the same position?
A. Well, I think there appears to be a consensus for a number of the ACMG criteria.

Q. Yes?
A. There has been some discussion about the criteria for what would be considered a well-accepted in-vitro functional assay, and I think that that's where there might be a possible downgrading depending on your interpretation of that phrase. I accept that, but at the same time I think that the arguments that have been put forward for why, you know, what is required to accept a functional assay are slightly at odds with what is normally performed in the real world and I also think that there have been, you know, we're talking about the functional assays as published in Brohus, but we now have additional functional information for variants in calmodulin which is compelling.

Q. There are some other topics which I want to address with you which I have also raised with your colleagues. So you may have had an opportunity to think

about them whilst being in Court.
A. Yeah.

Q. There's a comment made in the report of Professor Abrams about the need to, so he says, "robustly link genetic findings with concordant phenotype to infer causality". Do you agree with that statement?
A. Yes. I would like to again, if I may, just put some context to this question by just defining what my understanding of phenotype is.

Q. Yes please?
A. So phenotype are the outwards manifestations of the interactions between gene and environment. Now, some phenotypes are the outcome of the interplay of many genes, we can refer to this as the genetic footprint of the phenotype. Take for example height.

Q. Yes?
A. A very large genetic footprint. That phenotype might be refined, we might say, well, what is the genetic footprint of short stature. It might then be refined even further by considering additional features such as the proportion of the long bones and each of those phenotypic refinements leads to a refinement in the genetic footprint associated with that phenotype. In this particular case, considering the phenotype helps us understand the genetic footprint that we would consider as when we're looking for potential causal variants, remembering that a phenotype is the outcome of genetic variation interacting with environment.

Q. In this case what was your approach in terms of the phenotype of Sarah and Laura Folbigg?
A. Well, when I was initially asked to participate in this, it was effectively considering what might otherwise be called a molecular autopsy, attempting to explain the phenotype of sudden unexplained death, which is the phenomena that has a very broad genetic footprint. Not infinite though. Not - we wouldn't implicate all 20,000 human genes.

Q. Professor Abrams suggests that sudden death alone is not a phenotype in the absence of other clinical findings as it's non-specific. Do you distinguish between sudden unexplained death and what he says, as he put it, sudden death?
A. Well, I think it follows from what I've said that sudden death can be the outcome of the interplay between genetic variation and environment.

Q. You do consider sudden death alone as a phenotype?
A. Yes.

Q. Is it so non-specific as to render the task--
A. Well it's non-specific in the sense that it's one of these phenotypes that has a broad genetic footprint and that was one of the first tasks that we confronted was to define what that genetic footprint might be, and so we arrived at a list of genes by a consensus that could be considered that genetic footprint for sudden death.

Q. When you come a long way past that beginning point with the position as to phenotype with the broad footprint that you had, to use your language, in your assessment of the pathogenicity of the G114R variant, have you taken into account the fact of the two girls' deaths?
A. Yes, that was the - as my understanding the basis for initiating this investigation to determine whether there might be through whole genome or whole exome sequencing whether we might be able to identify any genetic variants that would provide a clue to the mechanism of that outcome.

Q. I may have expressed the question poorly. In the various considerations that bore upon your assessment of the pathogenicity of G114R variant, do you invoke the girls' deaths as an indicator that the G114R variant is pathogenic?
A. Sorry, I don't quite understand. I think that we were - we analysed the genetic variants that were obtained from the sequencing, according to the agreed upon gene list that we thought at the time constituted the genetic footprint of sudden death. And CALM2 was on that list.

Q. Have you considered there's a report that was prepared by Professors Kirk and Skinner, it's at Exhibit 7-03, red page 50, if I could have that on the screen. Do you see at the top of the page, just above the arrows, they write:

> "The fact of their deaths cannot be used as evidence in classifying the variant, because to do so would be to commit the illogical fallacy of circular reasoning. That is, the children died because they had the variant and therefore the variant is pathogenic, and because the variant is pathogenic, the children died because they had the variant."

Do you see how that's depicted in the report?
A. Yes.

Q. Have you used the fact of the girls' deaths as evidence in classifying the variant?
A. Well, I think that the criteria that we've relied on are the functional assay, its absence from controls, the presence of this arginine substitution in the same code on that's previously been reported to be pathogenic when a tryptophan substitution occurs, and that there is a low rate of benign missense variation, plus multiple lines of computational evidence, but that doesn't include the premature deaths of the children.

Q. Insofar as you've expressed views in your reports in relation to Kathleen Folbigg's phenotype, is the position this, that you refer to, for instance, views expressed by Professor Schwartz and Professor Wilde that she may have, for instance, CPVT?
A. Yes.

Q. In any event, Kathleen Folbigg's symptomatology has little bearing on whether the variant is pathogenic?
A. Yes, I think that this goes to the application of BS2 ACMG criterion, and before we consider whether or not Kathleen Folbigg has a phenotype that

might be compatible with calmodulinopathy, we have to consider that criterion, which demands that we're dealing with a disorder that is known to be penetrant at a young age and, I think, based on other published evidence, including Kato et al, Marsmen et al, that's not the case. So it becomes academic, or even irrelevant, to consider whether or not Ms Folbigg has a phenotype that would be compatible. The criterion is not applicable.

Q. Is it your perspective, having regard to the use of the ACMG criteria to arrive at your conclusion about pathogenicity, you say BS2, that criteria is not applicable and, from your perspective, that's the end of the exercise in terms of Ms Folbigg's phenotype?
A. Yes, I think if we're going to use the ACMG criteria, we need to look carefully at what they state and apply them accordingly.

Q. Your reports go into some detail about concepts such as variable expressivity and incomplete penetrance?
A. Yes.

Q. But as I understand your evidence, whilst that might help provide an explanation for why her symptomatology has little bearing, from your perspective, in the classification exercise, it's BS2 and its inapplicability that is as far as you need to go, in terms of her phenotype?
A. With, you know, strictly considering the ACMG criteria, yes.

Q. I can take you to the reference if you need, but in your joint report of 25 October, for the record, Exhibit 5-06, page 35, you refer to sources which demonstrate that lethal calmodulinopathy causing harm variance can be present in asymptomatic and healthy carriers?
A. Yes.

Q. As things presently stand, Ms Folbigg would potentially fall in the category? Depending on the position as to, for instance, CPVT?
A. Exactly. I think that - yes, I'm just looking at the report from Professor Wilde, for example, who looked at her exercise test and stated that the test was compatible with CPVT. So, you know, that's important, but, as we've discussed now over several questions, it's still somewhat academic, because the criterion is not applicable.

Q. Arriving at the ultimate conclusion that you've expressed, that there is a reasonable possibility the deaths of Sarah and Laura Folbigg were caused by fatal cardiac arrhythmia attributable to the G114R variant, what have you - what, if anything, causes you to come to that conclusion in circumstances where carriers of the variant can present in asymptomatic and healthy?
A. Well, the - you know, I come back to our original task, which was to examine these genomes or a variant that might account for what was otherwise sudden, unexplained death. We identified such a candidate and then, as I said, I think that the functional evidence is compelling. Now, if you like, that's where - you know, that takes me to the extent of my expertise here. If we're talking about the variation in expressivity, the nuances of the interpretation of the exercise stress test, then, you know, I'm not the person to

do that, but in terms of reaching a conclusion about the variant that was identified, then I certainly pay careful attention to the outcome of the functional assays.

Q. If I take you to the opinion expressed in your report of 25 October, Exhibit 5-06, red page 158.
A. Yes.

Q. Do you see that's headed, "Opinion of Professor Matthew Cook."
A. Yes.

Q. And you make reference to the functional evidence?
A. Yes.

Q. You just referred to that in your oral evidence. You say, "the number of cases of calmodulinopathy has increased, revealing further variation in penetrance and expressivity." So, that's by reference to the calmodulin register?
A. Yes.

Q. And you say this means the probability that calmodulinopathy was the cause of death that carried this variant has increased, and conversely, you're not aware of any new evidence that argues against that conclusion; that the variant is functional and damaging. And nor that you're aware of any new evidence for an alternate explanation of the death.
A. Yes.

Q. So, in circumstances where you're not aware of evidence for an alternate explanation for the death, and this additional information and evidence is available as to the variant being functional and damaging, is it in those circumstances that you express your view as to the possibility that the variant caused the death of the two girls?
A. Well, I guess there are two steps there. The first is two assess the evidence in support of this being a pathogenic variant, and what I've attempted to do there, I'm not sure how effectively, is to express my view that there have been a number of strands of evidence that collectively have contributed to that conclusion. And having arrived at the conclusion that this is a pathogenic variant, then it follows that it is a reasonable explanation for - for the deaths.

Q. You co-authored a report with professor Vinuesa on 1 February 2023 in relation to the possibility of a modifying variant in the Folbigg children?
A. Yes.

Q. You were here when I asked Professor Vinuesa questions about that report?
A. Yes.

Q. Did you wish to add anything to the position, that is that this raises a potential avenue for further enquiry?
A. I think that that's a - that's a good summary. It does go to this question

which is another big question for the field; why is there variation in penetrance and expressivity of - of genetic variants and interaction with other genetic variants, or indeed interaction, in some cases, interaction with different variants within the same gene is a topic that's being actively explored. The REM2 variant came to our attention because of an article that had been published which was summarising the evidence to that point for potential genetic modifiers of - of - of monogenic arrhythmic genes, and so that prompted us to go back and examine the genomes for variants of the - for the specific variants that were on that list. And having identified REM2, we felt that it was important to report that. But it remains a postulate.

CALLAN: Those are my questions, thank you.

JUDICIAL OFFICER: Yes, thank you, Ms Callan.

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

<EXAMINATION BY MR JORDAN

Q. I just didn't hear the last word, Professor Cook. The questions that you were just asked concerning your conclusion are on the last report concerning modified genes. Can you just restate your last piece of evidence because I just didn't hear it.
A. With regard to the REM2--

Q. Yes.
A. --it's a putative modifier. Well, that's it. It's a putative modifier. It would require much more experimental evidence to prove that it was so.

Q. Okay, thank you.

JUDICIAL OFFICER: Anyone else? Thank you very much, Professor.

WITNESS: Thank you, your Honour.

JUDICIAL OFFICER: It's most helpful. You get away much more quickly than your colleagues.

<THE WITNESS WITHDREW

CALLAN: Your Honour, before we adjourn until 5pm, Exhibit 2-E, tab K was a video tendered at trial of Laura Folbigg. In the 2019 Inquiry, it was missing. It's been found. Can I hand up a USB?

JUDICIAL OFFICER: Yes.

CALLAN: Which contains that video. And your Honour's already indicated receipt into evidence, but can I hand up for formality, the slides that were shown by Professor Arsov during his evidence which had been or will be

marked Exhibit 5, tab 10. And, your Honour, the slides displayed by Professor Vinuesa during her evidence this morning, to be marked Exhibit 5, tab 11.

SHORT ADJOURNMENT

AUDIO VISUAL LINK COMMENCED AT 5.05PM

JUDICIAL OFFICER: Professor Schwartz, is it? Can you see us and hear us?

CALLAN: Professor Schwartz, just confirming you can see and hear us in the Court room?

SCHWARTZ: Hello, yes. I see you, but I don't see myself anymore.

CALLAN: We can see you. Can I just confirm you see Mr Bathurst who is conducting this Inquiry?

SCHWARTZ: Pleasure to see you and meet you.

<PETER JOHN EUGENE SCHWARTZ, AFFIRMED(5.06PM)

<EXAMINATION BY MS CALLAN

Q. Professor, could you tell us your full name?
A. Sorry, one favour. I see you in a very little corner, and I see a blown-up image of myself which I don't need. So, I wonder if the technicians could help. I would like to see the Court and not my gigantic self.

JUDICIAL OFFICER: I can understand that. I always feel the same. Is there anything we can do about that?

WITNESS: Okay, now it is much better. Thank you.

CALLAN

Q. Thank you, Professor. Could you tell the Court your full name?
A. Peter John Eugene Schwartz.

Q. And in terms of your qualifications, you graduated in medicine in 1967 from the University of Milan. Is that correct?
A. Yes.

Q. You became a Specialist in Cardiology in 1973?
A. Yes.

Q. Is it the case that from 1988 to 1992, you were the chairman of a working group on arrhythmias of the European Society of Cardiology?
A. Yes.

Q. And from 1995 to 2013, you were the Professor and Chairman of Cardiology and the Director of the School of the Board in Cardiology at the Department of Molecular Medicine at the University of Pavia?
A. Correct.

Q. You're currently the director of the Centre for Cardiac Arrhythmias of Genetic Origin?
A. Yes.

Q. And of the Laboratory of Cardiovascular Genetics.
A. Yes.

Q. At an institute in Milan. Can you just assist me. I don't want to get the pronunciation wrong. What's the name of that institute.
A. Yeah, it's called "Istituto Auxologico" which has to do with the fact that institute, about 70 years ago, was primarily concerned with the development and growth. And “Auxologico” is a Greek term.

Q. Your current position as the director of that Centre for Cardiac Arrhythmias of Genetic Origin.

A. Correct, yes.

Q. Is it the case that your main areas of research in your lengthy professional career have been sudden cardiac deaths?
A. Yes.

Q. That's included pathophysiology, risk stratification, therapeutic approaches and genetic mechanisms?
A. Right.

Q. Is it the case that your two main subareas of research are automatic nervous system and the Long QT Syndrome?
A. Right.

Q. I just want to confirm communications and reports that you have authored in relation to this matter. You recall being approached by Professor Carola Vinuesa in 2019, which caused you to furnish a letter which, you may be aware, was tendered in that Inquiry dated 30 June 2019, and it's about the CALM2-G114R variant?
A. Yes.

Q. You recall you issued that letter to Professor Vinuesa setting out your views at that time and what you could say, based, for instance, on your Registry of Calmodulinopathies?
A. Yes.

Q. Your Honour, for the record, that's Exhibit 2-BT. Professor, you were also a contributing author to what is described as the Crotti article, which was an article reporting on insights from the International Calmodulinopathy Registry published in the European Heart Journal in 2019?
A. Right.

Q. Your Honour, a copy of that is at Exhibit 2-BU. You recall reading a response that had been prepared by Professor Vinuesa and now Professor Arsov in the context of the 2019 Inquiry into Kathleen Folbigg's convictions which--
A. Sorry, I begin to miss - sorry for interrupting. I missed some of your words, so--

Q. I'll move on. You were a contributing author to the Brohus article, as we call it, which was the--
A. Yes, I was.

Q. --article published in 2021 with the title "Infanticide vs inherited cardiac arrhythmias"?
A. Yes.

Q. What was your role or, if I can describe it that way, contribution to the formulation of that article, the contents?
A. Well, I reviewed the text contributed, I think, primarily to part of the

discussion for what I recall. It was primarily my role in describing the importance of modifier genes, which are those relatively common variants which may either increase or decrease the clinical severity of any mutation and that role, I must add immediately, right now, has become so extremely relevant because of the new findings that we discovered two days ago and which will have a major impact on our future discussion this morning.

Q. We'll come to that. Would you describe yourself as sharing senior authorship of this article with Professor Toft Overgaard and Professor Vinuesa?
A. Sorry, what is the question?

Q. Would you describe yourself as having shared senior authorship of this article?
A. Yes.

Q. The other senior authors were Professor Toft Overgaard and Professor Vinuesa, was that your--
A. That is correct.

Q. Did you select the title of this article?
A. Sorry?

Q. Did you come up with the title for the article?
A. That's entirely possible. This is one of the things that I often like to do.

Q. In terms of your contribution to this article, you say that it was primarily in relation to the importance of modifier genes. Is that your evidence?
A. Well, that is one of the things that I recall. I publish about 20, 30 articles every year, and I don't recall exactly the specific contribution to any direct articles. I contributed to the discussion, we discuss it with the other authors and I put in specific the parts that were more relevant to my expertise.

Q. You provided a report at the request of this Inquiry on 24 October 2022. Your Honour, for the record, that's at Exhibit 8, tab 04. Professor, do you have a copy of that report with you there?
A. Sorry, it's the one of which date? November 8 or--

Q. It's 24 October.
A. October. Yes. I have it.

Q. Then you provided an addendum which was dated 8 November 2022?
A. Yes, I have that, as well. Yes. I have them.

Q. Your Honour, that's also at Exhibit 8-04, commencing at red page 38-1.
A. Yes, I have all my reports with me.

Q. To confirm, the next report was dated 22 December 2022? Your Honour, that's at--
A. I have that, as well.

Q. –Exhibit 8-05. There's a report of 24 January 2023 and that's at Exhibit 8-06?
A. I do have it. Yes.

Q. You have your report of 3 February 2023?
A. I have.

Q. That's Exhibit 8-07, your Honour. Can I ask you please about the Calmodulinopathy Register? Did you create that Register, Professor?
A. We call it a Registry actually.

Q. Sorry, Registry?
A. Yes.

Q. Were you the originator of that Registry?
A. Yes, I was, and there is a specific reason which I think is relevant here. The first time I did it, when I became involved in the Long QT Syndrome which was in 1971 and when very little was known about the disease when my first patient looked like it was the 20th or 30th in the world, so there were very few cases, I realised very soon that it was necessary to have broad information from all over the world. So in 1972 when I was 29 year old I started - to everyone who established a few papers on it, I rapidly arrived to 200 patients and then with my American partner, the late Dr Moss, in 1977 we decided to establish an International Registry which started in 1979, continued for 25 years and has provided the essential information about the Long QT Syndrome. What we did learn with that Registry was fundamental in suggesting there's a need to repeat something like that with calmodulinopathies because we were also facing a sort of a new disease that apparently extremely rare where there are very few cases were available here and there, and we needed to place them all together in order to begin to understand the clinical history, the response to therapy and the natural cause in other words, and this is what we started to do in that 2015, we published a first report as you said correctly in 2019, we submitted in mid-January the new report. I expect an answer by the journal in any day now. There are things we'll have to complete and carry on, because when you're dealing with a rare disease, it is extremely important to rapidly increase the number in order to make correct statements about that disease.

Q. How do you obtain the data that is included in the Registry?
A. Sorry, the question is about how we got the data?

Q. Yes, how do you get it, as to the patients?
A. Yes. Well, people in the area know about my group, my work on Long QT Syndrome and ever since we started to publish the - report on calmodulin-related Long QT Syndrome and the Danish investigators did the first one on CPVT, it was an easy things for me to involve other investigators, primarily Mike Ackerman at Mayo Clinic in the United States, and then things happened on the grapevine. I mean in the work of science people talk, people knew that they we had established the Registry and then there was the flow of business coming in, which is increasing by the day, I could say.

Q. What, if any, steps are taken to verify the data that you received from colleagues about these patients?
A. Sorry, could you repeat that?

Q. What if any steps are taken to verify the data that you receive about these patients from your colleagues?
A. I think that will be very improper. I mean, these other calls come from an experienced cardiologist, I don't know how I could question their ability to make the diagnosis or to make a statement. It is not a clinical trial, it is a collection of the data on patients seen by experienced investigators, so we have to rely on what we are told.

Q. Who has access to the data, if I can put it - as you say, you publish the results and your findings, but who keeps the data and has access to it, Professor?
A. I'm sorry, your voice was trailing or my microphone is not working well. I have some trouble in understanding. Sorry, are you asking me is the data available to the public community or something similar?

Q. Correct?
A. Well, the data are available, they will be available in terms of what we publish, then if people ask specific questions we are always - to share this information with anyone whose asking them. I mean, but it would be bad to say we reserve for the - we don't lead them away until there is a specific reason. I'm sorry for the noise but we have some helicopters on our head because there is a fire nearby, so that is the noise is from the helicopters.

Q. How many patients are presently on the Registry?
A. Sorry?

Q. How many patients are presently on the Registry?
A. I think the latest number is 134 in the manuscript, but, you know, at one point you sort of lock the data so we can manage it while data continued to come in. I believe that we actually have data around 139/140, but it is constantly changing, but the new manuscript I think will deal with 134.

Q. Those patients on the Registry, do all of them have a calmodulin variant?
A. Of course. That is the prerequisite to enter in the Registry, unless they died and there isn't DNA available. In that case, we do exactly what we have done in the past with the Long QT Syndrome Registry. If we have a sudden death in a family with the calmodulinopathy occurring below age 40 and there is no other explanation, then we assume that the sudden death was due to the same mechanism. This is what is done traditionally in genetic diseases.

Q. Is the Registry limited to the CALM variants which have been classified as pathogenic or likely-pathogenic?
A. No. I don't think that specification is particularly useful at this time of changing of age. So, we base ourselves on the finding of a variant in the calmodulin genes.

Q. With the patients on the Registry, do all have a demonstrated phenotype of calmodulinopathy?
A. That's an interesting question. In our report, we are now indicating that whereas there are phenotypes that one can appropriately label as similar to Long QT Syndrome, or similar to CPVT, there is a growing number of cases where the variant associated is a - is a calmodulin variant. But the phenotype is mixed. We see more cases where there is an overlap between Long QT Syndrome and CPVT. There is a group that we now call "uncertain diagnoses" and these two groups are accounting for 15% of the total. But it's very difficult to decide if the patients or the victim had Idiopathic Ventricular Fibrillation, CPVT or CALM.

What we are learning by the new data coming in is that the picture is no more black and white than we initially thought, but is becoming much greyer, which is not an unnormal thing in medicine, and which fits particularly well with the fact that the calmodulin genes are, as I think it had been said already by the Danish investigator, the linking with so many proteins and different ionic channels that it's almost impossible to predict what is going to be the clinical phenotype. We have to expect a much more blurred situation compared to the initial one, and in my opinion, it would be naive to try and pigeon hole these clinical phenotypes. We have to accept that calmodulin is affecting so many different sensors and channels and proteins, that we cannot yet figure out completely and always the clinical phenotype.

Q. Are there any patients on the CALM Registry who are asymptomatic?
A. Yes.

Q. In--
A. Sorry, by the way, this is absolutely normal in any genetic disorder. I mean, I think the model where everyone involved in this trial..(not transcribable)..is what we learn to do in the last 50 years with the Long QT Syndrome. Where now, we are dealing with thousands and thousands of patients, and it's very clear that you may have in the same family individuals with a very clearly phenotype and individuals either without the phenotype or with the very mild phenotype. That is why in the same family it is very common to have two siblings; one who has the complete phenotype and dies suddenly; another one who also has clinical phenotype but doesn't die and nothing happens or doesn't have the phenotype. We are seeing all these permutations all the time.

Q. Just to be clear, that example you gave, the person who has the CALM variant but has no phenotype, they are included in your Registry as one of the patients within that family?
A. Of course. Well, if they have the genotype, that is a critical point to enter into the Registry. It's the presence of the mutation. Then among patients in the same family with the same mutation, you may have some with the phenotype and some without the phenotype.

Q. In your report, your first report, which is 24 October 2022.
A. Yeah.

Q. Exhibit 8-04, red page 28.
A. Sorry, you say page 28?

Q. It's your page 6 at paragraph 2.2.
A. Just a second. 2.2, yes?

Q. Yes. You there state the ICalmR, which is the Registry, provides extremely important and unique information to correctly assess whether the known phenotypes of Kathleen, Sarah and Laura Folbigg fit or do not fit with the most advanced knowledge on patients with calmodulin mutations. Do you see that there?
A. Sorry, are we talking about topic two?

Q. Yes. Paragraph 2.2
A. And there are two questions; 2.1 and 2.2

JUDICIAL OFFICER

Q. 2.2, Professor.

CALLAN

Q. 2.2.
A. Yeah?

Q. Second sentence, commencing with the word: "The ICalmR provides extremely important".
A. Sorry, I'm reading my answer. Is my answer to the one that starts, "this question is unclear to"?

JUDICIAL OFFICER

Q. Yes.

CALLAN

Q. Correct.
A. Yeah, okay, and--

JUDICIAL OFFICER

Q. Ms Callan's referring you to the next sentence.

CALLAN

Q. I'm referring you to the next sentence.
A. I'm very sorry. I think I have it in front of me, but I don't understand the question.

Q. I haven't asked a question yet, Professor. I'm drawing your attention to

something you've said in your report. With that in mind, can I ask you this, in your subsequent report of 8 November 2022, for the record that's at Exhibit 8-04, red page 38-8, you say, "We cannot use the Registry to say what is typical or what is exception for calmodulinopathy". If that's your position, Professor Schwartz--

A. Sorry, I'm losing you. I am on the addendum sent on November 8. At which page are we talking about?

Q. Page 8. Do you see the paragraph commencing with the word "the bottom line"?

A. Sorry, my pages are numbered. If you could give me the page number.

Q. Eight.

JUDICIAL OFFICER

Q. Page 8 of your addendum. You'll see there's a paragraph commencing, Professor, "The bottom line".

A. I'm really sorry, I'm - the bottom line. Let's go in order. I mean, my thing here starts with Part A. Are we on Part A?

Q. No.

A. No. Okay. So we go to probably there will be a Part B. Commentary on the report of Professor Skinner and Kirk?

Q. Do you have--

CALLAN

Q. The page before that. Part A.

A. Sorry.

Q. Yes, it's the page immediately before that. Part A, page 8.

A. Page 8. Yes. "The bottom line is that the expert", is that the line you're referring to?

JUDICIAL OFFICER

Q. That's the one, yes.

CALLAN

Q. Correct.

A. Okay. Thank you. Yes, I'm ready to listen.

Q. You there say, can I put it this way, you express criticism of any experts saying what is typical or not typical based on the 70 cases on the Calmodulin Registry? You say, "We still know so little about calmodulinopathies", and you--

A. Well, yes, I mean, the knowledge is growing all the time and I kept saying

from the beginning that it was premature to make statements about what may or may not be seen.

Q. Taking you--
A. We have very, very few cases of calmodulinopathy. They are increasing and as they are increasing, we see a changing pattern. That is what I am trying to say. That is why I am worried when anyone says, "We have never seen that". Yes, we may have never seen that so far, but we can see that tomorrow, because this is what happens with rare diseases. So my point is that we all, bearing testimony in a trial as important of this one, have to be very careful in the statements we make, and one thing is to say we have observed a fact or to say we have not yet observed the fact, and it's a very big difference.

Q. Do you say it is dangerous to speak about whether the known phenotypes of Kathleen, Sarah and Laura Folbigg fit or do not fit with what was contained in the Registry?
A. Well, there's nothing special about them. We have two girls who were found suddenly dead and they carry a calmodulin mutation, the same calmodulin mutation was found in the mother and, as far as I know, based on the Professor Peter Fleming report, there were no other signs of cause of that. Under those circumstances, anyone with experience in this disorder will assume that is the genetic variant that has caused the death, and this was before all of the new findings emerged a few weeks ago.

JUDICIAL OFFICER

Q. Does it amount to this, the children, or the two girls and the mother, had the variant, it's a variant that, at least it's been established, can cause death, and in the absence of any other cause, you proceed on the basis that the death was attributed to the variant, irrespective of whether or not particular cardiac conditions fit the general pattern at the present time?
A. I'm very sorry, your Honour, I didn't understand all the words you said. I mean, I'm getting a general feeling, but I'm not quite sure that I've fully understood what you say.

Q. I'll try again. Your point in the passage that you've just been referred to is that it's dangerous to suggest that the variants only produce particular phenotypes; is that right?
A. That is right, yes.

Q. In the present case, even though the children didn't present with what might be called the "typical phenotypes", it would be dangerous to conclude that the deaths were due to the particular variant? Is that the point?
A. I think it - you know, I am trying to guess between your words what is the question. Let me rephrase my point of view. When someone dies suddenly and when a proper post-mortem analysis is unable to show a clear evidence of another cause of death let's say, and you are left with a genetic variant that is known to be detrimental and associated with life threatening arrhythmias, this is in the medical situations when you are dealing with experts is meant the

diagnosis is that related to the specific gene. I have listed at some point some of the previous experiences I had years ago when in the Long QT Syndrome cases there were sudden infant deaths occurring in the families where no one else was affected and of course there were questions about the cause of death until we found that in our own very large cohort of patients we had patients dying within cardiac arrest with the same exact mutations. So it's simply a question of time, but all the evidence provided by cardiologists with specific experience in the Long QT Syndrome will tell you, your Honour, that if you find a disease causing mutation, and as far as we know the overwhelming majority of calmodulin mutations are pathogenic because the genes are extremely conserved over evolution, then that has to be the diagnosis.

JUDICIAL OFFICER: I think that's what I was putting to you, probably inadequately. Ms Callan, thank you.

CALLAN

Q. Professor Schwartz, you refer in your report to a paper and one of the authors is Kato, K-A-T-O, which addressed the N138K variant, are you familiar with that paper?
A. Sorry? Which paper are you referring to?

JUDICIAL OFFICER: The Kato paper.

CALLAN

Q. Kato. It's referred to in your addendum report, Part A, page 5.
A. Are we still talking of the November 8 report?

Q. Yes?
A. Yeah, you said page 5?

Q. Yes?
A. Yeah, and where are we now, on blanket phenotypes within families?

Q. Yes, there's a paragraph commencing with the words, "Another recent example"?
A. Yes. Yeah.

Q. You refer to the Kato paper?
A. Yes.

Q. You have commented that what was found there that N138K had an impairing effect on the binding of calcium but potentiates potassium, acted almost as a modifying gene influencing the clinical impact in a direction opposite to that expected producing milder clinical phenotypes?
A. Yeah.

Q. Do you accept there is the same potential here with the variant G114R?
A. Yeah.

Q. As to other modifying effects that may be discovered with further research?
A. You're reading something that I am - the Kato article the article by Kato et al was important to show that why there is a large variability in the expression of the disease, because some of these genes also have a modifier effect. I think that - I'm trying to figure out exactly what your question is, but the main message is that. I mean the Kato et al investigators have found that one of the features of their mutation was to sort of re-protect against the fact of the same mutation. And it is a point that they raise since day one that it will be naive to make interpretations both about what may happen to any individual who carries one of these variants if we analyse them in isolation. You cannot do that because our DNA includes so many additional variants, some of which act as modifier gene and thereby can either increase the clinical severity or to decrease it. Not to take this possibility into account is leading to a major error.

Q. If you take that possibility into account in relation to the G114R variant--
A. To any gene.

Q. --doesn't it follow that it might be erroneous to conclude that the two Folbigg girls died as a result of the variant?
A. Well, I think it's a very naive approach to attempt to predict that the phenotype simply based on the presence of a variant. In some cases it's worse, some cases it doesn't, and this is the common experience we have had with the Long QT Syndrome for the last 50 years, five zero. We see this all the time, so there is actually nothing new in realising that within a family where a number of individuals carry the same identical mutation, the phenotype cannot be predicted in advance because some of the affected individuals may have or may not have either protective or detrimental variants. My simple point is that one needs to be very careful in making statements about things that we don't fully understand or comprehend. But we should use our experience and see what has already happened because we have been there already. I think one of the issues is that I've seen the history of the Long QT Syndrome unfolding because I start seeing Long QT Syndrome since 1971 in January. And they've seen all the changes. As I mentioned at one point, until the late 80s, no one would think that Long QT Syndrome patients would die during sleep. Everyone assumed that they would die only during intense emotions or physical stress. It was only when some reports appeared indicating some deaths during sleep that we start wondering. But we still could not figure it out, until in 2001, we demonstrated that individuals with Long QT Syndrome and with a mutation on the sodium gene were more likely to die at night-time during sleep. So, I see history repeating itself, and I think that is why I am asking to be very cautious in the making - before making statements that can be proven wrong in a short while.

Q. Is it that experience that you had in relation to Long QT Syndrome that causes you to express in such firm terms that the diagnosis here for the cause of death for the two girls was sudden cardiac death due to calmodulin mutation? Is that experience that causes you to say it's that way?
A. No. I don't think I've said that. I can - I have no idea on what was the cause, actual cause, of death of the two girls. What I'm saying is that the presence of that mutation is a very valid explanation. Now, if you had told me

that turning over the bodies of the two girls, you found that they had been stabbed to death, I would say that that was the cause of that. But absent of a clear cause of death, then the presence of this mutation is a fully valid explanation, and is the one that should be medically accepted. I'm not making any - any suggestions about what killed the two girls. I am only saying, and I wish to be absolutely clear, that these mutations are providing a very valid and medically-sufficient explanation.

JUDICIAL OFFICER

Q. Can I put it to you this way? What you're saying in effect is this is it; that absent any other identifiable cause, the mutation is a reasonable explanation for the death of these children?
A. Yes, your Honour.

Q. You cannot say for certain that that caused their death. You can only say that it's a reasonable explanation. Is that right?
A. That is right. I don't think anyone can. I mean, that is why I mentioned going to extreme. That if - I mean, any person who has a little genetic variant can be killed in many different ways. But if you don't find a cause of that, and I'm relying on Peter Fleming, Professor Peter Fleming, who is the leading expert in the world in Sudden Infant Death Syndrome, to say that there was no evidence of other mechanisms.

Q. I understand, I--
A. If there are no other explanations--

Q. I understand that. You're working on the assumption that there is no other explanation for the death. Is that right?
A. That is - I am - I am basing myself on Professor Peter Fleming's testimony.

Q. Professor Fleming in effect says, "there is no other explanation." I'm not criticising you for doing it. I'm just asking.
A. Sorry?

Q. Your position is this: you have proceeded in reliance on Professor Fleming, among others, to say that there is no other identifiable cause of death other than that arising from the existence of this mutation. Is that right?
A. That is right. I have to respect his authority.

Q. That's perfectly--
A. And experience.

Q. And it's perfectly valid for you to do so. I understand that. But even then, all you can say, I think, is that it is a reasonable hypothesis that they died as a result of that mutation. Would you agree with that?
A. I'm - I'm - I'm very sorry, your Honour.

Q. No--
A. I really am struggling to understand your words. I mean, it's either the

microphone is not working well, or I'm missing some of your words. I apologise.

Q. I'll try again. Absent any other identifiable cause of death, your position is that a reasonable explanation for their death is the existence of the mutation in the two girls. Is that right?
A. Yeah. The presence of those mutations is a sufficient..(not transcribable)..I think it's important that at one point, we also bring into the picture the new findings about the detrimental variants that have been discovered recently.

Q. Yes, I understand that.

JUDICIAL OFFICER: Yes, Ms Callan?

CALLAN

Q. That takes us to the information you've provided the Inquiry about the updated numbers in the Registry. That information is in your addendum report of 8 November 2022, Part B, page 10.
A. Sorry, you said November 8?

Q. Correct.
A. Yeah. Which page, please?

Q. 10.
A. I lost--

JUDICIAL OFFICER

Q. Page 10.
A. Just a second. I lost you. Sorry, I don't see you anymore. I'm in some - something has happened, and I don't see anyone anymore. Okay. Something happened on my screen and I lost - can you hear me?

Q. We can hear you, yes we can.
A. Yeah, but I lost the - I don't know if you see me but I don't see you anymore. I don't see anything, I see just my screen, I don't know why. I'm sorry, I don't know what happened here. I have no idea what has happened.

JUDICIAL OFFICER: Just wait one moment, Professor, we're trying to see if we can sort out the problem at our end. Can you still hear us, Professor?

CALLAN: No.

JUDICIAL OFFICER: I think perhaps I'll adjourn for a couple of minutes.

CALLAN: Yes, your Honour.

SHORT ADJOURNMENT

JUDICIAL OFFICER: Thank you, Professor. Ms Callan.

CALLAN

Q. Professor Schwartz, in your Registry as things presently stand, is there any case of familial variable penetrance?
A. Yes, absolutely. There is a number of familial cases are growing significantly in the last few years. By the same time the number of so called *de novo* variants are decreasing. This is a natural type of thing with any rare genetic disorder because in the first few years it's only the most severe cases that come to medical attention. As people begin to make the diagnosis more frequently as genetic testing including the calmodulin gene, we are bound to see many more cases of lesser clinical significance and this is exactly what is happening.

Q. There is an example you give of that in our report of 8 November?
A. Yes.

Q. Page 6?
A. Page 6, yes.

Q. You see number 2 commencing with the words, "At birth"?
A. Yeah, I see that.

Q. That's an example from the Registry of familial variable penetrance?
A. Yes.

Q. The final sentence in that example you say, "Of special note, the father carries the same mutation but has no phenotype", do you see that?
A. Yes.

Q. Are there any other patients in the Registry which have the same descriptions?:
A. Yeah, this is a case that it was very obvious, but again there's nothing extraordinary in it. Even one of my initial cases of Long QT Syndrome with four kids affected in a family of five, and three cases of sudden death there they were coming from the mother who was affected, that's a genotype and practically no symptoms. I mean this is an important example because it happens in calmodulin but it's nothing extraordinary in medicine.

Q. I appreciate your point about that, Professor Schwartz, but if I can ask you to be patient with us and focus just on the information in the Calmodulinopathy Registry. Other than this patient, this familial example, are there any families in the Calmodulinopathy Registry which present a child with the phenotype and a parent with no phenotype?
A. Well, the Folbigg case would be an example.

Q. Aside from that?
A. Well, I don't recall specifically but again it's what I am trying to point out, there is nothing extraordinary about it. It is a question of having more

numbers. Some in the families that we are collecting, there are a number of asymptomatic individuals, so individuals without a phenotype. So, I'm sorry, but I'm puzzled by the fact that there is a difficulty to understand that what we have so far is not the end of the story. We need more information, to rely on the insufficient information is going to be very misleading.

JUDICIAL OFFICER

Q. Professor Schwartz, my difficulty is I've got to make a decision on this Inquiry now, I can't wait for science to fully develop, which I think Professor Vinuesa said this morning may well take years. So, I have to ask you, accepting all the time that there will be developments, will be changes, what I think I have to focus on, bearing it in mind all the time, is the position at present, and that's a difficulty I understand but that's a difficulty of the task that's allotted to me. I think what Ms Callan's asking you about, accepting that danger is, what is the present position as far as the Registry is concerned?
A. Sorry, the question is, what is my present position?

CALLAN

Q. The present information in the Registry in terms of cases of familial variable penetrance? You've given this example--
A. Yeah, there are many of them.

Q. How many, families?
A. Well I don't know the numbers off the top of my head, and quite frankly that number has very little relevance. There are a number of them. Sorry you are not satisfied with that, but as I - we said at one point, well let me see because I did ask some information there are - nine cases with at least one family member who has the variant and within the same families there are other individuals which do not show a clear phenotype or are still asymptomatic. But I think it could be very misleading if we focus on the small numbers that we have, because what I keep saying is that the pattern is changing and I've seen already in the Long QT Syndrome in my 50 years' experience, so I - what worries me here is that apparently there seems to be an attempt to focus on the little we know on the little we have without realising that the picture is changing and what we see now in one or two cases we will see tomorrow in an additional five. It's too early to make statements, that is why I am not making statements, I am very careful in what I am saying, and I keep repeating that the only thing I can say is that what we have observed in the Folbigg girls is compatible with the nature of that. I cannot say anything else. But to deny that evidence would be equally wrong.

JUDICIAL OFFICER

Q. When you say, "Compatible", further evidence and further material that'll come in over the years might, as it were, firm up that position, make it even more clear that it's compatible. But at the moment, what you say is that it's compatible. Is that right?
A. I - your Honour, I apologise humbly. I - I don't know. It's maybe my fault. I

have troubles in the - I'm afraid of missing some of your words - to give an incorrect answer. Because I'm missing some of your words when you talk.

Q. Let me ask you in this way, and I'll put it directly. On the present state of knowledge, your position is that the deaths of these children is compatible with them dying as a result of the mutation.
A. It is compatible with that, without any question. Compatible does not mean that that was the actual cause. I don't know the actual cause.

Q. No, that's--
A. But I'm saying that--

Q. I understand that, Professor. That was precisely what I was trying to get you to affirm. I think we're at heated agreement on the point.

CALLAN: No further questions, your Honour.

JUDICIAL OFFICER: Yes, Dr Woods?

WOODS: Just one point.

WITNESS: I'm sorry, before we change button and - there is something I would like to say, either now or later. But I think that I wish to say something because I feel responsible as the Court has asked me to provide some opinion. So, there are a few words that I would like to say, your Honour. Either now or later about - in order to clarify without any doubts what are my views, also taking into account what I keep referring as the "new findings in Folbigg infants".

WOODS: Professor, can I--

JUDICIAL OFFICER: No, please. I think it's preferable if you want to add anything, you add it now so Ms Callan can ask you some questions about it if needs be.

WOODS: Very well.

CALLAN

Q. Yes, Professor?
A. Yeah, can I?

JUDICIAL OFFICER: You go ahead.

CALLAN

Q. Go ahead.
A. Okay, thank you. Well, let me just say something that I jotted down last night and I'll be happy to send it to you in writing. During the last six months I've spent so much of my professional and personal time with this case that I

believe I have the right to say a few things. My understanding is that I've been asked to help the judge, your Honour, to reach a fair decision in this case by sharing with him my 50-year experience on sudden cardiac death of genetic origin. Specifically, I'm supposed to clarify whether or not there is a natural explanation for the death of the two Folbigg girls. In a nutshell, the response is yes. The presence of the calmodulin mutation G114R is sufficient to explain the occurrence of sudden death once other causes have been excluded, as clearly stated by the world-leading authority, Professor Peter Fleming. The co-existence of a largely symptomatic mother with infants who die suddenly or carrying the same mutation is not at all rare.

JUDICIAL OFFICER

Q. Professor, could you go a little bit more slowly?
A. Yeah, sorry. I will slow down. I was trying to save your time, but I will slow down. The explanation for the phenotypic difference usually depends on the presence of modifier genes. These are relatively common genetic variants that can increase or decrease the arrhythmogenic potential of the disease-causing mutation. I have been working on modifier genes for the last 25 years. While I've always maintained that the presence of G114R is sufficient to explain sudden death, already my first report to you, written in October, I had mentioned that the different phenotypes between mother and girls could have been explained either by protective modifiers in the mother or by damaging modifiers in the girls. Rather amazingly, this is exactly what happened.

I was informed a few days ago that all four Folbigg infants were found to carry a variant of the so-called "REM2" gene which has been clearly demonstrated to increase calcium entry in the cells: a most arrhythmogenic action. This variant is not present in the mother and was clearly inherited from the father. This new finding is a game changer because it shows that most of the vows so strongly expressed by experts who kept stating that sudden death during sleep was not fitting with the expected phenotype have lost the right to exist.

I will try to clarify this point in simple words. The life threatening arrhythmias of calmodulin mutations are caused by a combination of increased calcium current and increased sympathetic activity such as during physical or emotional stress. Under this condition, catecholamines, adrenaline and noradrenaline, breach the heart, increase calcium release and trigger arrhythmias. Calmodulin mutation and those causing Long QT Syndrome and CPVT, created the arrhythmogenic substrate, which in the presence of sympathetic activation and/or further calcium entry, leads to lethal arrhythmias.

Many experts have said that during sleep, arrhythmias are unlikely when the CPVT is the phenotype. I have noted that during rapid-eye-movement sleep, sympathetic activities can increase genetic arrhythmias. A new finding shows that the two Folbigg girls had another genetic variant causing further increase in calcium current which is lighting the fuse into the barrel of dynamite. In this condition, it is not surprising at all that even a modest increase in sympathetic activity could have triggered sudden death. These girls had a double hit as if

they had two mutations, not just one. The combination of maternal and paternal DNA has represented a lethal cocktail.

If no other clear evidence is provided to explain the sudden deaths, the current scientific knowledge can only state what is already existing. These genetic variants is more than sufficient to explain the death of the Folbigg girls. I hope to have been sufficiently clear, but I'm ready to further clarify what I've said. And sorry to have had to make this statement, but I think it's very important because I feel the responsibility to you, your Honour, to clarify my point of view.

Q. Thank you, Professor. That's helpful.

JUDICIAL OFFICER: Ms Callan, do you want to ask anything arising out of that?

CALLAN: Just briefly, your Honour, I hope.

Q. Professor Schwartz, in the statement you've just made about the potential relevance of modifier genes, is that based on information contained in the 2018 article published in the European Heart Journal, "Modifier Genes for Sudden Cardiac Death", that you authored--
A. No.

Q. --with Lia Crotti and Alfred George?
A. No, it is information that was circulated, I believe, a few days ago, indicating that that there is a presence of this variant on REM2, present in all four infants.

Q. But the significance or relevance of the presence of that REM2 variant, comes from--
A. Sorry?

Q. --does that come from your report in your 2018 article that I just referred to?
A. No. In 2019 I was just expressing the general concept that modifier genes can alter everything and explain discrepancies in the phenotype. But the information, as I understand, is probably very new. I just heard about it a week ago, or ten days ago.

Q. Just to be clear, what you heard a week or ten days ago was about the presence of the REM2 variant in the Folbigg children, correct?
A. Yes.

Q. What you say you know about the REM2 variant, does that include what appears in the 2018 article?
A. No, in the 2019 article we didn't know anything - okay, no, no, sorry. Now I'm trying to understand what you're saying. In the - in 2018, we wrote and published an article on modifier genes where this gene was mentioned because my previous partner, Albert George, in the United States, had published evidence that REM2 was a variant that we incrementally factored

and increased calcium current.

Q. Yes.
A. To that, he was quoted in our review of modifier genes. But we didn't - I mean, I didn't know anything about it in the present case until, I believe, a week ago or ten days ago.

Q. Your statement as to the potential role of a REM2 variant as a modifying allele for sudden cardiac death, is that based on the research set out in your 2018 paper?
A. Yeah. It was quoted there. The actual finding was, I believe, published in 2017 by an American group. Among the authors there was Dr A. L. George.

Q. Do you accept that whether the REM2 variant has anything relevant modifying effect on G114R would have to be studied before drawing any conclusions?
A. I don't think that's necessary. I mean, the REM2 variant is probably relevant to any situation when you have the genetic variant that predisposes to cardiac arrhythmias. Because anything that favours increased calcium current to the cell is increasing the probability of an arrhythmia. It would apply probably not only to genetic disorders, but even to more common situations. Like, say a patient with an acute myocardial infarction who is at risk of ventricular fibrillation and sudden death, if this patient has two variants it is in all probability - I mean, we are actually going to test this at this point because this finding is leading to a number of future studies - but it is entirely possible that other substrates, BA, myocardial infarction, heart failure or myocarditis, in the presence of this variant which increases calcium current, could increase the probability of a life-threatening arrhythmia. It's a general phenomenon. I would not limit it to calmodulin.

Q. When you say, "this finding will be the subject of future study", what finding are you referring to?
A. Sorry, which finding am I referring to?

Q. Yes. You said, "this finding will be the subject of future study". What is the finding you are referring to?
A. What I'm trying to say is that the recent evidence on the role of REM2 opens a new area of research because as I'm carrying out a number of studies, trying with partners in Europe and founded by the European community, trying to understand the genetic basis of sudden death during an acute myocardial infarction. We're not talking about genetic disorders here. We are talking of acute myocardial infarction, a very common disease. We are going to examine whether the patient dying suddenly in the first few hours are or are not carriers of the REM2. This is nothing to do with the Folbigg study. What I'm saying is that the finding of the REM2 is opening a new field of research.

Q. And to date, no research has been conducted as to whether the REM2 variant has any relevant modifying effect on G114R, to your knowledge?
A. No one has tested that, but I would certainly bet that this is the case. It was

shown in Long QT Syndrome Type 2 by the A. L. George group, and essentially the message is that anything that increases calcium current in the cells is increasing the risk of a lethal arrhythmias if you have a substrate that predisposes to arrhythmias. It is a combination of things, it has a synergistic effect and it probably applies, I'm not focussing now on the G114, that is almost relevant, I think this is a general principle. Whenever you increase calcium current in the cell, you are increasing the probability of an arrhythmia.

Q. Finally from me, Professor, in your reports you criticise other experts because they give their opinions by reference to the old Registry data and you tell this Inquiry that your unique access to the Registry data gives your views greater weight. Will you please provide the Inquiry with the updated Registry data that is in your possession so that the other experts can consider the new data for themselves?
A. I will be happy to provide every data we have without any question as soon as we are replied by the manuscript and the manuscript is no longer under embargo.

Q. If the Inquiry's work concludes before that happens, do you accept that all of the other experts who you criticise on the basis that they do not have access to the new numbers, suffer a disadvantage?
A. Well, my criticism is related to the fact of--

JUDICIAL OFFICER

Q. Professor, how can the other experts be criticised on data that they do not have and that you presently cannot make available?
A. Well, the issue, your Honour, is that in my opinion one should make statements when all the information is available. What we have witnessed is a number of premature statements, statements made even before the Registry was published based on a few dozen cases. It keeps happening. There is nothing magic about the Registry, the Registry is simply showing that as time goes by, as more cases are brought to medical attention, the picture is changing. This should lead someone who has been asked to provide this Court with a meaningful information and suggestions about the interpretation of the data should lead to caution. I'm simply saying that is what I don't like it when people make statements with - few data, and I'm not claiming to have answers, I am simply saying that the new information is showing that the pattern is changing and premature conclusions are unwarranted. One thing is to say we have observed this phenomenon, a different thing is to say, so far we have neither observed this phenomenon because - the work so far implies that you can say the same thing in a month from now, so there is a question of caution which in a case like this I think is due by any respected expert. I am worried when I see people making statements without having all the data. I am the first in being very careful in not making statements.

JUDICIAL OFFICER: Thank you, Professor.

CALLAN

Q. Thank you, Professor.
A. Thank you.

<EXAMINATION BY DR WOODS

Q. Professor Schwartz, on this subject about the number of cases, you said that there was a growing number in the Registry of cases with familial variable penetrance. Then you said--
A. Yes.

Q. --the *de novo* number is decreasing, and then his Honour said to you that he was unable to wait several years before a very substantial number of cases were gathered and you said something like this, a number of them, then you said, nine cases with at least one variant and others in the family who are still asymptomatic. Now, have I misquoted you, did you mention the number nine?
A. I say that we have nine cases, so let's see here, that at least one family member was found to - okay, in there are at least nine cases where a family member carries the CALM variant in it identified in the index case, so we are talking of at least nine families with people having the mutation independently of the first one coming to medical attention. This is simply to say that one cannot make rules, because initially it looked like almost all of these cases were isolated, caused by *de novo* mutations, as the number of cases is increasing we see a different pattern and more familial cases are observed. The numbers by themselves are not particularly important because you have to put them in the framework of time. This is a moving target. More time passes, more information we have, larger are the numbers.

Q. Is this nine cases where there is variable penetrance?
A. Listen, I - I hate making - anyway, I'm not - I am at my home in South Africa and I do not have access in this moment to all the databases which include everything, and let me see what I have here. Well it's - quite frankly I'd be happy to answer in writing if I have a very specific question, because I can ask the person running the database to enter in the database and look exactly. I don't like giving numbers when I am not 100% sure. What I--

Q. Right. Can I take you to the question--
A. --no, sorry, I have it here, yes, there are nine, nine families with a certain degree of variable expressivity is present in all of them. Son, father, both are symptomatic. I mean there is we have nine of these cases so far, but even one would be sufficient, that is the point I am trying to convey to the Court.

JUDICIAL OFFICER: I think you've already conveyed that point, yes, we understand that.

WOODS: I'm sorry, your Honour?

JUDICIAL OFFICER: I think that point's already been conveyed.

WOODS: Yes. Thank you.

Q. Thank you very much, Professor.
A. Thank you.

<EXAMINATION BY MR JORDAN

Q. Professor Schwartz, can you hear me?
A. Yes, if you can speak up I would appreciate it.

Q. Can you hear me now?
A. Yeah, a little bit better.

Q. All right, I'll do my best. In your evidence you referred at various times to a new manuscript, new findings, concerning the discovery of the presence of the REM2 modifier in the four Folbigg children, do you recall that?
A. Yes.

Q. My note of your evidence is that you had only learnt of this in the last week or ten days. Is that correct?
A. Are you asking me when I heard about it?

Q. Yes?
A. I think it was within the last ten, something like that, I think there was a report showing something like that.

Q. Are you there referring to the report prepared by Professor Vinuesa and Professor Cook dated 1 February 2023?
A. I think that is probably it was, yes.

Q. All right, thank you.
A. You're welcome.

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

<EXAMINATION BY MS CALLAN

Q. Professor, you were asked questions about the nine families and whether they displayed variable penetrance. In your answer you referred to them displaying variable expressivity. Do you understand the difference between expressivity and penetrance?
A. Yeah, I do understand this, thank you.

Q. How many families - Professor, Professor, how--
A. But you know, again it's a - sorry, I do understand but--

JUDICIAL OFFICER: Professor please, just one moment.

CALLAN

Q. --how many families in the Registry have variable penetrance?

A. I honestly cannot answer in terms of numbers. I mean the issue of the about variable expressivity and variable penetrance is a technical definition which doesn't take into account what we see in the clinic because it's very difficult to discriminate between the two. These are excellent definitions for medical students to answer, but in practical reality the border between the two is minimal. We refer usually to different penetrance when you have people with the same mutation and someone is showing a full phenotype and someone is not showing a full phenotype, but this is where the area becomes confused because one this is to have a zero phenotype, a different thing is whether mild phenotypes. So from a clinical point of view I do not accept this, it is splitting between expressivity and penetrance. We were the one who - I mean I am the one who proposed that this may happen in the Long QT Syndrome in 1979. We did provide the evidence 20 years later in 1999 about the fact that you may have in the same family in the middle of - the same mutation, some with clinical manifestations, some without it. You want to call it low penetrance, you want to call it CPVT, I quite frankly don't care, the problem is a clinical one here is not a semantic problem. The question is that you may have a different variant and different manifestations, most likely they are the consequence of modifier genes which is the message that I'm trying to deliver to the Court. So you cannot take a variant, a genetic variant in isolation, you have to include this, it's a DNA that we have and our DNA is made but it's a maternal and paternal DNA, and then you have all possible permutations. The fact is that this permutation exists and I don't want to be bogged down and pigeon hole things with a definition that again is good in school but not in clinical work. Sorry for being--

Q. Professor Schwartz, on Monday, 13 February, those assisting the Inquiry sent you an email with eight questions, do you recall receiving that email?
A. Not specifically, I received so many. We are talking of February when?

Q. 13 February, that was Monday of this week, an email?
A. Yeah, an email report of February third?

Q. No, the email sent to you by those assisting the Inquiry which set out eight questions seeking some specific--
A. No honestly, I don't remember, but please help me and I'll clarify. I don't remember it by heart now.

Q. The email commences, "Counsel Assisting the Inquiry anticipates asking for some specific facts and figures in relation to the International Calmodulinopathy Registry data arising from your reports", and then it set out eight questions. Do you recall receiving that email?
A. Well, yeah, I know that there was some exchange about that.

Q. You sent three emails in response to that request and in none of those responses did you answer the questions, do you recall that?
A. Sorry, could you repeat that?

Q. I'll try this another way. When Mr Woods was asking you about the Registry, you said you would be happy to provide an answer to any question

about a fact or a figure in the registry if you were allowed the time to do so?
A. Yeah, of course. Yeah, of course I am happy to provide any - answers to any question if I may, yes.

Q. Well, could I ask you that within a short period of time you could answer the questions which were set out in the email sent to you on 13 February?
A. Okay. We have something. Am I able to ask my people to look at some of your questions now I understand what you are referring to, some of the questions were sort of repeating themselves or were not entirely clear. My associate sent these--

Q. What we might do, could you respond in writing to those questions please?
A. Okay. If you send again the question, I will respond in writing to the best of my knowledge. Some of the questions are a little bit unclear, especially when the issue of non-mosaic families are brought up, because on one hand we don't understand exactly what you are trying to find, and also specifically--

JUDICIAL OFFICER

Q. Professor, if you can't answer the question, simply say you're unable to answer it.
A. Okay. We will do - I'll do the best I can, your Honour.

JUDICIAL OFFICER: Thank you. We can't ask for more than that, Professor.

CALLAN

Q. Thank you, Professor.
A. Thank you.

JUDICIAL OFFICER

Q. Professor, thank you very much for making the time and we're grateful that you agreed to see to you answer those questions as much as you can. It's been very - the help you've given is very much appreciated, thank you.
A. Thank you, your Honour.

<THE WITNESS WITHDREW

AUDIO VISUAL LINK CONCLUDED AT 6.34PM

WOODS: Your Honour, may I ask that we be provided with a copy of that questionnaire?

JUDICIAL OFFICER: Yes.

WOODS: Thank you.

CALLAN: Your Honour, I'm happy to have marked for identification the email exchange that we had with Professor Schwartz on 13 February. I'll hand up

the bundle and we'll make copies available to the parties.

MFI #8 EMAIL EXCHANGE BETWEEN COUNSEL ASSISTING AND PROFESSOR SCHWARTZ DATED 13/02/22

JUDICIAL OFFICER: Thank you.

CALLAN: Your Honour, it's proposed in the hearing schedule to commence at 11am tomorrow morning with Professor Kirk.

JUDICIAL OFFICER: Yes. How long do you anticipate Professor Kirk would be?

CALLAN: I think examination-in-chief - approximately two hours.

JUDICIAL OFFICER: Very well. We'll adjourn.

ADJOURNED PART HEARD TO THURSDAY 16 FEBRUARY 2023 AT 11AM