SPECIAL INQUIRY

THE HONOURABLE THOMAS BATHURST AC KC

THIRD DAY: MONDAY 13 FEBRUARY 2023

INQUIRY INTO THE CONVICTIONS OF KATHLEEN MEGAN FOLBIGG

AUDIO VISUAL LINK COMMENCED AT 10.05AM

JUDICIAL OFFICER: I think we have the appearances now.

CALLAN: Yes, your Honour.

JUDICIAL OFFICER: Yes, Ms Callan.

CALLAN: Your Honour, this is the second tranche of hearings in the Inquiry into the convictions of Kathleen Megan Folbigg. This morning I propose to add only briefly to my lengthy opening back on 14 November 2022, which laid a substantial foundation for the evidence to be heard over the coming weeks. Your Honour's task in this Inquiry is to consider the evidence at trial and the conduct of the trial, in light of the further evidence and submissions received in this Inquiry, in order to determine whether, overall there is a reasonable doubt as to Ms Folbigg's guilt in respect of manslaughter of her first baby Caleb, malicious inflicting grievous bodily harm and murder in respect of her second baby Patrick, and of murdering her subsequent two young daughters, Sarah and Laura.

Upon conclusion of this opening, I propose to tender several volumes of evidence which have been obtained since the last occasion, and the parties will have an opportunity to make any application for non-publication orders.

Your Honour, the parties have been provided with a hearing schedule which would see the evidence conclude within two weeks, but a third week has been set aside if required. All witnesses giving evidence are experts, many of international renown. When these expert witnesses were engaged by the Inquiry, they were asked to comply with an expert witness code of conduct which emphasises an expert witness is not an advocate for a party and has a paramount duty to assist the Court impartially on matters relevant to the expertise of the witness.

Some experts will give evidence in person and others by audio visual link. The hearing schedule seeks to accommodate time zone differences and other professional commitments of these expert witnesses meaning that we will at times sit outside normal court sitting hours. We seek to use this Inquiry's time and the time of these experts in a process which is fair, effective and efficient, mindful that all experts have furnished detailed written reports. We seek to avoid repetition and maintain a keen eye on the material issues.

Your Honour, immediately after a directions hearing held the week before last on 3 February 2023, we conducted an all parties meeting. As with previous all party meetings, this was fruitful and reflective of the sensible and productive contribution all legal practitioners are making to the work of this Inquiry. Among other things, the parties discussed and have largely worked out an agreed order of examination of witnesses after those assisting your Honour conclude the evidence-in-chief of each witness.

Your Honour, in a moment I'll outline the evidentiary landscape which will be dealt with over the coming weeks. Before doing so, it's convenient to note that as your Honour would recall, on the eve of the last tranche of hearings, Professor Toft Overgaard informed the Inquiry of further functional assays he had just conducted in relation to the CALM2-G114R variant. The results were detailed in a report of Professors Toft Overgaard and Nyegaard provided on Saturday 12 November 2022.

In order to ensure the other expert witnesses, and the parties, were afforded adequate time to consider this further report, Counsel Assisting took the evidence-in-chief of Professors Toft Overgaard and Nyegaard, and shortly thereafter the hearing was adjourned to today. I should say, of course, that oral evidence was also taken from cardiologist Associate Professor Raju as this was confined to Ms Folbigg's cardiac history and not impacted by the further report of Professors Toft Overgaard and Nyegaard.

Your Honour, since November last year, the work of this Inquiry has been directed to two main topics. First, we have obtained further reports from experts in the field of cardiology and genetics in relation to the pathogenicity of the variant CALM2-G114R. I'll outline that evidence in a moment along with other related evidence we have received. Second, the Inquiry has gathered further evidence relevant to the diaries of Ms Folbigg, and I'll come to that evidence in due course.

Dealing though, first, with the further cardiac and genetic evidence. The Inquiry now has before it a weighty body of work from a range of cardiac and genetic experts addressing the pathogenicity of the CALM2-G114R variant identified in Ms Folbigg and her two daughters. The calibre of these experts and the time they have each taken to make their contribution to the work of this Inquiry is to be recognised. In my opening address on 14 November last year, I outlined the evidence contained in reports the Inquiry had before it from Professors Kirk and Skinner, which built on evidence they gave in the 2019 Inquiry; reports from Professors Vinuesa, Cook and Arsov which again built on evidence they gave in the 2019 Inquiry.

I also outlined in opening the reports we had received from additional cardiac and genetic experts engaged in this Inquiry, namely Professor Toft Overgaard, Professor Nyegaard, Professor Schwartz and Professor Wilde. I do not repeat what I previously said in opening as to the views of these various experts. What I will do now is provide a brief overview of the experts' reports we have more recently received.

Your Honour, the Inquiry has received a report of Professor Guicheney dated 9 November 2022. Those representing Ms Folbigg furnished a report of Professor Guicheney who is the Research Director in the field of genetics of cardiac arrhythmias and sudden infant death at the National Institute of Health and Medical Research in France. In relation to the CALM2-G114R variant, Professor Guicheney classifies it as pathogenic, considers Ms Folbigg is symptomatic, and considers it is a reasonable possibility the variant made Sarah more susceptible to sudden death in the context of her prior infection. It is not proposed to call Professor Guicheney to give oral evidence, but that contribution adds to the volume of material before you.

Your Honour, Professors Vinuesa, Cook and Arsov who will each give evidence this week have provided a further joint report dated 23 January 2023. They state the evidence of Professor Nyegaard relating to the evolutionary conservation of calmodulin and the further functional assays conducted by Professor Toft Overgaard, including as to the effect of CALM2-G114 on the binding of calmodulin to the sodium ion channel Nav1.5 reinforces their view that the CALM2-G114R variant is arrhythmogenic, pathogenic and a likely cause of sudden cardiac death in infants and young children, including during sleep.

In a further joint report from Professors Vinuesa and Cook dated 1 February 2023 they detail further genetic analysis indicating that each of the four children, but not Ms Folbigg, carry the REM2-G96A variant and refer to a study published in 2008 which identifies that variant as an aggravating modifying allele for sudden cardiac death. They suggest Professor Schwartz give consideration to the potential for the REM2-G96A variant to have a modifying effect on the CALM2-G114 variant on Sarah and Laura Folbigg, and when Professor Schwartz gives oral evidence later this week he will be asked about this topic.

JUDICIAL OFFICER: Professors Vinuesa and Cook didn't reach any conclusions on this issue; they simply asked Professor Schwartz to look at it; is that correct?

CALLAN: Correct. They undertook the analysis which identified the presence of that variant and identified Professor Schwartz as appropriately placed in terms of his expertise.

JUDICIAL OFFICER: And there is no material to know whether the children had the variant *de novo* or if it's – or if it was hereditary; is that correct?

CALLAN: There is a suggestion that it was not *de novo* in circumstances where it was present in all four children. I note Professor Schwartz's report of 22 December 2022 indicates his views have not changed by reason of the further report and evidence of Professors Toft Overgaard and Nyegaard. To reiterate, he considers the CALM2-G114R variant is pathogenic and the cause of death of Sarah and Laura Folbigg was sudden death due to calmodulinopathy.

JUDICIAL OFFICER: Now, is Professor Schwartz or Professor Vinuesa or Professor Arsov, do they suggest any clinical cause of death? They are both saying that the variant was pathogenic and caused the death?

CALLAN: Not in terms, your Honour.

WOODS: As an additive, your Honour, I think that it's fair to say--

JUDICIAL OFFICER: You'll have your turn. Go on, Ms Callan.

CALLAN: Professor Wilde, who will also give oral evidence this week, your Honour, provided a report dated 24 January 2023 in which he reiterates that in his view the CALM2-G114R variant is likely pathogenic, that is, potentially causing death. As to the further functional assay by Professor Toft Overgaard, Professor Wilde notes that theoretically a reduction of sodium channel function could lead to Brugada Syndrome, which has been linked to sudden cardiac death during sleep.

Professor Wilde considers that having regard to the ECGs available, there is no indication of Brugada Syndrome in Ms Folbigg or Laura Folbigg. He also notes that an eventual reduction of the sodium channel amplitude does not always translate into a pathogenic variant, pointing out that, at one point some 20 other genetic variants with reduced sodium channel activity were thought to be linked to Brugada Syndrome, but have since been downgraded to limited or disputed evidence.

Professor Wilde remains of the view that Catecholaminergic Polymorphic Ventricular Tachycardia, or CPVT, is unlikely for sudden death during sleeping children around the age of one, and that Idiopathic Ventricular Fibrillation, or IVF, seems unlikely. But he acknowledges that one cannot exclude a causal role of this variant in the deaths of Sarah and Laura Folbigg.

We have also received a report from Professor Kirk dated 15 January 2023. He addresses the difference between research and diagnostic assays. He notes that even without validation to a clinical standard, some weight can be placed on the results of a research assay in a diagnostic evaluation of a variant, but caution is needed. The most recent functional assays conducted by Professor Toft Overgaard do not change Professor Kirk's view as to the pathogenicity of the CALM-2-G114R variant.

Your Honour, to complement this body of expert opinion, the Inquiry has more recently engaged Dr Calum MacRae and Dr Dominic Abrams, plus has received a report from Professor Watkins. Dealing first with Dr MacRae, he is an Internist, Cardiologist, Geneticist and Developmental Biologist at Brigham and Women's Hospital and Harvard Medical School whose work focuses on the genomics and biology of disease. He will give evidence later this week. In Dr MacRae's report dated 27 January 2023, he sets out his reasons for concluding that there does not appear to be a reasonable possibility that the CALM-2-G114R variant caused Sarah and Laura Folbigg's deaths.

He raises doubts about the proposed pathogenicity of the CALM-2-G114R variant given the clinical findings in Ms Folbigg, Sarah and Laura, and observes that death during sleep is in general inconsistent with typical CPVT presentations. He also emphasises that because genetic variations can be modified or buffered by other copies of the same gene, by related genes or other pathways, this makes it difficult to base conclusions about a genetic variant on functional assays where single copy is studied in isolation from the normal gene in a single cell. And he emphasises the difficulties in assuming that functional assays are representative of arrhythmia risk.

Dr Abrams is Co-Director of the Center for Cardiovascular Genetics at Boston Children's Hospital and he will also give evidence in the Inquiry – it is anticipated it will be next week. Dr Abrams has furnished a report dated 27 January 2023, which sets out the basis for his view that the CALM-2-G114R variant is of uncertain significance – because whilst some considerations suggest pathogenicity, the fact a carrier – Kathleen Folbigg – is alive and healthy, suggests it is benign. Dr Abrams explains the central role of phenotype in assessing pathogenicity. He also observes the majority of deaths in early life relate to Long QT Syndrome, and there is no clinical evidence supporting a diagnosis of that syndrome in either Laura or Sarah (but he acknowledges that the cardiac investigations performed were insufficient to either make or refute the diagnosis).

He notes that Ms Folbigg does not have Long QT Syndrome, suggesting this phenotype is not evident in their family. Dr Abrams further considers that CPVT is an unlikely cause of death in the two girls. He urges caution in interpreting in vitro data, such as the functional assays conducted in isolation without concordant evidence of clinical disease. In his view, it is possible but unlikely that Ms Folbigg had a very mild form of CPVT, or has a very mild form of CPVT, and her two children died at very young age during sleep from either CPVT or another condition associated with calmodulin.

Finally, your Honour, I note a report dated 7 February 2023 from Cardiologist Professor Hugh Watkins, who established the Oxford Inherited Cardiac Condition Service. It is not proposed he be called to give oral evidence, but his contribution to this Inquiry is valuable. Professor Watkins recognises the expertise and high standing of, for instance, Professor Wilde, Professor MacRae and Professor Schwartz. He observes that reasonable, thoughtful and authoritative experts are all looking at the same data but drawing different inferences. He says this is because there is substantial uncertainty and so judgment, rather than interpretation of indisputable fact, is needed to reach a conclusion. Professor Watkins view is that the CALM-2-G114R variant is likely pathogenic. He agrees with Professor Schwartz it is plausible the variant could produce sudden death with a syndrome that does not comply with standard expectations. He says in his view it is plausible but not provable the variant was responsible for the sudden death of Laura and Sarah Folbigg.

Your Honour, over the coming week the oral evidence from various of these cardiac and genetic experts will focus on the considerations these experts raise in assessing the pathogenicity of the CALM-2-G114R variant along with

the factors they regard as relevant to their view as to the possibility the variant was responsible for the sudden death of Laura and Sarah Folbigg. As I said in my previous opening, no expert is expected to tell your Honour that the CALM-2-G114R variant definitely caused the death of either Sarah or Laura Folbigg, and equally no expert is expected to tell your Honour the CALM-2 variant could not possibly have caused their deaths. Rather, the experts divide on where is the middle ground they land in terms of the likelihood that this novel genetic variant could have had any role to play in their deaths, and their task is affected in no small measure by the incomplete underlying investigative information available as to Sarah and Laura Folbigg's cardiovascular circumstances.

JUDICIAL OFFICER: This is probably a very unfair question, but the way you've said this, would it follow that, leaving aside all the other evidence, which ultimately I can't do, that there's, even on this evidence, whichever way you look at it, a reasonable hypothesis inconsistent with guilt? Taken solely in isolation.

CALLAN: Yes, your Honour, in my submission that is the effect of the evidence.

JUDICIAL OFFICER: Yes. Go on.

CALLAN: Can I now turn to the field of forensic pathology. In my opening address to the Inquiry in November I outlined the evidence from forensic pathologists led at trial and dealt with in the 2019 Inquiry by Professors Duflou, Hilton, Cordner and Dr Cala. Your Honour may recall the common ground between the four forensic pathologists was that there was no unequivocal cause of death for the four Folbigg children. Earlier research as to there being an extremely low risk of more than one SIDS death in a family belied the possibility of a genetic basis for SIDS, which would result in subsequent siblings having an elevated risk. And that SIDS and fatal suffocation can be indistinguishable in infants due to an absence of discernible physical injury.

For this Inquiry, each of the four forensic pathologists have provided further reports addressing the implications of the evidence about the CALM-2 variant for their views about the cause of death of each of the four children. In addition, Ms Folbigg's representatives have engaged a further Forensic Pathologist, Dr Matthew Orde, who has provided two reports to the Inquiry.

Your Honour, Professor John Hilton, the Forensic Pathologist who performed the autopsy on Sarah Folbigg on 31 August 1993, prepared an affidavit dated 26 July 2022 for this Inquiry. He considered that intentional smothering was excluded as a cause of death on the evidence. In his view, there are natural causes of death for each of the four children, including by reference to the CALM-2-G114R variant for Sarah and Laura Folbigg.

Professor Cordner, who is an Emeritus Professor of Forensic Pathology at Monash University, and will give evidence next week, indicated in his report dated 1 March 2022 that he had given particular and further attention to the

issue of the absence of signs of smothering in any of the children. In his view, the discovery of the CALM-2-G114R variant in each of Sarah and Laura means their cause of death should be, respectively, unexpected death in an infant with a novel functional calmodulin variant, and myocarditis with a novel functional calmodulin variant. A follow-up report dated 13 December 2022 also addresses these topics, and by reference to the expert evidence of Dr Monique Ryan, by reference to this Professor Cordner states in his view, the cause of Patrick's death is epilepsy or undetermined – probable natural causes.

Your Honour, Dr Cala, who will also give evidence next week was the Forensic Pathologist who performed the autopsy on Laura Folbigg. Dr Cala's evidence before the 2019 Inquiry was to the effect that he would ascribe Caleb's cause of death as undetermined, Patrick's cause of death was not epilepsy, that Sarah's cause of death was undetermined, and that Laura's cause of death was not myocarditis but that it could not be positively excluded as a cause. In a supplementary report dated 13 December 2022 received by this Inquiry, Dr Cala states that none of the scientific or academic material he has read since the 2019 Inquiry causes him to change his views about the cause of the children's deaths. Dr Cala suggests that the photomicrographs of Laura Folbigg's heart slides referred to in the Brohus article showed one of the most severe areas of myocarditis, and were not representative of the whole picture, noting that some of the areas of the heart were only slightly affected by myocarditis or unaffected. He maintains that Laura's myocarditis was not florid.

Your Honour, Dr Orde is a Forensic Pathologist who is to give evidence next week. His report dated 21 December 2022 outlines his view that each of the Folbigg children died a natural death. He considers at least in older children, any attempt to smother would have likely resulted in injury and the absence of any identified injury to the facial region of the children was notable. Dr Orde notes that there is uncertainty regarding the potential significance of the finding of the CALM-2-G114R gene in Sarah and Laura, but states there is a possibility it could have posed an increased risk of sudden death. In his supplementary report dated 13 January 2023, Dr Orde comments on the degree and extent of myocarditis evident in the microscopic sections of Laura Folbigg's heart tissue. He describes the overall intensity of the inflammation as “moderate” with some areas of lesser inflammation and some with more inflammation, but features of myocarditis were present in each and every section of heart tissue examined. He considers that myocarditis would provide a highly plausible explanation for Laura's death, either independently or in combination with other factors.

JUDICIAL OFFICER: Of the slides presently available, is there any suggestion that Dr Cala, Dr Cordner and Dr Orde were looking at different slides?

CALLAN: No, your Honour. The evidence indicates that those three experts looked at the same set of slides which were taken in association with Laura's autopsy that Dr Cala performed. That is to say each of Dr Cala, Professor Cordner and Dr Orde are expressing their views as to what they see and say

about the myocarditis in the same set of slides.

JUDICIAL OFFICER: Is Dr Cala relying solely on the slides for his view?

CALLAN: As to myocarditis?

JUDICIAL OFFICER: Yes.

CALLAN: That's my understanding, yes, your Honour. Your Honour, lengthy oral evidence was given in the 2019 Inquiry by each of Professor Hilton, Professor Cordner, Dr Cala and Professor Duflou. It is not proposed to duplicate the terrain covered with those forensic pathologists, however, we will have the benefit of oral evidence from Professor Cordner, Dr Cala and Dr Orde addressing their views as to cause of death – including in particular the relevance of the evidence more recently available as to the G114R variant, and also as to Laura's myocarditis – there is of course an interplay.

It is convenient at this point to point out the other expert witnesses who will give evidence next week. Professor Peter Fleming is a Consultant Paediatrician and Professor of Infant Health and Developmental Physiology at the University of Bristol. In his report dated 3 November 2022, which I previously tendered, Professor Fleming addresses current knowledge in relation to SIDS and amongst other things, the significance of the absence of observable physical damage to each of the Folbigg children; that is, no observable signs of suffocation. Professor Fleming has provided a supplementary report dated 1 January 2023 in which he responds to the report of Dr Cala of 21 December 2022.

Your Honour, the Honourable Dr Monique Ryan MP has provided a report dated 23 September 2022 which was previously tendered. Dr Ryan is a Paediatric Neurologist who gave evidence in the 2019 Inquiry that Patrick Folbigg's clinical history was not consistent with neurological deficits resulting from a single hypoxic ischaemic episode. Dr Ryan considered that Patrick's observed arching of his back in a torticollic manner suggested the possibility of a pre-existing and underlying condition.

In her more recent report of 23 September last year, Dr Ryan states that she remains of the view that there were aspects of Patrick's history which were unusual or inconsistent with a single hypoxic-ischaemic insult, inflicted or otherwise, on the date of his ALTE. Dr Ryan considers it possible that Patrick had an undiagnosed neurogenic disorder and we'll explore this in oral evidence.

Finally, your Honour, can I turn to Ms Folbigg's diaries which is the final area of oral evidence to be dealt with in this hearing. As your Honour would recall, the diaries and journals in evidence did not span the entire decade from the birth of Caleb in 1989 to the death of Laura in 1999 – but do cover the period February to March 1989, the year 1990, and then June 1996 to April 1998. There are also diaries for 1999.

At trial, over and above relying on these diaries for tendency reasoning, the Crown case was that Ms Folbigg's diaries were an intimate, personal and exact analysis of what her thinking was during the times they were available. The Crown characterised certain entries in her diaries – particularly in combination – as admissions of guilt, suggesting the diaries were the "strongest evidence you could possibly have for Ms Folbigg having murdered her four children".

In support of Ms Folbigg's petition to the Governor, she squarely challenges that characterisation of the content of her diaries, relying on the reports of a number of experts to whom I'll refer shortly.

JUDICIAL OFFICER: The characterisation was, I think, consistent with the view taken by the Court of Criminal Appeal and by Mr Blanch in his Inquiry; is that right?

CALLAN: Yes, your Honour.

JUDICIAL OFFICER: That of course doesn't bind me in any way.

CALLAN: No, it does not, your Honour.

JUDICIAL OFFICER: And the psychological and psychiatric evidence has come in in the course of this Inquiry. None of that I think was available to either the jury, the Court of Criminal Appeal or Mr Blanch; is that right?

CALLAN: Correct, your Honour.

JUDICIAL OFFICER: Yes, go on.

CALLAN: Your Honour stated in a directions hearing last year on 6 September that you considered it will be appropriate to consider psychiatric and psychological evidence which may affect the view taken of what appears in Ms Folbigg's diaries. To that end, the Inquiry has received the originals of some of the diaries and those assisting your Honour have produced transcripts of the entire corpus of the diaries, to aid comprehension and navigation of that evidence.

Also, your Honour, a schedule has been created which lists the diary entries relied upon by the Crown at trial as admissions of guilt, or otherwise were the subject of questioning of Ms Folbigg at the 2019 Inquiry. That schedule has use having regard to the particular weight placed on discrete entries in the diary, but the evidence, in my submission, must be considered in its whole form; that is, those particular entries in their context and having regard to the overall contents of the diaries.

I'll now briefly outline the reports which were furnished by Ms Folbigg's representatives and will be tendered. It is not proposed to call these experts to give evidence in the Inquiry. The report of Dr Sharmila Betts of 13 April 2021 reflects the views of Dr Betts who is a Clinical Psychologist. The conclusion in

that report is that Ms Folbigg's mental state at the time of writing the diaries was consistent with psychological literature as to those who experience sudden infant deaths and non-bereaved mothers, and that Ms Folbigg's diary entries were not unexpected for a parent who had experienced recurrent sudden unexplained infant deaths.

There is also a report of Professor James Pennebaker of 5 July 2021. Professor Pennebaker is a Professor of Liberal Arts and Psychology. He conducted a computerised text analysis of Ms Folbigg's diaries to identify Ms Folbigg's psychological state across the years surrounding the death of her children. He cannot identify any language-based evidence that Ms Folbigg was involved in any pre-meditated murder of her children. It will be a matter for submission as to the weight that can be placed on this evidence.

JUDICIAL OFFICER: It's fair to say that that form of evidence is fairly novel in this country, I think.

CALLAN: It certainly is, your Honour.

JUDICIAL OFFICER: And did Professor Pennebaker produce the model on which he based his computerised text analysis?

CALLAN: There's some limited description of it in his report, your Honour, but no.

JUDICIAL OFFICER: So no-one has had the opportunity to examine the model.

CALLAN: Correct. Your Honour, the report of Dr Furst dated 21 July 2021 sets out the views of that Forensic Psychiatrist who comments on Ms Folbigg having, to his observation, emotional deficits including difficulties in relation to forming close bonds, insecurity, anxiety, and tendencies towards depression.

Your Honour, there are two reports from Associate Professor Janine Stevenson of 3 and 28 September 2021. She is a Consultant Psychiatrist and Psychogeriatrician and her reports address issues around the use and permissible interpretative process to be applied to journals.

Your Honour, there are also reports from Associate Professor David Butt dated 8 September 2021 and 2 December 2022. He is an Associate Professor in Linguistics at Macquarie University who addresses whether there is a plain meaning, or ordinary English meaning, that can be ascribed to Ms Folbigg's diaries. In his view, the diaries do not evoke one interpretation which is supportive of Ms Folbigg's guilt, and specifically that feelings of responsibility as a mother have been misinterpreted as admissions of agency in the deaths of the children.

Your Honour, there is a report of Dr Kamal Touma dated 13 September 2021. Dr Touma, who is an Analytical Psychotherapist, engaged in a number

of sessions with Ms Folbigg. He concludes that Ms Folbigg suffered from negative attributes of self which influenced the contents of her diaries, and they do not reveal evidence that Ms Folbigg harmed her children.

Your Honour, there is a report of Professor Anthony Korner of 5 September 2022 who is a Psychiatrist and Psychotherapist who gives evidence in relation to the concept of analytical psychotherapy which informed Dr Touma's approach to Ms Folbigg's assessment, and he reviews Dr Touma's approach to interviewing Ms Folbigg.

Finally, your Honour, there is a report of Dr Katie Seidler dated 23 February 2022. Dr Seidler is a Clinical and Forensic Psychologist who reviewed a number of Ms Folbigg's diaries as well as the reports of other experts in the Inquiry. She concludes the diaries do not contain confessions that Ms Folbigg killed her children, and do not exhibit indications of uncontrollable rage by Ms Folbigg towards her children. She explains how the diaries can be understood in light of the diagnosis of Ms Folbigg by Dr Michael Diamond as suffering from complex PTSD, amongst other things.

Dr Seidler subsequently assessed Ms Folbigg over a period of 3 hours and 45 minutes, and in a further report dated 26 October 2022, concluded nothing in that interview contradicted her earlier opinion about Ms Folbigg. She further concludes there was a lack of convincing evidence that Ms Folbigg was someone prone to violence, abuse, rage and dyscontrol. She also explains that some of Ms Folbigg's reactions which might be viewed as “abnormal” should be understood by reference to her history of trauma and her mental health.

I'll now turn to the evidence which has been obtained from experts who will be called to give evidence in this hearing segment about the diaries and the related question of Kathleen Folbigg's mental health.

Your Honour, as with the engagement of cardiac and genetic experts, by letters to the parties dated 5 December 2022 those assisting sought the input of the parties to ensure the right experts were engaged and that they were asked the right questions. The Inquiry received comments from Ms Folbigg's representatives and the Australian Academy of Science. The Academy proposed an additional expert, Dr Joanna Garstang, be engaged, and that has occurred. Otherwise, it was suggested some additional material be provided to the experts, and that occurred, and some questions were reworded, bearing in mind the comments received from those parties.

Your Honour, the psychiatric and psychology experts engaged by the Inquiry, Dr Yumna Dhansay, Dr Kerri Eagle and Mr Patrick Sheehan were asked to address the following questions: first, whether Ms Folbigg, at the time she wrote particular diary and journal entries, was suffering from a recognised diagnosable psychiatric illness; second, whether Ms Folbigg, at the time of writing the diaries, suffered from any other mental health concern, such as maternal postpartum adjustment in bereaved and non-bereaved mothers; third, whether any aspect of Ms Folbigg's mental health illuminates what is written in

her diaries, and the manner in which specific content in those diaries (namely those entries relied upon as admissions or demonstrations of guilt) should be read and interpreted, including whether these entries included admissions of guilt as to harming her children; and finally, what contextual considerations were relevant to reading or interpreting Ms Folbigg's diaries.

Your Honour, the experts were also asked whether they considered they could answer those questions in the absence of an interview with Ms Folbigg. Each of them, for various reasons, did not consider the lack of interview an impediment to being able to express their views. Reasons that were pointed to included the passage of time since the point when they were being asked to consider, that is, the time when Ms Folbigg was writing her diaries in the late 1980s and during the 1990s. They also pointed to the number of interviews that she had undertaken with other individuals, and the significant corpus of material that had been generated which dealt with her life up to that point.

Can I deal first with Dr Yumna Dhansay, who is a Child and Family, Forensic, Perinatal and Adult Psychiatrist. She will give evidence next week. In her report dated 13 January 2023, on the topic of psychiatric diagnosis, Dr Dhansay states that Ms Folbigg described symptoms of anxiety but it was unclear if she experienced significant symptoms of anxiety during the period in question. She also stated that Ms Folbigg had features of complex PTSD but did not fulfil the requirements for diagnosis. Ms Folbigg did not, in her view, suffer from psychosis during the time periods the diary entries were written nor did she fulfil the criteria for the diagnosis of borderline personality disorder.

In Dr Dhansay's view, Ms Folbigg suffered from low mood and fulfilled the criteria for the diagnosis of persistent depressive disorder, with periods of more intense low mood which represented episodes of major depressive disorder. In her view, Ms Folbigg had psychological vulnerabilities due to her anxious attachment style and the sequalae of her significant early childhood trauma. Dr Dhansay also considered it was possible Ms Folbigg had developed prolonged grief disorder with the duration and/or severity of her bereavement lasting several years.

In Dr Dhansay's view, Ms Folbigg likely struggled with maternal adjustment and becoming a mother herself may have also triggered emotions related to her childhood trauma. In relation to the diary entries, Dr Dhansay noted they are written to a large degree with little emotion, which is noteworthy since it would be expected that if Ms Folbigg murdered her children as a result of having lost control, or being in a state of exasperation or frustration, there would have been some expression of more intense emotion in her diaries. Dr Dhansay concludes the entries do not contain any admissions of guilt as to the harming of her children and that the diaries should be interpreted as having been written by a grieving mother who had suffered significant and repeated losses in the context of adjustment to parenting, grief, limited social support and marital discord, and on a background of significant disrupted attachment and history of numerous adverse childhood experiences and fragmented sense of self.

Your Honour, Dr Kerri Eagle is a Forensic Psychiatrist who furnished a report dated 10 January 2023 and will give evidence next week. By way of psychiatric diagnosis, Dr Eagle's view is that Ms Folbigg appears to have an episodic mood disorder such as a major depressive disorder of moderate severity. However, Ms Folbigg's mood symptoms do not appear consistent with a persistent depressive disorder. Whilst Ms Folbigg displayed some features of PTSD, Dr Eagle opines Ms Folbigg has no ongoing pervasive signs of complex PTSD since her incarceration. Dr Eagle's view is that Ms Folbigg would not satisfy criteria for a borderline, antisocial or any other personality disorder and, in her view, Ms Folbigg displayed signs and symptoms of maternal grief following the death of her children, with features which may be consistent with the proposed criteria for persistent complex bereavement disorder, which is not an existing diagnosis in DSM-5 but is a condition for further study. As to the diary entries, Dr Eagle concludes there is nothing in the diaries from a psychiatric perspective that would clearly indicate in and of itself an admission, including an admission by Ms Folbigg as to harming her children. Instead, the diaries were a coping mechanism for emotional distress throughout her life and were transitional objects in the context of motherhood, postpartum adjustment, maternal grief for her children and depression.

Your Honour, Mr Patrick Sheehan is a Forensic Psychologist who furnished a report dated 6 January 2023 and will give evidence next week. In his view, a diagnosis of persistent depressive disorder was available and some form of trauma symptomatology had been present during Ms Folbigg's period of journaling, but was not presented in a way consistent with the DSM-5 diagnosis of PTSD. He also expressed the view that a clear diagnosis of postpartum depression or similar was not available, but Ms Folbigg's problems with variable low mood and negative self-image were a recurring theme throughout the diaries. As to the diary entries themselves, Mr Sheehan concludes, the statement of personal responsibility in relation to the death of Ms Folbigg's children in the diaries was more in keeping with a troubled person attempting to cope with and make sense of the death of her children. Further, Mr Sheehan observes that expressions of resentment, desperation, guilt, self-disgust and fantasies of escape were normative experiences for women during early parenting.

Finally, your Honour, we have received the report of Dr Garstang. She is a Consultant Community Paediatrician in the United Kingdom with significant clinical and research experience working with families who have experienced sudden unexplained death of an infant. The conclusion of Dr Garstang's PhD research was that self-blame and guilt following sudden infant death is common and, when severe, may be related to underlying mental health problems such as anxiety or depression, and not related in any way to the cause of death or parental culpability. In her report to the Inquiry of 1 February 2023, Dr Garstang conducted a limited literature review of studies in relation to the psychological, physical and other reactions a mother may have in response to the sudden unexplained death of an infant. She critically appraises the studies and observes there is widespread recognition that bereaved parents suffer feelings of guilt and self-blame as part of their grief journey.

Dr Garstang also analyses relevant entries in Ms Folbigg's diaries. She concludes the expressions of self-blame and guilt in those diaries fit with those described in the literature or that she has witnessed in her clinical and research practice and does not consider them to be “true confessions of guilt”.

Your Honour, this body of evidence about Ms Folbigg's diaries from experts in the field of psychiatry, psychology and other relevant fields comprises one part of a broader evidentiary matrix concerning the diaries which is before your Honour. That broader matrix includes of course the diaries themselves. It includes Ms Folbigg's answers about the diaries during her police interview in 1999 as well as the evidence Ms Folbigg gave about the diaries in cross-examination in the 2019 Inquiry before Justice Blanch.

Your Honour, transcripts of both, that is the police interview and Ms Folbigg's evidence in the 2019 Inquiry, are in evidence. There are portions of the police interview in video format which will come into evidence and, your Honour, the whole of the audio of the evidence in the 2019 Inquiry, not in video form but in audio form, is also tendered and before your Honour. Your Honour, taking a step back, Ms Folbigg's diaries and the evidence relevant to those diaries in turn form one part of the overall body of evidence before your Honour. As I recognised at the outset of this opening, the ultimate task for your Honour is to consider all the evidence before you in arriving at a conclusion as to whether overall there is a reasonable doubt as to Ms Folbigg's guilt. That completes my opening.

JUDICIAL OFFICER: Before you do anything else, I think Dr Woods at one stage was rather anxious to say something. Has that anxiety dissipated?

WOODS: Indeed, your Honour, yes.

JUDICIAL OFFICER: Good. I take it no one else wants to say anything at this stage.

JORDAN: Excuse me, your Honour, if I may say something just very briefly.

JUDICIAL OFFICER: Yes, Mr Jordan. Yes.

JORDAN: As your Honour knows, for the record I appear for the Director of Public Prosecutions together with Ms Garrity. I just wanted to note in relation to some of this very recently obtained material, and I'm talking here directly about the very recent report in relation to modifier genes from Professor Cook and Professor Vinuesa. I think that was 1 February 2023. And I'm really just raising this more for your Honour's consideration at this stage. I'm not sure I have understood it correctly but the report does seem to indicate that there may have been some form of new testing on this topic of modifier genes, and if I have understood that correctly, I'm really just raising for your Honour's consideration what opportunities there might be in terms of having others being given an opportunity to review that testing and indeed to review the results of that testing.

JUDICIAL OFFICER: I think, Counsel Assisting will correct me, my understanding is that the additional testing was done by Professor Toft Overgaard and there was no additional testing done by Professor Vinuesa, I don't think. And, some additional testing, additional assays by Professor Schwartz.

CALLAN: Your Honour, I want to make sure we're not speaking at cross-purposes. The work, as I understand it,that was undertaken by Professor Cook and Vinuesa was to, as it were, reanalyse the existing whole genome sequences.

JUDICIAL OFFICER: I see.

CALLAN: And through that process identify this particular gene which they then posit may have the potential to have a modifying effect on the CALM2 variant but they - and that's partly, they say, or are supported by a 2018 article where that gene had been found to have a modifying effect elsewhere.

JORDAN: Your Honour, I'm very grateful to Counsel Assisting, that resolves the issue. It was my misunderstanding, there was no new testing conducted.

JUDICIAL OFFICER: That's certainly my understanding too.

JORDAN: Yes.

JUDICIAL OFFICER: Apart from, as I said, the assays done by Professor Toft Overgaard which were a bit earlier.

JORDAN: Your Honour, might I just note this from the very outset and it is important in terms of people who may be observing properly understanding the Director's role in relation to this non-adversarial Inquiry. We have listened carefully to your Honour's observations as to the need for efficiency in questioning, avoiding undue repetition, particularly in circumstances where in a non-adversarial proceeding the rule in *Browne v Dunn* has no work to do. In that context may we simply note that what may be perceived as a restrained approach to questioning on behalf of the Director of Public Prosecutions should not necessarily be taken to connote an acquiescent acceptance to all of the evidence and there may still be a lot of work to be done in relation to submissions after the evidence is heard.

JUDICIAL OFFICER: Let me make it quite clear for anyone who is listening. This is an Inquiry, it's not a trial, it's not an adversarial proceeding. A great deal of work has been done behind the scenes, both by Counsel Assisting me and those instructing them, and by the other parties. The evidence to be given is almost entirely expert evidence. I don't anticipate there would be cross-examination, in what I'd describe as a hostile form - for want of a better expression, and the absence of it won't affect me in my decision, nor will people be precluded from making submissions in relation to these matters.

JORDAN: Yes, thank you, your Honour.

JUDICIAL OFFICER: Does anyone else want to say anything at this stage?

CALLAN: Your Honour, if it's convenient to take a short adjournment so the courtroom can be reconfigured and then we'll deal with the tender of documents.

JUDICIAL OFFICER: Yes. We'll adjourn.

SHORT ADJOURNMENT

CALLAN: Your Honour, I hand up a list of exhibits on which by hand I've applied the date 13 February 2023, and by reference to that document can I explain a number of exhibits that I propose to tender?

JUDICIAL OFFICER: Yes. Thank you.

CALLAN: Your Honour, that is a 29-page document which, as your Honour will see, includes exhibits which have already been tendered before your Honour. Commencing at p 4, and I should say this document was circulated to the parties yesterday, your Honour will observe in red text reference to certain letters and briefing material, for instance, provided to the experts between November and now, and then for instance over on p 5 does your Honour see there has been further exhibits proposed still in red text by way of the further reports that have been received, for instance, from Professor Vinuesa, Cook and Arsov. Your Honour, it's through this document that we propose to tender the material which appears in the red text throughout this document, so that it may be before your Honour with the numbering that we've proposed as the exhibit numbers.

JUDICIAL OFFICER: Yes.

CALLAN: A significant proportion of this material are journal articles.

JUDICIAL OFFICER: This finishes at Exhibit 17, doesn't it?

CALLAN: Yes, and, your Honour, I'll come to exhibits after number 17 in a moment if I may.

JUDICIAL OFFICER: Does anyone want to say anything about the tender of this material?

WOODS: No, your Honour, we've checked it.

JUDICIAL OFFICER: Thank you. I admit into evidence those additions to Exhibits 5, 6, 7, 8, 9, 11, 13, 14 and 15 and 17 in the document handed to me this morning, marked in red in those documents, which I'll mark MFI 1.

MFI #4 INDEX OF EXHIBITS DATED 13/02/23 ADDITIONAL DOCUMENTS TO EXHIBITS 5, 6, 7, 8, 9, 11, 13, 14, 15 AND 17

CALLAN: Your Honour, I might just raise with the Court whether or not we've already - I think there were some MFIs marked on the last occasion.

JUDICIAL OFFICER: Were there? MFI 4, thank you.

CALLAN: Yes, your Honour.

JUDICIAL OFFICER: Did you want to say anything in particular about those documents? I didn't want to interrupt you.

CALLAN: No, your Honour, they have been progressively served on the parties and all I was going to observe was that Exhibit 15 comprises what is now a very large volume of articles, being articles that are referred to in the expert reports and we were concerned to ensure that they were before the Inquiry so that to the extent there's any particular reliance placed on those articles or reference made to them they're available to the Inquiry but also to the other experts. Your Honour, can I now hand up a schedule of tenders which are more relevant to the topic of Ms Folbigg's diaries? This is described as the proposed tender bundle for the second hearing block.

JUDICIAL OFFICER: Dated 13 February?

CALLAN: Yes, your Honour. Can that document be marked for identification?

JUDICIAL OFFICER: Yes.

MFI #5 SCHEDULE OF TENDERS RE KATHLEEN FOLBIGG DIARIES DATED 13/02/23

CALLAN: This document was also served on the parties yesterday, your Honour. Each item listed in this schedule is proposed to be tendered today, that is there's no different coloured font of relevance in that respect. Your Honour will see it includes originals of Ms Kathleen Folbigg's diaries. The diary compilation that I referenced in my opening, which is a transcribed corpus of all of the diaries, as well as the schedule of diary entries relied upon as virtual admissions in previous places, including at trial and in the 2019 Inquiry.

JUDICIAL OFFICER: Could I ask you this? You made reference in your opening to Professor Watkins. There doesn't seem to be any report of his in this document unless I'm mistaken. It's quite probable - as we go.

CALLAN: Your Honour, by reference to MFI 4, p 10, at p 10 we tendered the report of Professor Watkins as proposed Exhibit 14-10.

JUDICIAL OFFICER: Thank you. Is that tab 14-10?

CALLAN: Yes. Your Honour, coming back to MFI 5, I tender the documents and other items listed in this schedule which, as I've said, include the diaries, includes the briefing letters and reports of the experts engaged by this Inquiry

and also the reports that I refer to in my opening which were furnished on behalf of Ms Folbigg in support of her petition which pertained to the approach to be taken to the diaries. There is also, your Honour, as proposed Exhibit 32 a category of additional evidence which includes certain documents produced by Justice Health and Corrective Services, and a number of letters from Kathleen Folbigg to a friend which were the subject of consideration in, for instance, Professor Pennebaker's report, but were also furnished to the psychologists and psychiatrists briefed - engaged by this Inquiry to the extent they might relevantly assist in observing the way Ms Folbigg communicated with her friend over a substantial number of years. As I understand it, those letters are also relied upon by Ms Folbigg in respect of questions that were raised in the 2019 Inquiry of recent invention by her as to explanations for certain aspects of the diaries.

Your Honour, the tender list at MFI 5 also includes the reports of the more recently engaged cardiac genetic experts, Dr Abrams and Dr MacRae, and your Honour may observe proposed Exhibit 35 comprises journal articles which are cited in the reports we've received from psychiatrists and psychologists pertinent to, amongst other things, maternal bereavement and recurrent sudden infant death in infancy.

JUDICIAL OFFICER: The documents comprising proposed Exhibits 18 to 35 listed in MFI 5 should be admitted into evidence.

CALLAN: Your Honour, there are some non-publication orders in existence and also an application has been indicated on behalf of Ms Folbigg in relation to certain further non-publication orders which are sought. Ms Wootton will be dealing with those applications and the general topic of non-publication orders.

JUDICIAL OFFICER: Thank you. Yes, Ms Wootton?

WOOTTON: Thank you, your Honour. If I can deal with them sequentially, as it were. Your Honour made an order on 24 June 2022 at the request of Counsel Assisting. That order did not have a specified date of completion, but on 3 February 2023 your Honour made an order that all orders in the proceeding are to remain in force up to and including the commencement of the hearing today. In respect of the order made on 24 June I would seek to have that order extended until the conclusion of the Inquiry.

JUDICIAL OFFICER: Which order is that, I'm sorry. There's one of 24 June.

WOOTTON: It was 24 June. It was in respect of information given to the Inquiry about the Australian Genome Research Facility, and the Victorian Clinical Genetic Service in the form of--

JUDICIAL OFFICER: I see, yes. Does anyone have any objection to that order being extended to the end of the Inquiry?

WOODS: No, your Honour.

JUDICIAL OFFICER: The order made by me on 24 June 2022 in relation to the documents which have become Exhibit 14-03 shall be extended until the conclusion of this Inquiry.

WOOTTON: Your Honour, there was a second order which falls into that same category which was the order made on 3 February 2023 in respect of the discussion at the Directions Hearing on 3 February 2023, and I'd seek to have that order extended until the conclusion of this Inquiry.

JUDICIAL OFFICER: I'll just find that order. The non-publication order in respect of the fourth Directions Hearing made on 3 February 2023 shall be extended until the end of the Inquiry.

WOOTTON: May it please your Honour. The third matter is Counsel Assisting seek an order at the request of Corrective Services New South Wales in relation to the names of certain custodial officers. I believe your Honour has a copy and a copy has been circulated to the parties.

JUDICIAL OFFICER: Has anyone got any objection to that?

WOODS: We support that application, your Honour.

JUDICIAL OFFICER: Pursuant to s 12B of the *Royal Commission's Act 1923*, all names of Corrective Services New South Wales staff in the documents produced by Corrective Services New South Wales on 27 October 2022 and a related chronology contained in tabs 32-04 and 32-05 of the tender bundle are not to be published without the direction of the Inquirer or a judge of the Supreme Court. I will sign and date that order. Yes?

WOOTTON: Your Honour, there are a number of other orders which will lapse. Those representing Ms Folbigg have proposed a short minute of order which I understand my learned friend Dr Woods will deal with, following which an order in respect of Mr Folbigg's interests will also lapse and I understand my learned friend Mr Hastings of King's Counsel will deal with that order.

JUDICIAL OFFICER: Yes. Yes, Dr Woods.

WOODS: Your Honour, following on from the last directions hearing, we had discussions with Counsel Assisting about the formula of an order that could deal with matters relating to Ms Folbigg. Does your Honour have a copy of that?

JUDICIAL OFFICER: Yes.

WOODS: We press for orders 1, 2, 3 and 4.

JUDICIAL OFFICER: That's in the two-page document?

WOODS: It's the two-page document, your Honour, yes, headed "Non-Publication Order - 13 February 2023". The formula follows some

exchange of various versions between us and Counsel Assisting.

JUDICIAL OFFICER: Is there any objection to any of this?

WOOTTON: Your Honour, Counsel Assisting does not oppose the order being made.

JUDICIAL OFFICER: Have the other parties had an opportunity to see this order?

WOOTTON: Your Honour, it was circulated to all the other parties in hard copy this morning.

JUDICIAL OFFICER: Do any of the other parties have any difficulties with it? I make the orders in a document headed "Inquiry into the convictions of Kathleen Megan Folbigg Non-Publication Order - 13 February 2023", which has been signed by me. Yes, any others?

WOOTTON: Your Honour, there is a further order which will lapse. It was made in the interest of Mr Folbigg and I'd leave it to my learned friend Mr Hastings to indicate if he'd wish for that order to continue.

JUDICIAL OFFICER: Yes, Mr Hastings.

HASTINGS: Your Honour, may I ask that they continue as well, your Honour, till the end of the Inquiry.

JUDICIAL OFFICER: Why should these matters be suppressed?

HASTINGS: Sorry, your Honour?

JUDICIAL OFFICER: I mean, one of the issues in the case which I'm going to have to deal with at some stage, Mr Hastings, is the conflict of evidence between Mrs Folbigg and Mr Folbigg arising out of the circumstances of the death of Sarah. Now, that does involve - certainly not emphasising consideration of your client being involved in the death of the children - no-one's suggesting that and I should make that clear.

HASTINGS: Yes.

JUDICIAL OFFICER: But it does involve an evaluation of their evidence as to what occurred on that particular evening, Mrs Folbigg having given evidence in her record of interview and I think before Mr Blanch. Now, this material may have some relevance as to that, the to and fro which took place in connection with the various statements Mr Folbigg gave to the police.

HASTINGS: Well, the key word that your Honour just uttered was "may become relevant". As I see it at the moment, and I'm speaking from a position of little information, and it just doesn't seem to me to carry any weight at all, the other side of the equation is, your Honour, that these proceedings are

a cause of great distress to Mr Folbigg who's had to endure not only the loss of his children but constant reminders through these Inquiries to the point where even yesterday he was showing signs of distress about being reminded again, and one of the factors which would exacerbate it is the release of material which in the end is not really going to add anything to your Honour's determination. So I would ask that it at least continue until a point is reached in which it becomes necessary that your Honour bear it in mind.

JUDICIAL OFFICER: What do you say, Ms Wootton?

WOOTTON: Having regard to what my learned friend Mr Hastings has said, it may be, your Honour, that the balance would lie in favour of making the order until the conclusion of the Inquiry at which point when your Honour is ready to furnish a report, your Honour might form a more concluded view as to the relevance which would then inform whether this material should be subject to non-disclosure orders or not.

JUDICIAL OFFICER: Does anyone else want to say anything about it?

WOODS: Your Honour, may I have a moment? We support what Counsel Assisting has just said.

JUDICIAL OFFICER: I will extend the non-publication order in relation to the contents of the listening device transcript of 26 July 1999 which I made on 1 November 2022, up to and including the conclusion of the Inquiry. If I take the view at some stage it becomes necessary to take the contents of that device into account for the purpose of making my report, I will give the parties an opportunity to be heard again before I do so.

HASTINGS: Thank you, your Honour.

WOOTTON: Your Honour, there's one further matter which doesn't fall neatly into the area of non-publication but as your Honour would be aware, there are a number of documents in the tender bundle which have been the subject of redactions consistently with non-publication orders which either have been made or it was anticipated would be sought to be made. Can I make it clear that the parties at all times are able to access unredacted versions of those documents. It's not the case that they are redacted to the parties. It's only the case that they are redacted so that the versions can be made publicly available and not be the subject of non-disclosure orders.

Can I also indicate that it's proposed that at the conclusion of this hearing block, a confidential exhibit bundle would be prepared to make the record clear that unredacted versions are to be considered by your Honour and the parties.

JUDICIAL OFFICER: Thank you.

WOOTTON: Unless there's anything further from any other party.

JUDICIAL OFFICER: Thank you, Ms Wootton.

CALLAN: Your Honour, we're about to move to the evidence of Professor Toft Overgaard and Professor Nyegaard. Could we adjourn, your Honour, for 10-15 minutes in order to allow them to take their place in the witness box but also so that we can rearrange ourselves.

JUDICIAL OFFICER: I'll adjourn until you're ready.

CALLAN: Thank you, your Honour.

SHORT ADJOURNMENT

JUDICIAL OFFICER: Yes, Ms Roy.

<MICHAEL TOFT OVERGAARD AND METTE NYEGAARD, RECALLED(11.58AM)

ROY: Professors Toft Overgaard and Nyegaard, when your evidence concluded last year, you had shared with the Inquiry the details of your very recently completed additional functional assays concerning the CALM2-G114R variant and other variants. The Inquiry then adjourned to allow other experts assisting the Inquiry to consider that new evidence. In the time since the conclusion of the hearing last year, you've received a number of reports responding to your new evidence from the other experts assisting the Inquiry; is that right?

WITNESS TOFT OVERGAARD: Yes, that's correct.

WITNESS NYEGAARD: Yes.

ROY: You also received reports from some new experts that have joined the Inquiry, Professor Calum MacRae.

WITNESS TOFT OVERGAARD: Correct.

ROY: Professor Dominic Abrams.

WITNESS TOFT OVERGAARD: Yes.

ROY: And Professor Hugh Watkins.

WITNESS TOFT OVERGAARD: Yes, that's correct.

WITNESS NYEGAARD: Yes.

ROY: And it's correct that you've reduced your responses to these reports to writing in a further report which, for the record, is titled "Provision of additional material including comments to the evidence of Professor MacRae" dated 10 February 2023.

WITNESS TOFT OVERGAARD: That is correct.

WITNESS NYEGAARD: Correct.

ROY: This is a report authored by you jointly?

WITNESS NYEGAARD: Yes.

WITNESS TOFT OVERGAARD: Yes.

ROY: Your Honour, that report is found in tender bundle 2, Exhibit 6, tab 6 which was tendered by Ms Callan earlier this morning.

JUDICIAL OFFICER: Thank you, yes.

ROY: Is it correct that you've also prepared some further slides that you may wish to refer to in your evidence today.

WITNESS TOFT OVERGAARD: That is correct, yes.

WITNESS NYEGAARD: Yes.

ROY: Your Honour, for the record, a copy of that slideshow has been provided to those assisting your Honour. I will refer to individual slides by their number in the slideshow and then I propose at the conclusion of the Professors' evidence that those slides that they refer to will be compiled and added to Exhibit 6 in the same manner as the slides were done in their previous evidence.

JUDICIAL OFFICER: Thank you.

ROY: I would first like to ask you some questions about the article that appears in the tender bundle at Exhibit 15, tab 17, which is a pre-print article titled - and I don't need you to turn it up - titled "Proactive variant effect mapping to accelerate genetic diagnosis for paediatric cardiac arrest" dated 12 January 2022.

JUDICIAL OFFICER: Tab 15-17 is it?

ROY: Tab 15-17. The lead author is Brendan Floyd and Professor MacRae is a co-author.

WITNESS TOFT OVERGAARD: Yes.

ROY: You're familiar with the pre-print?

WITNESS TOFT OVERGAARD: Yes.

WITNESS NYEGAARD: Yes.

ROY: You respond to this article in the course of your response to Professor MacRae's report.

WITNESS TOFT OVERGAARD: Yes.

ROY: Incidentally, what is a pre-print?

WITNESS TOFT OVERGAARD: So it's something you can publish before it has been peer reviewed, which means it has not been looked upon by other experts.

ROY: And so this was a pre-print meaning it hadn't been peer reviewed.

WITNESS TOFT OVERGAARD: Yes.

ROY: And it has since been published?

WITNESS TOFT OVERGAARD: I think it's out now in an acceptance for publication motion so it has been peer reviewed as I understand and not published in its final version, so what we have is so-called proof pages that the author's made - make small corrections to.

ROY: The version of that, that's available at - to those assisting your Honour and the parties - appears in Exhibit 15, tab 257, published - the publication appears to be Circulation Genomic and Precision Medicine, 2023, edition 16 and the lead author is still Floyd. What does that--

JUDICIAL OFFICER: That's the one at tab 15-17 is it?

ROY: It's 15-17 is the pre-print and then with some minor amendments it's in an updated form behind tab 257 of Exhibit 15.

JUDICIAL OFFICER: I have it, yes, thank you.

ROY: In your words, what does this article report?

WITNESS TOFT OVERGAARD: Well, long or short?

ROY: Short please.

WITNESS TOFT OVERGAARD: So it reports on using - it's an interesting scientific approach so it attempts to assign a functional property to all possible calmodulin variants so that - and the functional property is measured in a yeast system, so it's a yeast complementarity approach, so what you do is sort of a high throughput, as we understand it, a high throughput screening of the - I think there's 2831 possible calmodulin variants and then you look at how the yeast with the variant will grow compared to the yeast with the normal calmodulin.

ROY: So to make sure I understand that. Every possible variant in CALM1, 2 and 3--

WITNESS TOFT OVERGAARD: Yes.

ROY: --has been put into yeast?

WITNESS TOFT OVERGAARD: I think they may not manage to get all of them in there. It's a sort of random approach but they get a pretty large coverage map and then they infer from that to the rest, and then this was presented in a paper in 2017.

ROY: So this builds on data that was presented in 2017.

WITNESS TOFT OVERGAARD: That's the yeast data. And then the Floyd paper take those data and uses a subset of known calmodulin human variants

and assigns a value to those whether they're pathogenic or benign, and they take those values from ClinVar or the gnomAD databases and then they computer generate or they generate an algorithm that predicts then the likelihood of cardiac pathogenicity for the other variants based on this yeast data.

ROY: So staying just with the yeast for the minute.

WITNESS TOFT OVERGAARD: Yes.

ROY: Not every variant but a large number of possible variants are put into yeast, one at a time.

WITNESS TOFT OVERGAARD: Yes.

ROY: And then the yeast is observed.

WITNESS TOFT OVERGAARD: And what they measure is how well the yeast divide or live you can say, so can they live with this particular calmodulin variant.

ROY: So how the yeast grows; is that right?

WITNESS TOFT OVERGAARD: How it grows, yes.

WITNESS NYEGAARD: Yes.

WITNESS TOFT OVERGAARD: So they just grow just like the normal.

ROY: That data was published in 2017.

WITNESS TOFT OVERGAARD: Yes.

ROY: And then what's happened in 2022 and now 2023 is what?

WITNESS TOFT OVERGAARD: They tried to couple those, that readout for yeast to cardiac pathogenicity likelihood score.

ROY: And this produces a predictive tool.

WITNESS TOFT OVERGAARD: Yes. That's the theme of the paper. I mean, the beauty of this is that you have then data for all possible variants so if you encounter a new variant never seen before, you would have some sort of functional data already made and a score from that.

ROY: What is the relevance of the growth of yeast to the functional effect of a variation in a human being? How do those two things translate?

WITNESS TOFT OVERGAARD: They may be difficult to translate. So in my mind this says something about the some core property of the calmodulin and

the effect of the variant, which is important for yeast growth which may or may not be important for cardiac pathogenicity.

ROY: Now, you took the underlying data that was published in that report and you have prepared in your report and on some slides--

WITNESS TOFT OVERGAARD: Yes.

ROY: --some visual representations of that data.

WITNESS TOFT OVERGAARD: Yes. I think it's slide 2 and maybe--

ROY: Can we look at slide 2, please.

WITNESS TOFT OVERGAARD: This is, of course, a little bit complicated but--

ROY: Can you explain what this slide shows?

WITNESS TOFT OVERGAARD: Yes. So here we - what we did was just take the data presented in the Floyd paper and plotted the relation between the yeast survival score, fitness score, which is on the X axis. I'll see if I can yeah, do it like this. So on this X axis this is a measure of how the yeast will grow with the particular variant in it. A measure of one, that's when you have non-mutated calmodulin. The dots that we have put in, that's the variants that were used to train this algorithm for predicting the cardiac pathogenicity score, and this is what is - the value from that prediction is on the Y-axis, so you can see if it's bad for the yeast you will be in this area, if it's bad for the heart--

ROY: If it's bad for the yeast it will be where the arrows are pointing to G114R, G11--

WITNESS TOFT OVERGAARD: To the left. To the left, yeah, so on the left-hand side.

ROY: --4W, yes?

WITNESS TOFT OVERGAARD: If it's bad for - giving you a--

ROY: Let me stop and try again. I think I was speaking over you. The X-axis to the left suggests that the yeast is not going very well?

WITNESS TOFT OVERGAARD: Yes.

ROY: Crosses over at one?

WITNESS TOFT OVERGAARD: One is the, you can say, the non-mutated calmodulin.

ROY: Then some actually improve the yeast growth?

WITNESS TOFT OVERGAARD: Yeah, but the variant here, with the value above one they will grow better than - they will be here. I don't know if that's visible but to the right of one, yes, they will grow better.

ROY: What does the Y-axis show?

WITNESS TOFT OVERGAARD: That's the Floyd paper output, so you can say that's converting this into a likelihood ratio for cardio pathogenicity.

ROY: So the higher it is on the Y-axis the more likely it is to be pathogenic?

WITNESS TOFT OVERGAARD: Yes.

WITNESS NYEGAARD: Correct.

ROY: According to the Floyd paper

WITNESS TOFT OVERGAARD: Yes.

WITNESS NYEGAARD: Yes.

JUDICIAL OFFICER: Then how does the conversion take place? Sorry, at the moment I'm trying to - I'm struggling to see the relationship between the X and Y-axes. I understand what you say about the yeast score I think but how does it correlate with what appears on the Y-axis?

WITNESS TOFT OVERGAARD: I think that's the exact topic of the Floyd paper, to try and convert the yeast data to a cardiac prediction score, and what they use are the exact green and red points on this, that's the training data set, and the red ones are - they take the pathogenicity value from ClinVar, so the ACMG scores, and the green ones are from gnomAD, so that's supposedly benign. So you can of course immediately see it's not all - I mean it's not a completely discriminative between these, but what you do note is that in this high likelihood of pathogenicity corner there is only severe ClinVar variants or pathogenic ClinVar variants.

JUDICIAL OFFICER: Yes.

ROY: Would it be right to interpret this however as being a poor predictor of non-pathogenicity?

WITNESS TOFT OVERGAARD: It would seem so if you just look at this input data.

ROY: You're indicating the N541 and the N98S variants, that area?

WITNESS TOFT OVERGAARD: Yes, so just for highlighting the ones that we have performed data on for the Inquiry, they are down here with a reasonably high yeast score and a low likelihood of cardiac effect.

ROY: Given the inability of the tool to accurately predict pathogenicity in those variants, is the tool otherwise useful?

WITNESS TOFT OVERGAARD: We may not be the best judge of that, but of course we can say that the - in this corner you actually only find pathogenic, so none of the gnomAD variants are up there, at least the ones they use for training there.

ROY: Would it be fair to say then that the tool appears to predict pathogenicity with a high degree of certainty but to not predict non-pathogenic variants well?

WITNESS TOFT OVERGAARD: I would hesitate to be the judge of that, the topic of the paper and the results they show, they use this predictor to actually assign pathogenicity to two variants that are VUS and then they use it to you can say down-classify or say that another variant that is a VUS is not - probably not pathogenic.

JUDICIAL OFFICER: Can I just put what I think Ms Roy is asking a slightly different way? You say it's effective to show pathogenicity in certain cases?

WITNESS TOFT OVERGAARD: That's what the authors state, yes.

JUDICIAL OFFICER: But what you're saying the weakness is is that whilst the authors can demonstrate it in some cases, it doesn't lead to a conclusion that other variants are or are not pathogenic, is that?

WITNESS TOFT OVERGAARD: I would agree with that. I think this is a scientific paper aiming at giving you a tool as a cardiologist to help clarify, and I think in some cases it might correlate and in other cases it doesn't.

JUDICIAL OFFICER: Sorry.

ROY: Does this study contribute anything in addition to the assays that you performed and the other assays reported in Brohus that tell us about G114R?

WITNESS TOFT OVERGAARD: So I think at least it shows us that this particular residue, the G114 is important, also for yeast growth. So it's a critical residue for calmodulin. I mean we believe all residues are critical but if maybe you recall, even this residue was even conserved down to the yeast calmodulin site, and I think this is what you see here, the yeast score is low and when you use the algorithm that they derive from using known pathogenic and non-pathogenic variants, the G114 variants end up in the really high likelihood of being pathogenic.

ROY: This is a predictive tool.

WITNESS TOFT OVERGAARD: Yes.

ROY: Your assays studied the actual functional effects of the G114R variant and some other variants on the binding--

WITNESS TOFT OVERGAARD: So, you can say here you study functional effects in yeast. The functional effects we look at are more directed to cardiac ion channel targets which are not present in the yeast.

ROY: So the assays you performed at least would be better predictors in terms of cardiac function than a yeast study?

JUDICIAL OFFICER: Or are they more directed to cardiac function?

WITNESS TOFT OVERGAARD: It's the at least - let me say it this way - I think we have a more direct idea of the potential mechanism from our assay than from this. I think they're complementary. Yes.

WITNESS NYEGAARD: Yeah, they are complementary. Yeah.

ROY: Professor Nyegaard, you don't disagree with anything that's been said I take it?

WITNESS NYEGAARD: I agree with everything, yeah.

ROY: You've made some other criticisms of that article which are in writing. I'll move now to the evidence that you shared with us last year, the additional assays after the Brohus article. You indicated an intention to seek to publish those results.

WITNESS TOFT OVERGAARD: Yes.

ROY: What's the status of those efforts?

WITNESS TOFT OVERGAARD: I'm ashamed to say we have not been able to prepare the paper yet, so we have it in an almost ready version, soon to be published, at least to the bio - bioRxives, yeah.

ROY: Where in the process of peer review is it, if anywhere?

WITNESS TOFT OVERGAARD: It's not in peer review yet, no, no.

ROY: I understand you added one further analysis, not an assay but a further analysis to that work?

WITNESS TOFT OVERGAARD: We did look at the G114W mutation as well.

ROY: Is that reflected in slide 1? Can you bring that up?

WITNESS TOFT OVERGAARD: Slide 1 is at least we can look at the--

ROY: While it's coming up, can you tell us about the G114W work that you did?

WITNESS TOFT OVERGAARD: Yeah, so we used G114W in the same assay

and saw the same reduction of binding to the sodium channel.

ROY: So it was a further assay, I apologise.

WITNESS TOFT OVERGAARD: Yeah.

ROY: Yes, and that's yet to be published?

WITNESS TOFT OVERGAARD: Yet to be published.

ROY: I am sorry, we were at cross-purposes. Can we still look at slide 1?

WITNESS TOFT OVERGAARD: Slide 1 is - for me?

WITNESS NYEGAARD: Yeah.

ROY: Can you explain what this shows?

WITNESS TOFT OVERGAARD: So this is - I think we were asked at some point if why we said this was a dramatic change, the Folbigg mutation, so I'm not sure, I mean it's hard to visualise because we cannot see the protein yet, so just wanted to show the difference in the amino acids and I brought the models if I can show them.

ROY: You're welcome to show us. Your Honour, I note for the record that Professors Toft Overgaard and Nyegaard have the models that are depicted in the photographs. I don't propose to tender them or mark them, they're reflected in the photographs.

WITNESS TOFT OVERGAARD: I don't know if that's useful but in normal calmodulin that we all have in position 114 we have a glycine residue which is the smallest amino acid we have.

JUDICIAL OFFICER: That's the first one on the slide?

WITNESS TOFT OVERGAARD: That's the first one to the left, yeah.

JUDICIAL OFFICER: Thank you.

WITNESS TOFT OVERGAARD: Now in a protein the nitrogen, the blue one would connect to another amino acid, and one of the red ones would connect to another amino acid, so it's part of a chain. So in the - you could say in the family that we also have in the Brohus article, there's a family with a G114W, so a mutation to Tryptophan. This is this guy. That's the third one and I think everyone agrees this is pathogenic for that particular family, so you can see of course the side chain, is called here, is the largest one we can find, and then if we take the mutation in the Folbigg family..(not transcribable)..so this is an arginine, so in terms of size it's pretty much the same size as the G114W. There's obviously a difference because this - yeah, this part is positively charged whereas this Tryptophan, so this likes water and negative

charge, this likes oil and it's hydrophobic, so it likes to be packed away inside. So they're similar in size but have slightly different properties.

ROY: What if anything does that tell you about the relevance of looking at the phenotype of the G114W family for the purposes of predicting pathogenicity of the G114R variant?

WITNESS TOFT OVERGAARD: So, I think as far as it's hard to imagine that you don't have an effect if you have changed into this arginine. We know that the glycine residue is critical for that exact site in calmodulin, it's helix terminating residue, it makes a turn, that's only possible if you don't have a side chain attached to it, so it's definitely changing something in the protein, and this is what is reflected in the data that we produce.

ROY: Yes, but this is looking at - we were looking at G114W because it appears in a family in the CALM3 gene.

WITNESS TOFT OVERGAARD: That's correct.

ROY: And Professor MacRae has suggested that it may not be valid to look at the effects of a variant in the CALM3 gene to infer what may happen in the CALM2 gene. You've responded to that in your most recent report on page 11, which is on page 117 of Exhibit 6, tab 6 in the tender bundle, and you've prepared some further information on a slide which is my slide 15; I'm not sure if it's your slide 15.

WITNESS TOFT OVERGAARD: I think so.

ROY: Can you explain what this shows, and is this better directed to Professor Nyegaard, this question?

WITNESS NYEGAARD: I think we can both answer that. So, when we found the first mutation it wasn't - this was in calmodulin 1, we were not sure that mutations in calmodulin 2 and 3 would produce the same phenotype but time has shown that this is actually the case. So this is what the data shows now, that you can have a variant in calmodulin 1 and you can have the same variant in calmodulin 2 and 3 and they produce the same phenotype. So at least for the cardiac arrhythmia they appear to be interchangeable.

ROY: Looking at this table in particular, and N98S, would seem to identify - indicate both for CALM1 and CALM2 mixed phenotypes in both--

WITNESS TOFT OVERGAARD: Yes, so the reason this particular variant is interesting, first of all, it's seen in 20 different individual families or persons; second, it has a - it's part of a Brohus article so it has effect on calcium binding that's very similar to the Folbigg variant and it can produce a range of different phenotypes, and personally I believe this because since the calcium affinity is only moderately affected, it's slightly variable which of the ion channels that calmodulin regulate is affected and to what extent.

ROY: So it's been demonstrated a number of times just through the course of your evidence that this is a very fast moving field with new research regularly.

WITNESS NYEGAARD: Yes.

ROY: As an example of that, just this morning you drew the Counsel Assisting team's attention to another pre-print article that was published in the last few weeks.

WITNESS TOFT OVERGAARD: Yes, the last few days I think.

ROY: The article is titled, "Arrhythmia-associated calmodulin variants interact with KCNQ1 to confer aberrant membrane trafficking and function", and the lead author is Po Wei Kang.

WITNESS TOFT OVERGAARD: Yes.

ROY: Those assisting your Honour only became aware of the article immediately prior to the hearing this morning, and I anticipate in due course seeking to tender it, to join the other academic cardio-genetic articles in Exhibit 15. In very brief terms, are you able to describe what that article reports?

WITNESS TOFT OVERGAARD: So just very briefly they have looked at a number--

JUDICIAL OFFICER: Do you have a copy of the article available?

WITNESS TOFT OVERGAARD: I don't at the minute, your Honour, I'm sorry.

JUDICIAL OFFICER: All right, that's all right. Go ahead.

WITNESS TOFT OVERGAARD: So they are looking - the authors are looking at a range of calmodulin variants and the effect of - on the potassium channel KCNQ1 potassium channel, and what they see is a rather specific effect - they look at the G114W variant among a number of others and they see that this variant seems to enhance the number of potassium channels that is - I forgot the word - translocated - transported to the cell membrane. So in order for the potassium channel to have an effect, it needs to be on the outside of the cell membrane, so the calmodulin is important for transporting potassium channels to the cell membrane. So this particular variant seems to enhance the transport.

ROY: Was that a similar effect to the variant identified in the Kato paper?

WITNESS TOFT OVERGAARD: It's similar in the fact that it affects the potassium channel but I think in the Kato paper they showed a difference in the channel's ability to, well the potassium ion current and so not - I don't think they looked at the transport as far as I recall.

ROY: So there's a different effect.

WITNESS TOFT OVERGAARD: It's a different effect but it of course affects you can say the overall potassium activity.

ROY: And so while the calcium channel effects of calmodulin variants is relatively well-documented, and then at the end of last year you identified an effect on a sodium channel in this variant, this paper identifies other effects on potassium channels including in relation to G114W; is that a fair summary?

WITNESS TOFT OVERGAARD: Yes. Yes, that's correct.

ROY: And would you agree that at this stage this effectively is simply opening up areas for further investigation.

WITNESS TOFT OVERGAARD: Yes.

ROY: And it's not possible yet to predict with any certainty what the implications are of those findings.

WITNESS TOFT OVERGAARD: I would say so. So for us it's just confirming what we are trying to say that this is rather complicated and the contribution of you can say the effect of each variant and calmodulin is unpredictable.

ROY: And it extends beyond calcium.

WITNESS TOFT OVERGAARD: And it extends beyond calcium.

WITNESS NYEGAARD: Yes. And this residue in particular seem to have played a role in many many things.

WITNESS TOFT OVERGAARD: Which seems different--

ROY: By this residue you're referring to G114.

WITNESS NYEGAARD: 114, yes.

ROY: Whether the variant is W or R.

WITNESS NYEGAARD: Yes. That residue in its normal form is very important for many things, yeah.

ROY: And that's because of its location.

WITNESS NYEGAARD: Yes. We, or nature shows because of the extreme conservation that every residue is important but this particular residue is now involving four things plus the yeast.

WITNESS TOFT OVERGAARD: I think what you can say is it is in a different position than we have seen many other pathogenic variants and

non-pathogenic variants. So it has the potential to do something different from what we know already.

ROY: Those are my questions, your Honour.

JUDICIAL OFFICER: Thank you. Now, I think the parties have agreed on an order for further questioning. I don't have that document.

ROY: We can hand up a copy and, your Honour, we will make a copy of that paper that was just referred to you available to you when we get it ourselves.

JUDICIAL OFFICER: Thank you. Sorry, I do have it. Yes, Mr Hastings?

HASTINGS: I have no questions, your Honour, thank you.

JUDICIAL OFFICER: Mr Jordan.

JORDAN: Your Honour, I have a very limited number of questions but only for Professor Overgaard.

JUDICIAL OFFICER: Yes.

JORDAN: Professor Overgaard, you are one of numerous authors of the--

JUDICIAL OFFICER: Mr Jordan represents the Director of Public Prosecutions who is responsible for criminal prosecutions in this State. He's appearing as part of the Inquiry not as a prosecutor in these proceedings, I should add.

JORDAN: Yes, thank you, your Honour. I should have made that clear, thank you. I just want to ask you a few questions leading to the development of the 2021 article entitled "Infanticide versus inherited cardiac arrhythmias" and for shorthand I'll refer to it as the Brohus article.

WITNESS TOFT OVERGAARD: Yes.

JORDAN: You are one of numerous authors of the Brohus article.

WITNESS TOFT OVERGAARD: That's correct.

JORDAN: How did you come to be involved in the development of that article.

WITNESS TOFT OVERGAARD: So in 2019, I believe it was in June, I was approached by email by Professor Vinuesa who asked - she mentioned yeah, this new variant never seen before in the - in a special case in Australia and whether we'd be interested in characterising the function of that at the protein level. I believe she was referred to us by - I forget his name - an American cardiologist, highly esteemed cardiologist who pointed to our laboratory.

JORDAN: And may I take it from your last answer that this was the first direct

contact you had had with Professor Vinuesa.

WITNESS TOFT OVERGAARD: Yes.

JORDAN: And are you able to identify in general terms how the various involved parties went about developing the article, given that there are so many authors covering such a wide range of different areas of expertise.

WITNESS TOFT OVERGAARD: I'm not sure exactly the breadth of the question but of course each expert within their theme gave their contribution. So we provided the data for the calmodulin characterisations. So we had really very little to say on the histology features or the potassium channel characterisations, the genetic description. That was not our area of expertise.

JORDAN: Maybe if I put it this way. Was there any particular person or persons who were the driving force behind the article and who took more responsibility for organising the various authors.

WITNESS TOFT OVERGAARD: I think it was quite natural that - that Professor Vinuesa was sort of coordinating because the origin of the article was the genetic new - the genetic sequencing and identification of variants in this family.

JORDAN: I'm not suggesting any criticism; I'm just trying to understand a little bit as to how it came about.

WITNESS TOFT OVERGAARD: I think we had a quite - if you look closely, so it was Professor Vinuesa and Professor Schwartz and I who were taking the responsibility as main or senior authors, or main authors.

JORDAN: Well, that leads to my next enquiry. Just to be clear, who are you identifying as the persons you describe as the senior authors of the article?

WITNESS TOFT OVERGAARD: That would be Vinuesa, Schwartz and me.

JORDAN: Okay. And did you each write different portions of the article and then put it together or for example, did somebody write the entire article with input from the others? How was it done?

WITNESS TOFT OVERGAARD: I'm not sure I can actually recollect that but we typically write the pieces that are, you can say, within our domain and then - then the writing process is when you are co-authoring, so many is that you circulate this or have a document that we are all editing at the same time.

JORDAN: In fairness to you, is it fair to say that given the passage of time you would not be in a position to look at the article now and say, "I wrote this bit, Vinuesa wrote this bit, Schwartz wrote this bit".

WITNESS TOFT OVERGAARD: Not sitting right there I think. I think maybe I

can go back and--

JORDAN: I don't want to take your time on that; I'm just trying to understand. Is it possible to show Professor Overgaard some of the transcript of the second day, particularly page 146.

JUDICIAL OFFICER: Is it possible to put that up on the screen or not?

JORDAN: Your Honour, if it assists, I can just show--

JUDICIAL OFFICER: Have you got a spare copy of it there?

JORDAN: Just the single page. I can show the hard copy directly to Professor Overgaard.

WITNESS TOFT OVERGAARD: Yes.

JORDAN: That's just one page. It's just the transcript of some of the evidence that you gave back in November, and if I could just take you directly please, Professor Overgaard, you see there at line 25 in the second sentence - and for the record I'll just put all of this out and read it out - in responding to one of the questions from Ms Roy you say at line 25:

> "I mean, I think what this is intended to mean is that the mutations in the CALM2 gene has been seen in sudden death in infancy which is highlighted in the paper the examples of that."

Ms Roy asks, "Is it also associated with deaths in other age categories?" You answer, "Yes." Ms Roy asks, "Is it particularly associated with sudden death in infancy and childhood as against other age categories?" You answer, "Not that I'm aware of." Then you go on to say, "Not that I'm aware of. I believe there are a range of ages for onset of disease." That's just so you've got the full picture there.

WITNESS TOFT OVERGAARD: Yes.

JORDAN: Firstly, just to confirm, that's still your position?

WITNESS TOFT OVERGAARD: If I may I think I may have - I may have misheard Ms Roy and only heard infancy. Because I am aware that you don't really get sudden death at a very high age, so.

JORDAN: Yes. Again, this is just by way of clarification. Would it be possible please to show Professor Overgaard tab 15-02, which is the Brohus article itself.

WITNESS TOFT OVERGAARD: Thank you.

JORDAN: Thank you very much. If the driver of the screen could please - thank you - go to page 17 using the red numbers. Do you have that in

front of you Professor Overgaard?

WITNESS TOFT OVERGAARD: Yes.

JORDAN: If I could invite you to look at the first sentence under the heading discussion, and there it says, "Our main findings are that the mother and her two female children were carriers of a novel and functional variant in the CALM2 gene associated with sudden death in infancy and childhood". Now, you'll I think anticipate my question. The evidence that you gave in November on the transcript was to the effect that your understanding was that this CALM2 variant could have consequences or application across all ages whereas the article appears to be indicating that it is pertinent to infants and children. Can you explain where you stand in relation to that question?

WITNESS TOFT OVERGAARD: So I would correct my evidence from November and say it's infancy and childhood. I think I probably heard Ms Roy as infancy.

JORDAN: The bottom line, the article is correct here and your evidence on this particular topic, very small topic admittedly in the scheme of things, you've now corrected?

WITNESS TOFT OVERGAARD: Yes.

JORDAN: Briefly, one other issue, as you are probably aware, there are two references in the Brohus article recording that child 4, that is Laura Folbigg, had been treated with pseudoephedrine. Are you aware of those references?

WITNESS TOFT OVERGAARD: Yes, but this was not my particular area of input.

JORDAN: Can you recall now who took responsibility for writing that part of the article?

WITNESS TOFT OVERGAARD: I don't think so. I would--

JUDICIAL OFFICER: You can look at the list of authors if that assists your recollection, professor.

WITNESS TOFT OVERGAARD: So sorry, your Honour?

JUDICIAL OFFICER: You can have a look at the list of authors on the - you don't have the whole article, do you?

WITNESS TOFT OVERGAARD: No.

JORDAN: It's on the front page of the article.

WITNESS TOFT OVERGAARD: From our working together and you can see the three main authors, most of the information from the Folbigg family was

provided by Professor Vinuesa which was natural because this is where the case came from.

JORDAN: Perhaps I can shorten it substantially by asking you this. Does the question of whether or not a particular substance, be it pseudoephedrine or something else, have any bearing on the death of Laura, is that something that is outside your particular specialised area of expertise?

WITNESS TOFT OVERGAARD: Yes.

JORDAN: Yes. Thank you.

JUDICIAL OFFICER: Thank you, Mr Jordan. Dr Woods.

WOODS: You've been shown the Brohus article, Professors. Had you ever known Kathleen Folbigg or had any contact with her or her family members before this?

WITNESS TOFT OVERGAARD: Not before this, no.

WOODS: Or indeed since?

WITNESS TOFT OVERGAARD: Not since we - I was at one point handed a phone and talked to her briefly.

WOODS: Yes. In relation to this matter, the preparation of the Brohus article, was your--

JUDICIAL OFFICER: One moment. One moment, Dr Woods. Dr Woods is counsel representing Ms Folbigg.

WITNESS TOFT OVERGAARD: Yes.

WOODS: Yes. Was your work done as a scientist or in some other capacity?

WITNESS TOFT OVERGAARD: No, as a scientist.

WOODS: The laboratory which is associated with your name conducts numerous experiments or studies of this kind?

WITNESS TOFT OVERGAARD: Yes. We - our main purpose is to understand the workings of calmodulin through the human's mutations or variants that arises.

WOODS: You referred a moment ago to the article by is it Po, the very recent article?

WITNESS TOFT OVERGAARD: I think - have I got that here?

JUDICIAL OFFICER: The one Ms Roy referred you to, we don't have it.

WOODS: It was just referred to a moment ago

WITNESS TOFT OVERGAARD: Frank Po I think maybe.

WOODS: Yes, is that right, and did you bring that to the attention of counsel?

WITNESS TOFT OVERGAARD: Yes.

WOODS: Is it your practice to keep up to date with all the latest genetic work?

WITNESS TOFT OVERGAARD: Yeah, we have an automatic search machine that looks for scientific papers related to calmodulin.

WOODS: Right. Very well. In the Brohus work, the studies that you conducted in that context, how many laboratories were involved?

WITNESS TOFT OVERGAARD: So we performed a very basic characterisation of the impact on calmodulin and then we invited our collaborators, so Professor Wayne Chen from Calgary.

WOODS: From?

WITNESS TOFT OVERGAARD: Calgary.

WOODS: Yes, Calgary is it?

JUDICIAL OFFICER: Canada.

WITNESS NYEGAARD: Canada,

WITNESS TOFT OVERGAARD: In Canada, and Professor Ivy Dick from Maryland, US.

WOODS: From the US and your laboratory is located in Aalborg, Denmark?

WITNESS TOFT OVERGAARD: Yes.

WOODS: Both of you work in the field at Aalborg University?

WITNESS TOFT OVERGAARD: In separate labs, so she is doing genetics and I am doing protein, yeah.

WITNESS NYEGAARD: Different departments as well.

WOODS: Very well. Yes. When you communicated with your Calgary colleagues and your colleague from the United States, did you correspond about this issue and pass drafts to each other of what you were working on?

WITNESS TOFT OVERGAARD: I'm not sure I get your question. We I think we--

WOODS: Did you circulate drafts between yourself and various other persons involved? Is that the way that you would work?

WITNESS TOFT OVERGAARD: Yeah, so all co-authors would approve the manuscript. We would also, you can say, discuss results when they come in of course.

WOODS: Yes. Then finally you'd get to a certain point where everybody would agree with the final version?

WITNESS TOFT OVERGAARD: Yes.

WOODS: That would be then presented for peer review?

WITNESS TOFT OVERGAARD: Yes.

WOODS: Very well. Is peer review a normal process of publishing in reputable journals?

WITNESS TOFT OVERGAARD: It's an essential process, yes.

WOODS: Essential part of it. Does it always perfectly ensure that every aspect of the document that you have published is--

JUDICIAL OFFICER: Dr Woods, how could he answer that? Perhaps I interrupted you. Finish the question.

WOODS: Does the process of peer review guarantee the accuracy of everything in the article?

WITNESS TOFT OVERGAARD: Of course not, and I - understand from Professor Wilde that I may have expressed that too rigorously in one of the reports.

WOODS: Yes. Nonetheless there is a significant difference in the value of publications which are peer reviewed as distinct from those which are not peer reviewed?

WITNESS TOFT OVERGAARD: Yes, because the non-peer reviewed has not been looked at by any other than the authors themselves.

WOODS: You've seen various comments on the material that you've produced. You've just referred a moment ago to some comments by Professor Wilde. Does anything that Professor Wilde say in his most recent commentary, referring to your work, cause you to alter your previously expressed opinions about the relevance of the sodium channel?

WITNESS TOFT OVERGAARD: No.

WOODS: In the course of the report which you produced dated 10 February,

which is tab 6-06, you set out in writing under four different headings your responses on various points. Now, I am not going to invite you to read it all or indeed read it to you because it's in black and white, but I do want to take you to a few parts of it. The first of the themes which you address in that report is a discussion about a difference between a genotype first approach to the questions that you're looking at, and a phenotype first approach. Can I ask you to explain what is the difference between those two approaches?

WITNESS TOFT OVERGAARD: I think perhaps Mette will explain.

WITNESS NYEGAARD: Yeah, maybe I can.

WOODS: Yes, thank you, Professor Nyegaard.

WITNESS NYEGAARD: Yeah, so a phenotype first approach would be that you collect patients representing the same phenotype or the same disease and then you look for genetic variants that are shared among those patients. In a genotype first approach you kind of go the opposite way where you find individuals carrying the same genetic variant and then ask what is the phenotypic spectrum of these, and this is a method that has become possible with all the whole genome sequencing efforts of a large amount of individuals. So, it has the advantage that you don't have to know in advance the actual phenotype of those patients and it's actually very good for rare disorders where a variant can affect or produce different phenotypes. Yes. So we brought this today to try to, you could say, understand some of the - it's just two different approaches and they both work.

WOODS: They both work in different contexts.

WITNESS NYEGAARD: Exactly.

WOODS: So you've got people who see patients every day taking a clinical approach. That's not your situation, is it?

WITNESS NYEGAARD: No, we are looking for something new. Yes, so in a way both are important. It can just - kind of help us to understand why there are these disagreements in ways of thinking.

JUDICIAL OFFICER: Can I ask you this, Professors. One of the critical differences perhaps between you and Professor Wilde, Dr Abrams and Dr MacRae is that they have adopted what - or come from is probably a better way of putting it - from what might be called a phenotype first approach.

WITNESS TOFT OVERGAARD: Yes.

WITNESS NYEGAARD: Yes.

WOODS: You've referred in your paper to some work, a study by Wilczewski of 2023. Could you explain the significance of that?

WITNESS NYEGAARD: Yeah, so we brought forward this particular paper not because it's about calmodulin. It's more to show that it is actually working right now, that when you take individuals with the same variant you can broaden the phenotypic spectrum so it's not just a theoretical possibility. So what is - what is hard in - for calmodulinopathy is that variants are so rare that it's almost impossible to collect - you know - enough amount of individuals with exactly the same variant. So it's really - it was brought more as - as a way of trying to understand how - you know - some of the differences, yeah maybe different ways of approaching, yeah.

WOODS: Is that reflected in your remark at page 109 of your report.

JUDICIAL OFFICER: It's page 3 of your report.

WOODS: Page 3 of your report, page 109 in the transcript for the Inquiry, "The advantage of the genotype-first approach is that it may better allow researchers to understand the full spectrum of symptoms."

WITNESS NYEGAARD: Yes.

WOODS: Very well. Now, you showed us a few moments ago some plastic devices illustrating certain matters, in particular--

WITNESS NYEGAARD: Molecular models, yes.

WOODS: The models. They're molecular models that demonstrate changes that can occur and which you've described under the heading "Visualisation of the G114R and G114W amino acid substitutions", and at page 110 - page 4 of your report - you've illustrated the normal, the Folbigg version and what you say is the pathogenic version. Do I understand you correctly in suggesting that the size of the Folbigg version is similar to the size of the known pathogenic version and that that size and position tends to suggest, but doesn't prove, that it also is pathogenic.

WITNESS TOFT OVERGAARD: It's correct. I mean, it's - I don't think we're suggesting the size as we are showing them as they actually are but just go to suggest that the change is similar in terms of the size of the amino acid that you have in this position.

WITNESS NYEGAARD: So you can - you could say that this position 114, I read in one of the reports that it was in a domain that was not important but that is not correct. So it has this - the smallest amino acid in the world because it's turning - it is sitting between two helixes that has to turn and there is not space enough for anything other than the smallest one.

JUDICIAL OFFICER: I think it was Dr Abrams who made that comment that because of its particular location, it didn't have the same effect; is that your recollection?

WITNESS TOFT OVERGAARD: Yes. So--

WOODS: What's the difference between location and residue?

WITNESS TOFT OVERGAARD: So I think it - it can refer to the same thing, so location in the amino and the protein is a particular residue. So residue means amino acid residue, so that's the particular building block in that particular location.

WOODS: Very well. Now, the slides that you produced yesterday, the first one of which was this slide with the photo of the molecular models, are there any other slides that you think may assist us in our understanding of these matters?

WITNESS TOFT OVERGAARD: If I should bring up one thing it would be to show the correlation between calcium binding and the particular phenotype that is the QT--

WOODS: Were these the ones that you prepared yesterday?

WITNESS TOFT OVERGAARD: Yes.

WOODS: Is it possible to show those?

JUDICIAL OFFICER: Which one do you want shown?

WOODS: The one that follows on from the - well, the first one of that series.

WITNESS TOFT OVERGAARD: It's probably a few slides down.

WOODS: We've dealt with that one.

WITNESS TOFT OVERGAARD: Yeah, so we go a couple of further slides.

WOODS: That's it, yes.

WITNESS TOFT OVERGAARD: So this one is - that's a different point but we can take that as well.

WOODS: Well, I'll come back to that when we deal with Dr MacRae.

WITNESS TOFT OVERGAARD: Yep.

WOODS: If we just leave that for the moment. Now, the second theme that you address in your document of 10 February is this: in vitro assays and whether they can inform on clinical phenotype. Now, first of all, what is an in vitro assay?

WITNESS TOFT OVERGAARD: So in vitro means that we are looking at things outside the body.

WOODS: Outside?

WITNESS TOFT OVERGAARD: Of the body and the cell where it's always working.

WOODS: So it's lab work in effect.

WITNESS TOFT OVERGAARD: Lab work.

WOODS: As distinct from having the patient in the clinic and talking to the patient and looking at their leg or whatever.

WITNESS TOFT OVERGAARD: You can see - yeah, an ECG is an in vivo measurement or you're measuring in vivo.

WOODS: You say you agree with various of the reports that in vitro assays are not to be or not necessarily useful for characterising something diagnostically. They're not used for diagnostic purposes.

WITNESS TOFT OVERGAARD: That's correct. It's not the intention to diagnose in these assays.

WOODS: But you say if I can understand it correctly, that they perform a foundational function in relation to which or on the basis of which further clinical work can be carried out.

WITNESS TOFT OVERGAARD: So what we determine is what the variation, what impact it has on the protein and that's you can say the building block for a potential effect in the full organism.

WOODS: You make the point at page 4 about the core function of calmodulin. Could you elucidate that briefly? How important it is it in processes of the heart?

WITNESS TOFT OVERGAARD: It's - I think we cannot over-estimate the function of calmodulin in the heart, so it's main function is to bind and sense changes in calcium and relay that change in calcium to ion channels, enzymes and other proteins.

JUDICIAL OFFICER: Dr Woods, is that a convenient time?

WOODS: Yes, your Honour.

JUDICIAL OFFICER: Just one thing. In the line of questioning you're asking now, I'm not going to stop you, but Professor Toft Overgaard and Professor Nyegaard in their evidence-in-chief gave a very detailed explanation of the importance of it.

WOODS: I'll bear that in mind, your Honour, after the break.

JUDICIAL OFFICER: Because it may only obscure it if you go further. The Court will adjourn until 2 o'clock.

LUNCHEON ADJOURNMENT

Yes, Dr Woods.

WOODS: Thank you, your Honour. Professors, just before we conclude, there was some mention about the pre-print article by Po Kang, Po Wei Kang?

WITNESS TOFT OVERGAARD: Yes.

WOODS: Do I understand this to be something that you brought to the attention of the Inquiry because it tends generally to support certain propositions you make?

WITNESS TOFT OVERGAARD: I think it shows something new, so it aligns with our proposition that we cannot expect to know everything and that this shows us maybe even the potassium channel could be involved with this.

WOODS: It was a pre-print article published 11 January 2023, is that right, your recollection?

WITNESS TOFT OVERGAARD: That's probably right, yeah.

WOODS: Very well, well we'll deal with that in due course and I'll have it tendered, your Honour, if I may, but I'll return to the report which we're dealing with, your report of 10 February. Now as I said, I won't take you through this all in detail because you've carefully prepared it. You've prepared it under the various themes that you've numbered one, two, three and four. You stand by the material contained in your report?

WITNESS TOFT OVERGAARD: Yes.

WOODS: Written report?

WITNESS NYEGAARD: Yes.

WOODS: Thank you very much. You stand by your work in relation to the Brohus article?

WITNESS TOFT OVERGAARD: Yes.

WITNESS NYEGAARD: Yes.

WOODS: I'll return to various slides in a moment, the ones from yesterday, but the third theme you deal with is something that relates to Dr MacRae's paper, Professor MacRae's paper or report. At page 8 of your report, you deal from the middle of page 8 to about the middle of page 9 with what you suggest is a point of agreement with Dr MacRae, but also something which you say is incorrect in his report. Do you stand by of course that material pointing out what you say is the incorrectness?

WITNESS TOFT OVERGAARD: Yes.

WITNESS NYEGAARD: Yes.

WOODS: You refer to the LLR algorithm in Floyd being highly inflated. Could you explain what you mean by that?

WITNESS TOFT OVERGAARD: So perhaps not the LLR algorithm itself, but the number of variants that the authors select for training the algorithm from the gnomAD data repository.

WOODS: When you say gnomAD, you mean G-N-O-M-A-D--

WITNESS TOFT OVERGAARD: That's correct.

WOODS: --being a proprietary collection of data relating to genetic variants?

WITNESS TOFT OVERGAARD: Yes, that would be necessary actually.

WITNESS NYEGAARD: Yes. So they will present around 120,000 individuals who have been sequenced and they are in a data repository that everybody can use and it's a really valuable tool to see what genetic variation are within the population, the human population. Yes.

WOODS: Why is the question of the rarity or otherwise of calmodulin significant?

WITNESS NYEGAARD: So--

JUDICIAL OFFICER: The rarity of calmodulin variants?

WOODS: The rarity of the - I'm sorry, the rarity of the variant, your Honour, I stand corrected.

WITNESS NYEGAARD: Yes, so for those genes - we explained that when we were here in November - how you can look at our genome and for those genes where you see less genetic variation compared to what you would expect by chance, those genes are what we call constrained. This means that they are depleted for genetic variation and it means that if there is a variation, there is an evolutionary force to remove them because individuals carrying variation in these genes will have what we call a lower fitness, so they will either die early, they cannot have children, they can work in many ways but they have lower fitness.

WOODS: The error that you suggest is apparent in Professor MacRae's report, what is that?

WITNESS NYEGAARD: Yes. Yes, so, the reason why we dived into this supplementary data that is in the publication is because he removed a particular paragraph that had to do with the specific variant G114R. And so

the - you could say the variant that he's using as he called them “benign”, we don't think that there are any benign variants but we don't have data exactly showing, but let's just say benign variant. So, in that table there are 38 missense variants listed - in CALM2, and all the calmodulin genes are equally constrained, meaning that this is way too many missense variants. So any expert in calmodulin would immediately pick out that there's something wrong, there are not that may missense variants in calmodulin 2, in gnomAD.

WOODS: How does that relate to the report which Professor MacRae has prepared in this case?

WITNESS NYEGAARD: Yes, so, this makes us worried that he is - he has a biased opinion about calmodulin 2 thinking that there are many more variants than there actually is - are.

WOODS: Thank you. If he were suffering from that misunderstanding, what would it mean for the opinions he offers about G--

WITNESS NYEGAARD: Yes, so if you think there are many missense variants in calmodulin 2, then you would probably downgrade the pathogenicity, kind of the rarity of this particular variant that we're talking about today.

WOODS: Yes, thank you very much. You set out at the bottom of page 9, the second half, a further explanation about that paper but I won't go into that in detail, you've written it. The fourth theme is genetics, which appears at page 10, and you accumulated a number of observations there, mostly about Professor MacRae's report, generally you've made that fairly clear I think and I won't invite you to regurgitate it all. One question appears to be significant, that is the question of supposed interchangeability or the non-interchangeability of calmodulin genes. There is a comment which you cite from his report in the middle of page 10 to the following effect, "The data do not support the assertion that all calmodulin genes can be treated as a single interchangeable protein for the purpose of variant analysis in vitro or in vivo". Could you explain why you don't agree with that comment?

WITNESS NYEGAARD: Yes, so first of all, it's a little bit peculiar because he is actually part of a study doing exactly that.

WOODS: Part of the pre-print study?

WITNESS TOFT OVERGAARD: Yeah.

WITNESS NYEGAARD: Yes. There they take one calmodulin molecule.

WITNESS TOFT OVERGAARD: And infers you can see the effect on all three genes because it's the same protein.

WITNESS NYEGAARD: Yes.

WOODS: Very well, thank you.

WITNESS TOFT OVERGAARD: But perhaps I can add what we also state here. If you look at the combined number of known calmodulin variants causing disease, the collection that Peter Schwartz is organising in the calmodulinopathy registry, we see several variants that is present in two or three of the calmodulin genes imposing the same phenotype. I believe you saw this table earlier today with the examples. We made another example on page 11.

WOODS: Page 11, yes?

WITNESS TOFT OVERGAARD: So just for looking at the CPVT phenotype, that--

WOODS: This is the table about two-thirds of the way down the page?

WITNESS NYEGAARD: Yes.

WITNESS TOFT OVERGAARD: Yes, so this is listing the number of individuals affected with CPVT in the calmodulinopathy registry and then versus the total number of people for that - each particular gene, and what we can see is that it's approximately 20% no matter what gene the mutation is , that is affected by CPVT.

WOODS: Do I take it that the general thrust of your comment about Professor MacRae on this subject is that he tends to underestimate the extent to which the three versions may be regarded as being similar?

WITNESS TOFT OVERGAARD: Yes.

WITNESS NYEGAARD: Yes, so at - you could say, like I mentioned before lunch, we could not have known that when the first variants were discovered and linked to CPVT that we did. We could not have known back then if it was like that but the data have shown us that it is like that, it appears to be interchangeable. The data are very clear on that and in particular the updated calmodulinopathy registry.

WOODS: You've also said at page 10 that you agree with Professor MacRae's statement that, "the clinical consequences of individual calmodulin variants are not readily predicted from existing data". I take it that when you refer to the interchangeability, you're qualifying it with that possible unpredictability as to what may arise in the future.

WITNESS TOFT OVERGAARD: That is correct so that it's adding on the complexity that we cannot foresee.

WOODS: And you point to another error at page 11 from what you say is page 35 of Professor MacRae's report where he appears to mis-cite your original work from 2012 when the original discovery was made; is that correct?

WITNESS NYEGAARD: Yes, that's correct. So he's stating that we identified

two regions in the genome that were equally - that both segregated with disease but the full publication identified only one region where we found the variant and then we validated the link to CPVT by identifying another patient with a *de novo* variant. This is the way that - this is kind of the golden standard within genetic studies. So I think he just maybe didn't read the full paper.

WOODS: Well, can I say on the subject of errors in scientific publications, you would agree that even highly qualified and distinguished scientists occasionally make errors.

JUDICIAL OFFICER: Like lawyers, Dr Woods.

WOODS: No doubt your own laboratory over the decades has made the odd blunder. Would that be true?

WITNESS TOFT OVERGAARD: I wouldn't know that but probably.

WOODS: Very well.

WITNESS NYEGAARD: This is the nature of the science, yes.

WOODS: Yes, very well. And the other comments that you've made, continuing there, carefully analysing Dr MacRae's report, you stand by those commentaries.

WITNESS TOFT OVERGAARD: Yes.

WOODS: Very well. And then you conclude on this report by saying that:

> "Having read the additional reports of Professors Schwartz, Vinuesa and others, Wilde, Kirk, MacRae, Abrams and Watkins, our conclusion has not changed from our first two reports."

Is that correct?

WITNESS TOFT OVERGAARD: That is correct.

WITNESS NYEGAARD: That is correct.

WOODS: Very well. Now, the final thing I want to do is take you to the slides that you prepared yesterday which may illuminate some aspects of what you presented in that report. Now, this has been reproduced in a paper form which I have. Your Honour, I'm told if it becomes evidence it may be Exhibit 6, tab 7.

JUDICIAL OFFICER: Yes.

WOODS: Do you have that in front of you, Professors?

WITNESS TOFT OVERGAARD: Not currently but probably on its way.

JUDICIAL OFFICER: It may be convenient to tender it now.

ROY: It may be a convenient point to tender the hard copy. By my count it should become Exhibit 6, tab 7.

JUDICIAL OFFICER: Six tab 7 that's right.

EXHIBIT #6 TAB 7, ADMITTED WITHOUT OBJECTION

ROY: I understand that hard copies have been distributed.

WOODS: Do you have it on the screen in front of you?

WITNESS TOFT OVERGAARD: Yes.

WOODS: Very well. Can I take you to the third of those which is coloured green and yellow.

WITNESS TOFT OVERGAARD: Green and red I think.

WOODS: The table. Relating to the LRR algorithm relating to the Floyd paper.

WITNESS TOFT OVERGAARD: And I'm sorry that's actually a mistake. It's the LLR algorithm.

WOODS: That's right.

WITNESS TOFT OVERGAARD: It's the LLR algorithm.

WOODS: It's LLR?

WITNESS TOFT OVERGAARD: Yeah.

WOODS: I'm sorry.

WITNESS TOFT OVERGAARD: Probably put it wrong.

WOODS: Just proving my point.

WITNESS NYEGAARD: Exactly.

WOODS: What can you tell us that assists the Inquiry arising from that table?

WITNESS TOFT OVERGAARD: So if I, with my limited knowledge of this I can perhaps explain. So all - each line here is one variant that was used to train the LLR algorithm. So all the green ones we checked and these should be variants that are present in humans. All the red ones are not found in humans so they are a mis-annotation because of the way you annotate variants so they are from the gnomAD - no, but you can find them there but

they are a mis-annotation so they don't exist in real life.

WOODS: They don't exist?

WITNESS TOFT OVERGAARD: No

WOODS: Very well; thank you. And the following figure is headed "isoforms". Could you tell us what significance that has in relation to the report.

WITNESS NYEGAARD: Yes, so this is - this is why the mis-annotation of the variants happens. It's a very common thing. My post doc did it as well. So if you don't know calmodulin you will have all these variants listed. So I will try to explain why it happens if - so to understand isoforms, I need to take you a little bit back to what is called the central dogma.

WOODS: The central?

WITNESS NYEGAARD: Dogma. Yeah. So this is how when you have a recipe in your DNA for a gene, how is that converted into a protein. This is what the body does. So you have the gene, you're on the top, this is DNA and it's double-stranded. It's this helix we all know.

WOODS: It's the top line?

WITNESS NYEGAARD: Yes. So if you think about the gene starting - yeah, so the - when a body needs the protein from that gene, it will first make a strand of something we call RNA or a transcript, so that's the second line. That is single stranded. And now the body can do different things. It can take blocks of this strand and use it as a recipe for a protein, and it can take either all these blocks that are shown on this figure--

WITNESS TOFT OVERGAARD: Some of the coloured blocks.

WITNESS NYEGAARD: Yeah. Or they can take some of them, and this is the way for the body to use the same gene to produce different proteins so that we get the complexity we have in the body so we can make more proteins than - than we have genes, yeah. So in the bottom line is shown how this particular transcript can be spliced. We call it spliced into three different - so either it can use all the boxes. We call them exons. In the middle one it has skipped the one in the middle, yeah, and in the last one it has skipped the little blue one, all right.

WOODS: Skip the?

WITNESS NYEGAARD: The little second-last - on my screen it's greenish.

JUDICIAL OFFICER: Greenish.

WOODS: This is the alternative splicing is it?

WITNESS NYEGAARD: Exactly, alternative splicing, yeah. So for calmodulin2 there is only - the body uses one transcript and this is the one that's producing the 149 amino acids, yes. But if you don't know that, there are in the databases lots of different transcripts from calmodulin2. So if you at the DNA level see a variant, we could imagine that it is in the red box. Calmodulin is not using that red box so that will not turn into a variation in the protein, all right. But if you don't know that, you would think that this is a missense variant that is being part of the protein.

WOODS: Are you saying that that - overlooking that point is what--

WITNESS NYEGAARD: Yes, many people do that, yeah. It's a very common mistake.

WOODS: Right. And do you say that the significance of that is that it causes those involved with the Floyd paper to--

WITNESS TOFT OVERGAARD: They over-estimated the number.

WOODS: To over-estimate the number of benign possibilities.

WITNESS TOFT OVERGAARD: Yes.

WOODS: Whereas in reality, the situation is different.

WITNESS TOFT OVERGAARD: Well, they used 38 variants. Only six of these are present in--

WOODS: Whereas only six are present.

WITNESS TOFT OVERGAARD: Only six out of the 38.

WOODS: Very well, thank you. Now, the following diagram, does that tell us anything more than we've established now?

WITNESS NYEGAARD: Yes. Yes, it shows us how do we know--

WOODS: Could I just say that for the record, this diagram says - it starts off, "CALM2 has only one major isoform". Yes?

WITNESS NYEGAARD: Yes.

WOODS: And the significance of that diagram?

WITNESS NYEGAARD: Yes. So one could ask how do we know that calmodulin has only one isoform. Where do we know that from? And we know that from a big project that has sequenced all the transcripts from a lot of different tissues from a lot of different people, and in this kind of table up here you can see that the transcripts are each labelled with this ENST. T stands for transcript. They have different numbers. So the one on top is the very major

form, so this is where we know that from, yes. And I have lined it out here on the bottom screenshot which one is the correct one.

WOODS: So the conclusion you reach at the bottom is, "If there is a missense variant or variants in an isoforms not used, they are not true missense variants".

WITNESS NYEGAARD: Yes. This is my way of trying to explain why it happens.

WOODS: Very well, I understand. Now, can I take you to a further diagram, the next - the fourth one over on page 10 headed, "Correlation between calcium binding reduction and one observable phenotype QTc".

WITNESS TOFT OVERGAARD: Yes, I believe that's probably mine.

WOODS: Sorry?

WITNESS TOFT OVERGAARD: That's probably my area.

WOODS: Very well. Can I ask you, Professor Overgaard, having that in front of you, what is the significance of that diagram relevant to the Inquiry?

WITNESS TOFT OVERGAARD: So we made this visualisation because of the reluctance from several of the experts to give our in vitro assays any clinical or final phenotypic value, and so what we have tried - what I've tried to do here is to visualise what the impact on calcium binding translates to in difference in QT interval for a number of individuals.

WOODS: Now, QT is the distance between two certain points in the heart rhythm process.

WITNESS TOFT OVERGAARD: Yes. So what we have done is taken published QTc values for variants where we have either in our lab determined calcium binding effect or in the publication that actually came with the variant, they determined the calcium-binding impact.

WOODS: Right, and what does this show?

WITNESS TOFT OVERGAARD: So what this shows is if, on the bottom here, this is the impact on calcium-binding and it may be a little counterintuitive so the higher the number the lower the calcium affinity, so the - you could say the more problematic or the--

WOODS: So when you look at the Y-axis vertically there are a number of fairly high results and you say that shows what?

WITNESS TOFT OVERGAARD: So, if you diminish calcium-binding, it seems there's a correlation with a longer QT interval. And then we just did some conservative statistics showing that there is a really strong correlation between

these two traits.

WOODS: Between?

WITNESS TOFT OVERGAARD: Between these two impacts or measures of a variation, so this is just stating that if you have a problem with the core property of calmodulin binding calcium, this correlates with an impact on your QT interval.

WOODS: You say that the binding anomaly is a core part of the calmodulin effect?

WITNESS TOFT OVERGAARD: That is a core - that's a core part of what calmodulin do, is, it binds and senses changes in calcium, so if that is disturbed, we can see this correlates with an impact on the QT as well.

WOODS: Is the following diagram broadly to the same effect, but reproduced using a logarithmic scale?

WITNESS TOFT OVERGAARD: This is just to show that this correlation seems to be logarithmic more than linear.

WOODS: Very well. The following diagram is headed “Examples of variable expressivity for the observable phenotype QTc”. The c in QT means that it's corrected to standardise the pulse beat, the heart beat--

WITNESS TOFT OVERGAARD: That's our understanding, yes.

WOODS: Yes. Could you explain the significance for this Inquiry, given that you would understand that variable expressivity is an issue, could you explain what this diagram indicates?

WITNESS TOFT OVERGAARD: Yes. So here we are actually showing why there is not a full and complete correlation between impact on calcium-binding, and QTc or at least in examples there's not a complete correlation, so if you take the green area here, these four individuals all have the N98S variant but they clearly display very different QT intervals.

WOODS: Those are the green ones?

WITNESS TOFT OVERGAARD: These are within the green box, yeah. The two red here are diagnosed with CPVT and the two black ones are diagnosed - actually with both Long QT and CPVT, the two are mixed. So what this indicates is that even with the same variant you can have a rather variable expression of, and this is just one trait that's a QT interval, so it's exemplifying that other factors are important for the expressivity of a particular trait.

WOODS: Does this relate to the issue in this Inquiry, as you understand it, about the potential difference, for example, between the condition of

Ms Folbigg, Kathleen Folbigg who is alive, and the children who are deceased?

WITNESS TOFT OVERGAARD: That is correct.

WOODS: I haven't taken you to all those diagrams, but are there any others - can I take you to the diagram at page 15, which is headed, "Examples of identical calmodulin missense variants in different CALM genes". In relation to this question of variable expressivity, does that diagram inform us of anything that assists?

WITNESS TOFT OVERGAARD: I think it probably even expands what I said before, if you look at the N98S variants here, they come out with either Long QTs, CPVT, a combination or I believe it's from the calmodulinopathy registry, so UD is undetermined, so that before they had a chance or they don't have an electrocardiogram to diagnose.

WOODS: Is the suggestion from what you're saying there that the conditions of Long QT Syndrome/CPVT, it can as it were alternatively appear?

WITNESS TOFT OVERGAARD: Yes.

WOODS: Very well. Now, I'll just consult my colleagues here. Unless there's anything else you want to volunteer to assist his Honour on the subject of your report.

WITNESS TOFT OVERGAARD: I think we're good, or do we?

WITNESS NYEGAARD: Maybe we could talk just a little bit about the - there is a table with three different genes shown.

WOODS: Do you have the document in front of you? If you don't, I'll - we'll find it in a moment.

WITNESS TOFT OVERGAARD: It'd be a couple of slides back I think.

WITNESS NYEGAARD: So it says count 2 - yes.

JUDICIAL OFFICER: Page 15, that's got, isn't it, it's got three?

WOODS: Yes. No, I think it's page 8.

WITNESS TOFT OVERGAARD: Page 8 maybe, yeah.

WOODS: Page 8?

WITNESS NYEGAARD: Yes.

WOODS: It's headed, "Why it is difficult to distinguish pathogenic from benign variants in large genes and why calmodulin is different". Professor Nyegaard,

could you assist us with the meaning of that diagram?

WITNESS NYEGAARD: Yes, so I was putting in two you could say genes in coding different channels to compare with calmodulin just to have a feeling of how constrained is calmodulin and why is there so much talk about this benign versus pathogenic and why is it difficult to distinguish in most genes. If you look at this gene here in the middle, SCN5A, you can see you would expect because a gene is so big you would expect more than 1,200 missense variants, and you see something like 967. If you see, some of these variants are very common in the population and so I did a quick calculation, in gnomAD there's more - in this version of gnomAD there's more than 14,000 individuals carrying a missense variant and there's a mixture of pathogenic and benign. So of course it's very difficult, so that's why this variant of unknown significance, you know, is invented, and it is actually very difficult for the large genes, and so in - there was this error in genetics where people were sequencing patients and when they found a variant they attributed it to be pathogenic. Then there was this - when this large gnomAD resource came about, everybody - it happened in all fields - could then see, okay, they cannot be pathogenic--

WOODS: When you say all fields, do you mean not only cardio?

WITNESS NYEGAARD: --hearing loss, yeah, all fields, yeah, all fields in genetics, it happens in all fields, that we put too many variants in the box that was labelled pathogenic. So there was this shift where - there was a clean-up in the field that variants were downgraded based on their frequency in the population and this is what MacRae's saying.

WOODS: Professor MacRae says that?

WITNESS NYEGAARD: Yes. Yeah, so it's to respond or a comment to his report.

WOODS: Do you say the calmodulin is--

WITNESS NYEGAARD: Is very different, yeah. So you can see that the observed divided by expected, so how many missense variants do you actually see and how many would you expect. So for calmodulin there is - you see only 10% of the variants you would expect by chance. So even though the other genes are also genes involved in monogenic diseases, calmodulin is much, much more constrained than these two genes and there's very, very little variation, and the variation there is is only seen in one of very few people. So I'm putting this just so that people can understand that calmodulin cannot be treated as the large cardiac channels when you do variant filtering.

WOODS: Thank you. Look, can I take you on that point since we've seen the letter Z appearing in the last diagram that we've spoken about? Could I ask you to go to slide 7 which is on page 7, it's the one before the one I've just taken you to and it's called Z-score? Does this relate to the explanation you've just given a moment ago?

WITNESS NYEGAARD: Yes, because this is, some of the experts, they keep saying that this Z-score is lower than the threshold for constraint gene in the ACMG Guidelines. So, Michael didn't want me to put this plot in but I do dare do it. Okay, I'm going to show you what it is. The blue dots are all the genes in the genome. Because there are so many genes the points are melting together. So on the X-axis is the expected number of missense variants.

WOODS: Right.

WITNESS NYEGAARD: Yeah?

WITNESS TOFT OVERGAARD: We have 70-something here.

WITNESS NYEGAARD: Yeah, and on the Y-axis is this Z-score.

WOODS: Is the observed Z-score?

WITNESS NYEGAARD: Yeah, the Z-score for missense variants. Yes, so what it shows is that if you have a gene with very little expected missense variants, this score just cannot get any higher. So you have calmodulin lying here on the edge, they have the highest Z-score of all genes that are small.

WOODS: Of all small genes?

WITNESS NYEGAARD: Yeah.

WOODS: Very well. I think that's. If you go to slide 6, does that also refer to a misapprehension commonly made?

WITNESS NYEGAARD: This is back to the transcripts, that because it's a common mistake, not just for calmodulin but we want to only call variants or identify variants in transcripts that are actually used by the body. So gnomAD has developed this new score called pext and here you can see the variants - any variant, is it actually in a transcript that is existing in a reasonable proportion of the total amount of transcripts.

WOODS: The transcript is the RNA is it?

WITNESS NYEGAARD: Yes.

WOODS: Which goes between the DNA and the protein.

WITNESS NYEGAARD: Yes. So I'm - so this is - so this table is really back to the transcript problem.

WOODS: Yes, it is, yes.

WITNESS NYEGAARD: That all the missense variants with the - with a little cross, those are variants found. You can see the pext score zero meaning they are found in a transcript that constitutes zero per cent of the total amount

of transcript for calmodulin2. So it's basically - it's kind of the end of the transcript story.

WOODS: And that supplements what you've said in your written report of 10 February.

WITNESS NYEGAARD: Yes.

WITNESS TOFT OVERGAARD: That is true.

WOODS: Thank you. Yes, thank you. Thank you, your Honour.

JUDICIAL OFFICER: Does anyone else wish to ask any questions?

WOODS: I'm sorry, your Honour.

JUDICIAL OFFICER: Does anyone else wish to ask any questions? Yes, Ms Roy.

ROY: Thank you, your Honour. Excuse me one moment. Just a few matters of clarification. Professor Nyegaard, I wanted to clarify something that you said in response to a question from Dr Woods this morning about the location of G114. It's correct that it's not located in an EF-hand motif.

WITNESS TOFT OVERGAARD: Perhaps I can - this is probably my core expertise. So we do not put this into our report but there's a slight, I think, mis-conception of what an EF-hand is. So an EF-hand is a helix-loop-helix motif that looks like a hand and so most experts misinterpret that as opposed to the calcium binding sequence, which is only 12 residues out of an EF-hand which is approximately 30 residues. But the G114R is - so if these are two helixes, the G114R is a terminating residue from the second helix in EF-hand 3.

ROY: So I didn't misunderstand it. You did intend to say that it is on the EF-hand.

WITNESS TOFT OVERGAARD: It's terminating - you can say that it's terminating the EF-hand so it's probably part of what you would call a very small linker between the two EF-hands in the C-domain.

ROY: And in any event, the point of the evidence was regardless of its location--

WITNESS TOFT OVERGAARD: Outside the--

ROY: --outside of the EF-hand domains, it's still an important location for calmodulin function specifically in relation to sodium.

WITNESS TOFT OVERGAARD: As it turns out this exact area is in touch with the sodium channel when it binds so that's correct.

ROY: Thank you. The second matter for clarification was regarding the misidentification of the CALM2 missense variants in the Floyd paper. First of all, if we could have slide 6 back up. I just wanted to clarify as a matter of fact, I think in your evidence and your paper you said that there were six missense variants properly identified.

WITNESS NYEGAARD: Yes. In this version of gnomAD, yeah.

ROY: I'm just counting the 097's in the pext column in this table. I count eight.

WITNESS TOFT OVERGAARD: I think there are eight but they use six. So the numbers we refer to is the number from the Floyd paper.

ROY: I see. There are in fact eight in the database.

WITNESS TOFT OVERGAARD: There are in fact eight, that is correct.

ROY: There are six used in the Floyd paper that were valid.

WITNESS TOFT OVERGAARD: That is correct.

ROY: And in relation to that error, in your view does the error in over counting the CALM2 missense variants affect the accuracy of the predicted algorithm that's used in the Floyd paper.

WITNESS TOFT OVERGAARD: We - we don't know but I'm not so sure because those particular variants will not have an associated yeast score. So depending on how the algorithm is, it may just not count that algorithm because it doesn't have an associated functional score.

ROY: So is it the case that you're not sure but it's possible it does not invalidate the predictive.

WITNESS TOFT OVERGAARD: That's - that's correct. You would need to ask the actual author, yeah.

ROY: And in any event, I understand that the thrust of your concern, and correct me if I'm wrong, is that the authors of that report, one of whom is Professor MacRae, may, as a result of that mistake, be under a misapprehension as to how CALM and CALM2 variants are generally.

WITNESS TOFT OVERGAARD: That's correct, yes.

WITNESS NYEGAARD: Yes, that's why we raise it, yes.

ROY: You're concerned that that might be influencing his interpretation of the uncontroversial data.

WITNESS NYEGAARD: Yes.

ROY: The final thing I'd like to seek clarification on, Professor Toft Overgaard you mentioned speaking to Ms Folbigg on the phone briefly.

WITNESS TOFT OVERGAARD: That's correct.

ROY: Can you tell us how that occurred?

WITNESS TOFT OVERGAARD: We were at a - last time we were here we were at a gathering where - where one of - sorry, Kathleen's friends were and she had her phone and we were together and Kathleen was on the one end.

ROY: And was this in November of last year?

WITNESS TOFT OVERGAARD: That was in November, yes.

ROY: When you were here?

WITNESS TOFT OVERGAARD: Yes.

ROY: How long did you speak?

WITNESS TOFT OVERGAARD: One minute I think.

ROY: And can you tell us what was said?

WITNESS TOFT OVERGAARD: I can't recall. I guess it was - it was a bit awkward but just I think general comments.

ROY: And that conversation occurred before or after you gave your evidence?

WITNESS TOFT OVERGAARD: Just before.

ROY: And did anything said in that call influence any of the evidence that you've given.

WITNESS TOFT OVERGAARD: No.

ROY: And Professor Nyegaard, have you ever spoken to Ms Folbigg?

WITNESS NYEGAARD: Yes. I was handed the phone first, yes. I remember saying we would do the best we can and this is also what we say to everybody else, so we come here as scientists. We present the science and we will do the best we can in presenting that.

JUDICIAL OFFICER: Would it be fair to describe your conversation with Ms Folbigg as a brief and perhaps a somewhat awkward exchange of pleasantries?

WITNESS TOFT OVERGAARD: Yes.

WITNESS NYEGAARD: Yes.

ROY: I have no further--

WITNESS NYEGAARD: Yeah, I remember someone was stung by a bee so that kind of got the centre of attention. I don't remember--

ROY: Apart from that conversation have you had any other conversations with Ms Folbigg?

WITNESS NYEGAARD: No.

ROY: Your Honour, that leaves only the tendering of the new article that was referred to this morning, which I understand is in Exhibit 15 behind tab 263, that was the article, lead author is Po Wei Kang. I have no further questions.

EXHIBIT #15-263 ARTICLE "ARRHYTHMIA-ASSOCIATED CALMODULIN VARIANTS INTERACT WITH KCNQ1 TO CONFER ABERRANT MEMBRANE TRAFFICKING AND FUNCTION", ADMITTED WITHOUT OBJECTION

WOODS: Your Honour, may I correct something which I need to? It's on page 9 of the report. It just struck me as odd. I know the answer but I don't think it should remain in the situation it is. Page 9 of the report of 10 February, Professors, about eighth lines from the bottom, the second last words is the printed figure's 16. 16 gnomAD, G-N-O-M-A-D, and then at the top of the page there's a reference on the sixth line down to only six are correctly annotated.

JUDICIAL OFFICER: Which page?

WITNESS NYEGAARD: Yes.

WOODS: Page 9 of 14.

WITNESS TOFT OVERGAARD: Perhaps I can explain.

JUDICIAL OFFICER: Until his Honour gets the reference. Go ahead.

WOODS: It's the sixth line down, it says, "only six are correctly annotated". Then eight lines up from the bottom it refers to 16. Is there some discrepancy there or is there an explanation?

WITNESS TOFT OVERGAARD: No, the six are from the CALM2 gene but then there is an additional ten from CALM1 and 3 together. So in total they used 16.

WOODS: So it's an added figure?

WITNESS TOFT OVERGAARD: It's an added figure, yes.

WOODS: Right. So 16 is correct?

WITNESS TOFT OVERGAARD: 16 should be correct and these are the ones that are plotted in the diagram after.

WOODS: Very well, thank you.

WITNESS NYEGAARD: Yes, across three genes, yes.

WOODS: Sorry?

WITNESS NYEGAARD: Yeah, across the three genes.

WOODS: Across the three genes, yes. Thank you, your Honour.

JUDICIAL OFFICER: Professors, that, I think and I hope, concludes your evidence. Can I express my appreciation on behalf of the whole Inquiry as to the assistance you've provided, it really has been very helpful and I can only admire your ability to explain extremely complex concepts, thank you. You can step down.

WITNESS TOFT OVERGAARD: Thank you, your Honour.

<THE WITNESS WITHDREW

ROY: Your Honour, we're otherwise--

JUDICIAL OFFICER: Where do we go from here?

ROY: --we don't have another witness this afternoon, your Honour, we have Professor Todor Arsov scheduled to commence at 10am tomorrow.

JUDICIAL OFFICER: Is Professor Vinuesa straight after him or are they at fixed times?

ROY: She is straight after him with the luncheon adjournment in between. She commences at two.

JUDICIAL OFFICER: So it's expected Professor Arsov will take the morning, is it?

ROY: Presently, yes.

WOODS: Your Honour, from my perspective he may not take the morning, but--

JUDICIAL OFFICER: Other people may want to ask questions as well, Dr Woods.

ROY: If you would like to use the afternoon we can make enquiries as to his availability.

JUDICIAL OFFICER: No, I don't mind, I just wanted to get a feel for where we are.

ROY: We can make those enquiries, your Honour.

JUDICIAL OFFICER: All right, well we'll adjourn until 10 o'clock tomorrow morning.

AUDIO VISUAL LINK CONCLUDED AT 2.53PM

ADJOURNED PART HEARD TO TUESDAY 14 FEBRUARY 2023