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TRANSCRIPT OF PROCEEDINGS

INQUIRY INTO THE CONVICTIONS OF KATHLEEN MEGAN FOLBIGG

WEDNESDAY, 17 APRIL 2019 at 10.00am

PRESENT:

Legal representatives
Gail Furness SC, Senior Counsel assisting the Inquiry

Sian McGee, counsel assisting the Inquiry
Jeremy Morris SC, Senior Counsel for Ms Folbigg
Robert Cavanagh, counsel for Ms Folbigg
Isabel Reed, counsel for Ms Folbigg

Witnesses
Professor Edwin Phillip Enfield Kirk, Genetic Pathologist and Clinical Geneticist, Senior Staff Specialist in Clinical Genetics at Sydney Children's Hospital and Senior Staff Specialist in Genetic Pathology for NSW Health Pathology
Dr Michael Francis Buckley, Genetic Pathologist and Clinical Director of the New South Wales Health South Eastern Area Laboratory Services at the Prince of Wales Hospital in Sydney
Dr Alison Fiona Colley, Clinical Geneticist and the Director of Clinical Genetic Services for various local health districts in New South Wales
Professor Maria Carola Garcia de Vinuesa de la Conta, Co-Director of the Centre of Personalised Immunology and Professor of Immunology, John Curtin School of Medical Research at the Australian National University in Canberra
Dr Todor Arsov, Senior Research Fellow at the John Curtin School of Medical Research and Centre for Personalised Immunology
Professor Monique Maree Ryan, Paediatric Neurologist and Director of Neurology at the Royal Children's Hospital in Parkville, Victoria (by AVL)
Professor Michael Collingwood Fahey, Paediatric Neurologist and Director of Paediatric Neurology at Monash Children's Hospital (by AVL)

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SPECIAL INQUIRY

THE HONOURABLE REGINALD BLANCH AM QC

WEDNESDAY 17 APRIL 2019

INQUIRY INTO THE CONVICTIONS OF KATHLEEN MEGAN FOLBIGG

PART HEARD

<ALISON FIONA COLLEY, MICHAEL FRANCIS BUCKLEY, EDWIN PHILLIP ENFIELD KIRK, TODOR ARSOV AND MARIA CAROLA GARCIA DE VINUESA DE LA CONCHA, CONTINUING (10.00AM)

MORRIS SC: Just in relation to the testing for Hunter Syndrome, Professor Kirk, is it the case that an available technique might be electron microscopic examination of the stored tissue for Patrick?

WITNESS KIRK: Yes, that would be a, an option. I believe there were samples collected for that purpose but I don't know if it was done.

MORRIS SC: Work on the basis that there's no evidence that's been produced to us that that's been done, but that would be a useful step to take.

WITNESS KIRK: It could be considered.

MORRIS SC: Yes, okay. Dr Colley, in relation to the urine sample which was taken for testing, and to this extent I refer you to the genetic tender bundle, which is exhibit AC, and that's at page 258 at tab 70--

WITNESS COLLEY: Yes, this is what you spoke about yesterday.

MORRIS SC: I think that's what you spoke about the other day.

WITNESS COLLEY: Yes.

WITNESS BUCKLEY: Yeah.

MORRIS SC: I want you to assume that that sample was taken on 25 October, Dr Colley, and we actually don't know the date of testing, do we?

WITNESS COLLEY: I can't see that there. This report is - I think the date of 8 November is probably the report date when it was sent back to Dr Ian Wilkinson, the paediatric neurologist, but there's no date there that I can see that actually tells us the date it was, the testing was performed. Usually testing is performed within five days of sample, but obviously there's nothing there that actually tells me that. I do though know, and perhaps my learned colleague here who's worked in this field can tell us more, the laboratory usually makes

an assessment, in fact, always makes an assessment when they receive a sample on whether they believe that sample is too old or hasn't been conveyed to the laboratory in a proper manner, and for clinicians like myself many a time we've received a, an email, a, a, the good old-fashioned phone call from the laboratory saying, "Look, we're really sorry but this sample just didn't make it in time. It's six days or seven days old," or something happened with the bundle, with the package and, therefore, that would refuse to test it. So I have great faith that if the laboratory did the test and issued a report they were happy with the sample quality, quantity and timing that they received it.

MORRIS SC: Or otherwise if there was any other documentation and if a report was furnished you'd expect to see some qualification or warning given to you?

WITNESS COLLEY: Yes, absolutely.

MORRIS SC: Is that a general--

WITNESS COLLEY: Yes.

WITNESS BUCKLEY: Yes, it would be routine laboratory practice for a pathologist or a, a senior scientist, principal scientist to note on the report any concerns about sample quality.

MORRIS SC: I see, and is this a test for dicarboxylic acid?

WITNESS KIRK: No.

MORRIS SC: No?

WITNESS KIRK: Well, hang on, if you could pass me the report.

WITNESS COLLEY: Yeah, sure.

WITNESS KIRK: So the, the mucopolysaccharide screen is not but just below that you can see the urine organic acids and that will pick up dicarboxylic acids.

MORRIS SC: I see, and is this about carnitine value, this test?

WITNESS KIRK: Yes, just below there there is a carnitine total and free and acylated so acylcarnitines can be markers of certain metabolic conditions.

MORRIS SC: What would they be indicative of?

WITNESS KIRK: Mostly conditions of fat metabolism. So there's a group of conditions called "fatty acid oxidation disorders". One of those is MCAD deficiency which has been the subject of some previous documentation in relation to these children, but there is actually quite a large group of conditions for which this kind of test might be relevant.

MORRIS SC: And they can give rise to epilepsy and problems like that?

WITNESS KIRK: Epilepsy wouldn't be a usual feature. I guess, sometimes with these conditions, if you have a very severe first presentation, there can be a brain injury from that that might lead to subsequent epilepsy. I don't remember actually seeing any patients with conditions in this group with seizures but I think it's conceivable.

MORRIS SC: What about some sort of cardiac problem, can you get that?

WITNESS KIRK: Yes. So there are, not so - for the longer chain fatty acid oxidation disorders, cardiac problems, particularly cardiomyopathy, is a common feature.

MORRIS SC: Now, your Honour, I'd like to take Dr Colley to the forensic pathology tender bundle and just see if she can clarify something for me, page 200. It'll come up on the screen, I think.

WITNESS COLLEY: Thank you, it might take us a minute to find it otherwise.

MORRIS SC: Dr Colley, in this regard, you had some communications with Bridget Wilcken, who is the clinical geneticist down in Adelaide?

WITNESS COLLEY: No, Bridget Wilcken is at the Children's Hospital in, Westmead Children's Hospital in Sydney.

MORRIS SC: I'm sorry, right, okay.

WITNESS COLLEY: But I did, indeed, have some communication with her when I first met Mr and Mrs Folbigg because at that time in the early 90s I was aware that children may die unexpectedly of inborn errors of metabolism. It was a very new growing field at the time and we had an expert in New South Wales and that was Bridget Wilcken, so I enlisted her advice.

MORRIS SC: So if we could just turn to page 200, thank you, your Honour, this is a letter to you from Bridget Wilcken dated 10 December 1991 and I'd just like you to read this letter to yourself and I'll ask you some questions once you've finished.

WITNESS COLLEY: Yep. Sure.

MORRIS SC: In relation to this letter, are you confident that this letter relates to the test results which I was showing you before on the screen?

WITNESS COLLEY: I believe so.

MORRIS SC: The issue I've got that I want to draw your attention to - and, sorry, this letter was generated after Patrick's death but at a time when the Folbiggs were expecting - I'm sorry.

WITNESS KIRK: I'm sorry, I just want to clarify something. It appears there were two samples--

WITNESS COLLEY: Yeah.

WITNESS KIRK: --because the, the letter say, "A urine sample was sent to us." So that would be the New South Wales laboratory. So there are two separate samples, one that was sent to Adelaide - it may have been a split of the same sample - one sent to Adelaide and one sent to the New South Wales laboratory.

MORRIS SC: Right, okay. So that might indicate that there's another test result floating around somewhere?

WITNESS KIRK: Yes. In fact, I think I may have seen it.

WITNESS COLLEY: From Westmead Children's Hospital.

WITNESS KIRK: Yes.

WITNESS COLLEY: Yes.

MORRIS SC: We'll make an inquiry about it but the issue I want to raise with you is we see that there's a statement about six lines down, "Of course, normal urinary findings would rather depend on the relationship between the date of the urine sample and the actual date of the episode, but if it's within a day or so I rather think it would argue against it;" do you see that?

WITNESS COLLEY: I think Professor Wilcken is talking about the urinary sample they would have taken from Patrick after his acute life-threatening event when he was admitted to the hospital and they were investigating him for that and they would have got off a urine sample probably within a day and sent it to Westmead Children's Hospital. That's my understanding.

WITNESS KIRK: Yeah, it seems likely and do you want me to explain what the timing difference makes?

MORRIS SC: That's what I want.

WITNESS KIRK: Yeah. So for some of the fatty acid oxidation conditions, such as MCAD, you would expect abnormalities in a urine sample whenever it was taken, but there are some of them where the urine may normalise in between episodes and so getting a sample fairly close to any event that might be a metabolic event is important because, if you don't do that, you are less confident that you would have picked up any abnormality that may be diagnostic.

MORRIS SC: Right, okay, and with respect to any test for Hunter Syndrome - we talked yesterday about the time between--

WITNESS KIRK: Yep.

MORRIS SC: --the taking of the sample and the time it's tested - it's possible, depending on how it's stored and how it's transported and the time, that could give rise to the risk of a false negative; do you agree?

WITNESS KIRK: I see. Now I understand. Okay, no, so this is a bit different. The, the molecules that we're testing in the GAG screen are very large molecules and they are stable. So this is quite a robust test to sample handling. When we do urine metabolic screening, because we're testing lots of different things and some of them are quite variable in terms of the fragility of the different compounds, there is a great emphasis placed on correct handling and transport, but for the glycosaminoglycans those are relatively stable compounds and less likely to be affected by those problems.

The main exception to that would be if there were very serious bacterial contamination of the sample which we would expect to show abnormalities on the urine organic acids which are not reported in the Adelaide report and they're something they're aware of. So I would say that's very unlikely, not inconceivable but very likely.

MORRIS SC: We talked about that there's a certain percentage of risk of false negatives with the sort of Adelaide testing yesterday?

WITNESS KIRK: Yes, it's a very low risk in - I went back overnight and reviewed the, the publication from Adelaide about their setting the test up and they had 100% sensitivity with not huge numbers and I spoke to the director of the laboratory who has been running that lab for 25 years and she's not aware of any false negatives during that time. Again, you should subtract a few years in case there was a miss in the last few years. So I would regard it as a very high quality test but it is certainly true that any test has got a potential for a false negative.

MORRIS SC: And that's the sort of thing that could be reconciled with an electron microscope examination?

WITNESS KIRK: If there were normal electron microscopy then that would be strong additional evidence against, against Hunter Syndrome, yes.

MORRIS SC: We were talking about microarray yesterday and in particular in relation to the MYH6 gene and the CALM2 gene and I just wanted to clarify with you briefly what significance you placed on that again?

WITNESS BUCKLEY: Sorry, if, if the question is what is, what does a normal result in that context means--

MORRIS SC: Yes. You performed the microarray test and you formed some conclusions. Can you just run us very briefly as to what you--

WITNESS BUCKLEY: So I, I didn't perform a microarray test.

MORRIS SC: I'm sorry.

WITNESS BUCKLEY: I requested that the data be generated and that it be interpreted by a colleague of mine at the Children's Hospital Westmead who is probably the most experienced senior scientist in this area. He concluded that he didn't find any medically-significant copy number variants in any of the three samples, subject to a sample quality issue for one sample which was Patrick.

MORRIS SC: Right, and so when we're talking about copy number variants, we're not saying that the generic variants MYH6 and CALM2 were not present. It's just that you've excluded--

WITNESS BUCKLEY: We've excluded larger events also involving that, that locus. So we've, we know that the MY - we know exactly from the DNA sequencing in whom the MYH6 and CALM2 variants are present. We have that documented and this was just to explore the hypothesis that there might be more than one thing going on in that locus that would make it more complicated or make it more likely to shift what I still consider, I'm afraid, to be a, a variant of uncertain significance into an area that is perhaps more likely to be pathogenic by, by adding in an additional variant. That was requested and wasn't seen.

MORRIS SC: Professor Carola, do you agree that that's the effect of the microarray analysis?

WITNESS VINUESA: Yes, I agree, it is useful. I think it would be very useful to have the raw data so we could explore all the other loci associated with cardiac arrhythmias and not just from the medically significant point of view, but we do know that if there were any other coding variations that are structural it would be quite useful.

WITNESS BUCKLEY: So the raw data were provided to you, Professor Vinuesa, I remember packaging them up into the package and sending it to you, but it's on a small USB disc associated with the large 1 terabyte hard drive that you received.

WITNESS VINUESA: Okay, it was--

WITNESS BUCKLEY: It's available to you.

WITNESS VINUESA: So thank you, it might be worth - do we have time to analyse that?

MORRIS SC: I doubt it. Today is really the day I'm afraid.

FURNESS SC: It's not quite correct what my friend said. Professor Carola Vinuesa has had that material for weeks, if not longer, and team Sydney have

had the material for the same length of time and have analysed it. So it's not the case that there's not time to analyse it, it's happened.

JUDICIAL OFFICER: It has been analysed.

WITNESS VINUESA: May I, may I say something along those lines? We were told we were going to receive a report by an expert on that type of analysis and I was disappointed when the report only mentioned medically significant variants. I was expecting that perhaps uncertain variants in candidate genes would have been mentioned as well. So we would probably not have had time there to analyse it when the reports were - since the time the reports were sent to us but I, I understand what's been said and, and -

FURNESS SC: In my submission there's been ample time to analyse it and the results are in.

JUDICIAL OFFICER: Well it has been analysed, yes. Yes, Mr Morris.

MORRIS SC: Thank you, your Honour. In relation to the phenotypes, we talked about phenotypes yesterday, and to that extent is it a fair comment - I know that the postulated phenotype has been sudden infant death, unexplained infant death, for the purpose of everybody's analysis. And is it fair to say that because of the breadth of the phenotype it's a little difficult from a genetic point of view to target genetic investigation or not really?

WITNESS COLLEY: Maybe I can start with that. The phenotype is not only both sudden unexpected early death, but also normalcy. The children were well grown, appeared normal, did not have any dysmorphic features, did not have any birth defects or malformations, were meeting their milestones, and then had a catastrophic acute onset life threatening event. Now, because of that we don't have a particular disease phenotype that we were targeting, so that's why we used Whole Genome Sequencing and when we couldn't, Whole Exome Sequencing, to look with as much breadth as possible at all possible genetic causes of being entirely normal and then having a catastrophic event.

So no, I think that phenotype was quite clear because it was so consistent between the four children, including Patrick up to four and a half months.

MORRIS SC: Okay.

WITNESS BUCKLEY: I could also add to that saying that I think all people who are analysing the data were quite well aware that sudden unexplained death is a portmanteau of a whole bunch of different diagnoses, so we did not only hypothesis-free, but we did hypothesis directed testing, and we in addition looked for anything that might possibly have been called pathogenic. So I'm very aware that, I can't speak for Professor Carola, but I think we were very comprehensive in the sorts of analyses that we tried to do. We were quite open-minded. I think nothing would have delighted us more than to have found something but--

MORRIS SC: I understand. But the point about it is in determining your phenotype you look at the clinical features of the presenting child--

WITNESS BUCKLEY: And the mother.

MORRIS SC: And the mother, and to that extent it may well be, and Dr Colley I think you mentioned this just a moment ago, if you don't have a disease phenotype then - you can have a disease phenotype or you can have a normal child phenotype and really as I understand your evidence, Dr Buckley, you took a broad approach to try and trim it down?

WITNESS BUCKLEY: Yes, and we also - we tried to take into account the possibility that there might be a diagnosis there that someone had missed or that someone had - that there was a complex diagnosis where a presenting feature might not have been recognised, and again we don't--

WITNESS COLLEY: Can I just say also I think it's the - as you say, hypothesis-free plus directed, hypothesis directed assessment, Whole Genome, Whole Exome and microarray analyses. On the background of the post-mortem reports, the urine metabolic screens, the metabolic studies and the other experts who've given their opinions, there seems to be consistency here. We haven't found something in a phenotype which is not in the genotype or vice versa, and that would have worried us if we'd had inconsistency. We would definitely have gone back and done further testing, or worried about what that might have been, but we didn't find any inconsistency.

MORRIS SC: Okay. I'd like to ask you a question, particularly the Sydney team, did you actually have access to Patrick's treating records at all?

WITNESS BUCKLEY: I can start by saying no, I've not looked at any clinical records as it's outside my area of competence.

MORRIS SC: Dr Colley?

WITNESS COLLEY: Not at this stage, no. When I was in the Hunter and remember I met Mr and Mrs Folbigg at a time soon after Patrick had died, I had access then and I looked at those files then, but I thought they were certainly - I took counsel from the paediatric neurologist, the treating paediatricians and the post-mortem.

MORRIS SC: Right.

WITNESS COLLEY: But I hadn't seen them recently now.

MORRIS SC: Okay. Professor Kirk, have you seen them?

WITNESS KIRK: Not directly. I've seen summaries prepared by pathologists and so on but not the originals.

MORRIS SC: I don't know whether this is going to be a useful exercise or not, Professor Kirk, but the issue is that, and I've spoken to your colleagues Dr Buckley and Dr Colley, who feel disinclined to undertake a review of the clinical records to try and tease out the features, and I don't know whether that's a matter which you would feel comfortable with, or whether you would defer to a paediatric neurologist.

WITNESS KIRK: I think if a paediatric neurologist has done that exercise, it's probably redundant for me to do it again.

MORRIS SC: Okay. Your Honour that being the case, we're going to substantially comply with the hour and a half. So we'll leave that for the paediatric neurologists.

JUDICIAL OFFICER: It'd depend on your assessments Mr Morris as to time.

MORRIS SC: Yes. I'm going to try and give you credit, your Honour.

JUDICIAL OFFICER: Thank you.

MORRIS SC: On listening to me. Another issue that was raised by, in part I think, by your team and also in part by the Canberra team, is this issue of Rett syndrome, and I think some genes were identified with respect to Rett syndrome, and to that extent exhibit AF, your Honour, which is the report of Professors Vinuesa and Cook, and it's page 27 your Honour. If we just go to the bottom of that page, 9.4.2. The Sydney team, MECP2 was not identified, or no variants were identified, but as I understand it eight or ten years ago Rett syndrome was considered to be, had a reasonably strong association with MECP2, is that correct?

WITNESS KIRK: That's correct.

MORRIS SC: And I think that ten years ago or so about 70 to 80% of Rett syndrome sufferers, they were able to identify the MECP2 gene, or a genetic cause for it, is that about right?

WITNESS KIRK: That sounds about right.

MORRIS SC: In the recent three or four years, that satisfaction has come up to about 90% I think, is that about right?

WITNESS KIRK: That sounds plausible. I'd have to review the figures.

MORRIS SC: Okay. In about the last four or five years there have been papers published which identify the FOXG1 gene as being associated with it?

WITNESS KIRK: Yep.

MORRIS SC: And also the CDKL5 gene?

WITNESS KIRK: That's been around for a bit longer than five years, yeah.

MORRIS SC: And I think there was also a combination between - I'll just see what date this was - I think there was an article by Scala and others about - it doesn't much matter but there was an association between the CDKL5 and the STK9 gene.

WITNESS KIRK: Yep.

MORRIS SC: Which is more recent. The fact is that Rett syndrome is a very, very rare condition.

WITNESS KIRK: Mm-hmm.

MORRIS SC: You'll have to say yes or no.

WITNESS KIRK: Sorry, yes, yes.

MORRIS SC: And it's a rare condition in boys?

WITNESS KIRK: Very rare in boys.

MORRIS SC: And the fact is that what is obvious is that over years there's been further research in the genetic field about what causes Rett syndrome.

WITNESS KIRK: Yes.

MORRIS SC: And through that process they've discovered other gene and gene combinations which has a strong association with Rett syndrome, do you agree?

WITNESS KIRK: I don't know about gene combinations.

MORRIS SC: I was just talking about the CDKL5 and the STK9.

WITNESS KIRK: Right, but - you're talking about interactions between those genes?

MORRIS SC: Just an association rather than an inter-reaction.

WITNESS KIRK: Right, I couldn't comment on that, sorry.

MORRIS SC: Okay. To that extent it's fair to say that because of the relative rarity of the event we've really got to await further development as to the firming up of the gene association and whether there might be other genes associated with Rett syndrome, is that fair?

WITNESS KIRK: Yes, I think it's possible there'd be more genes to be discovered, yep.

FURNESS SC: Your Honour, I rise because I certainly didn't understand my friend's reference to "the event", whether that was a reference to Patrick or to something else.

MORRIS SC: I'm sorry, I'll clarify that. The point is well taken, thank you. The fact is that Rett syndrome is associated with sudden death in boys at a young age, isn't it?

WITNESS KIRK: Well the boys who've been reported as Rett syndrome mostly have a very severe neurological problem from birth, and I believe they may die suddenly. Certainly in girls, older girls with cardiac arrhythmia problems have been reported, which could lead to sudden death. I think in a boy, certainly with MECP2 or CDKL5 particularly you'd expect a very abnormal condition from the beginning, and that it's conceivable that a child with that might die suddenly. I think I'd probably defer to the neurologists on the likelihood of that.

MORRIS SC: Okay. In relation to that association, I want to suggest to you that in fact a lot of boys don't survive the neonatal period with Rett syndrome?

WITNESS KIRK: Yes.

MORRIS SC: And there's another group of boys who, having been born, developed normally for about six to nine months, 12 months?

WITNESS KIRK: I'm not aware of that.

MORRIS SC: Okay. So--

WITNESS COLLEY: Can I just say, I, I - that would be more in keeping with the phenotype of a girl, being - having a period of being normal and then deteriorating with Rett syndrome.

MORRIS SC: Okay. Well, in terms of the presentation, is this one of those matters about which you'd defer to a paediatric neurologist?

WITNESS KIRK: Yeah, I mean, I - both Alison and I have certainly seen people with Rett syndrome and it's a condition that we have some awareness of, but you'd expect a neurologist to know more about it than we would.

MORRIS SC: But just in general terms, there is a strong history of sudden death with boys suffering from Rett syndrome?

WITNESS KIRK: In the context of severe neurological problems, yes, I think that's probably true. That may be true.

MORRIS SC: Okay.

WITNESS COLLEY: Yes, you certainly wouldn't expect a, a sudden death in an otherwise healthy, normally developing, meeting normal language and

motor milestones, no.

MORRIS SC: Well, the fact is that Rett syndrome can be associated with epilepsy, severe epilepsy in boys?

WITNESS KIRK: Yes.

WITNESS COLLEY: In boys.

WITNESS KIRK: Yes.

MORRIS SC: Cardiac arrhythmia, in boys?

WITNESS KIRK: I, I would imagine that's true, I - I've heard of it in girls--

WITNESS COLLEY: Yeah.

WITNESS KIRK: --but I don't know - I'm not sure about boys.

MORRIS SC: I'm just talking about boys--

WITNESS KIRK: Yep, okay.

MORRIS SC: --because boys seem to be a specific subgroup of the Rett syndrome spectrum, do you agree?

WITNESS KIRK: Yes.

WITNESS COLLEY: Yes.

MORRIS SC: Professor Vinuesa, do you have anything to add on this debate at this time?

WITNESS VINUESA: No. No.

MORRIS SC: No, okay. Girls, on the other hand, are quite different because girls, in general terms, statistically can live into their 20s, 30s and 40s, although they end up with profound cognitive difficulties. Do you agree?

WITNESS KIRK: Yes.

WITNESS COLLEY: Yes.

MORRIS SC: And they develop these dysmorphic features, which we were talking about?

WITNESS COLLEY: Yes.

MORRIS SC: And I want to suggest to you that the dysmorphic features in girls can develop as the child is progressing through infancy, is that correct?

WITNESS COLLEY: It's correct. By the time the child is one year of age though, you usually have quite a significant phenotype and, certainly, you'd probably expect here if either Sarah or Laura had Rett syndrome you would be seeing some deviation from normal.

MORRIS SC: Okay, but with respect to Patrick, he died before that time and--

WITNESS COLLEY: But he was male and, of course, we expect an early onset severe neurological phenotype in a male.

MORRIS SC: And when we talk about a severe neurological onset, we're talking about developmental regression, are we?

WITNESS COLLEY: Yes, in fact, failure to develop neurologically in the beginning. So, we're not talking about a period of being normal and then regressing, we're talking boys with Rett syndrome actually having deficits from early on, neonatal period.

MORRIS SC: I want to suggest to you that - well, look, if it's outside your expertise, would you defer to a neurologist on this question?

WITNESS COLLEY: Yeah, yeah.

WITNESS KIRK: Yeah, I mean, I agree with what Dr Colley has said though, the - what we expect in a boy with Rett syndrome is exactly that, that there are severe abnormalities from birth.

MORRIS SC: I want to suggest to you that in an article by Amir, published in Nature and Genetics (as said), volume 23, pages 185 to 88(as said), published in 1999, the summary states:

> "Rett syndrome is a progressive, neurodevelopmental disorder and one of the most common causes of mental retardation in females with an incident of 10,000 to 15,000. Patients with classic RTT appear to develop normally until six to eight months of age and then gradually lose speech and purposeful hand use, develop microcephaly seizures, autism, ataxia, et cetera"?

WITNESS COLLEY: That would be true of females, yes. Sometimes, in hindsight - hindsight's always easy for all of us doctors - when we look at a child and the diagnosis is made, we might look back at around five months to six months and, and see some slowing of development and perhaps not the appropriate purposeful hand movements developing that we might have missed prospectively. But, generally, what you said I would agree with for females, not males.

MORRIS SC: And in males would we expect to see signs of cerebral irritation as they developed?

WITNESS KIRK: I think it depends on what you mean by that. They, they can certainly be irritable in their behaviour--

WITNESS COLLEY: Irritable, cry a lot.

WITNESS KIRK: Cry a lot, be hard to console.

MORRIS SC: What other features would--

WITNESS KIRK: Seizures from very early on, that's a major feature, feeding difficulties, lack of - really, lack of any development--

WITNESS COLLEY: Yeah.

WITNESS KIRK: --would be the main expectation.

MORRIS SC: What about things like torticollis, would that fall into that category?

WITNESS COLLEY: No.

WITNESS KIRK: I, I couldn't say for certain, it's not something that, that comes to mind, but I couldn't exclude it.

MORRIS SC: What about back arching?

WITNESS KIRK: Yes, I think you possibly could see back arching.

WITNESS COLLEY: Yep.

MORRIS SC: Thank you. Now--

JUDICIAL OFFICER: Before you leave that, in your views, is there any realistic possibility that Patrick had Rett syndrome?

WITNESS COLLEY: No.

WITNESS KIRK: We've no evidence of that at all.

WITNESS COLLEY: No.

WITNESS KIRK: And clinically the features don't seem to fit.

JUDICIAL OFFICER: And can I ask you the same question in relation to Hunter Syndrome, is there any realistic possibility that he had Hunter Syndrome?

WITNESS KIRK: In my opinion, no.

WITNESS COLLEY: I would defer to Professor Kirk, but I agree.

WITNESS BUCKLEY: That's outside my area of competence, your Honour.

JUDICIAL OFFICER: Thank you. Yes, thank you.

MORRIS SC: In the light of that, your Honour, Professor Kirk, would you want to - in order to form the view about the realistic possibility in your view about the existence of Rett syndrome--

WITNESS KIRK: Yep.

MORRIS SC: --you have not taken any clinical records into account, have you?

WITNESS KIRK: I have taken information I have been provided into account.

MORRIS SC: Right, but you haven't actually looked at the health records of Patrick's attendance at the hospital--

WITNESS KIRK: No, I'm deferring to my colleague--

MORRIS SC: -- from 18 October 1989?

WITNESS KIRK: No.

MORRIS SC: 90, sorry, 1990? You haven't taken that into account?

WITNESS KIRK: No, I'm taking into account the information that I've been provided, including by Dr Colley, the records that I was provided with and the fact that we found no genetic evidence of this condition.

MORRIS SC: No, I understand that. But there were genetic variants consistent with Hunter Syndrome identified, weren't there?

WITNESS KIRK: There was a variant of uncertain significance identified in relation to Hunter Syndrome and it was certainly a variant that, in the person with the right condition that we would consider further and, and consider follow up testing.

MORRIS SC: And you relied heavily on the urine screen to minimise the impact of that genetic variant, is that correct?

WITNESS KIRK: Yeah, and I think that's fair to say. But we, we independently assessed it as a variant of uncertain significance and then, on top of that, we added the, the information about the biochemical testing.

MORRIS SC: And the fact is that to determine whether it's a variant of uncertain significance or likely pathogenic, one of the things you've got to look at is the clinical history. Do you agree with that?

WITNESS KIRK: It would not be that helpful in a child of this age because, as we've discussed, the features of Hunter Syndrome don't usually manifest in a prominent way by this age.

MORRIS SC: Professor Carola, do you have anything to say on the - your opinion about the possibility of Hunter Syndrome or Rett syndrome in Patrick?

WITNESS VINUESA: I mean, as we explained yesterday, our classification for that variant was likely pathogenic and, as you have indicated from the, the presentation, the manifestations can be unusual at a young age. We were concerned that we found reports that, that can be false negatives in urine testing and, particularly, we found reports that there are age-related changes in that glycosaminoglycans peak from years 10 to 19 and are surprisingly uniformly low in small children. So, my question was, has this been analysed against reference for, for young children?

And, also, there are reports that there are overlapping ranges between healthy individuals and Hunter Syndrome patients. So, the criteria for diagnosis, the recommendation is measurement of I2S activity in the right cell types, which are leukocytes, fibroblast or plasma, and I understand that wasn't performed. In the context of that diagnosis and molecular diagnosis, can confirm Hunter Syndrome in a child with unusual presentation and lack of urinary evidence of glycosaminoglycans.

From our point of view, with this likely pathogenic mutation and some of the characteristics that we have heard, clinical characteristics that we, we think might be compatible with cardiovascular manifestations, respiratory manifestations, seizures, combined makes a picture that we think it could be possible that there was Hunter Syndrome.

MORRIS SC: Now - sorry, Professor?

WITNESS KIRK: Can I respond to that or--

MORRIS SC: Yes, certainly--

WITNESS KIRK: Yeah?

MORRIS SC: --please do.

WITNESS KIRK: Look I think, possibly, your Honour, I should walk back slightly on what I said. I think there is a very remote possibility that this child had Hunter Syndrome. My confidence is more about whether this was the cause of his death. I'm extremely confident that this was not the cause of his death. So, I think it's very unlikely he had the condition and if he did, then it would not have been the cause of his death.

In relation to the specific issues that Professor Vinuesa raises, I looked at the paper that, that Mr Morris provided me last night regarding the levels of glycosaminoglycans and this was a study done - it was published in a

nephrology journal, a kidney journal, and the age ranges were less than ten, ten to 19 and so on. The ranges that we use are, are calibrated more, more, precisely than that. So, although this paper talks about precise calibration, the ten-year range in childhood would, would be far too broad.

What we find in small children is that at birth the levels are quite high and they gradually fall, and then there may be a peak - actually the, the paper's a bit inconsistent because the ranges that they give for each age group actually overlap, so it's a little bit hard to interpret that, although they say there is a significant difference between those aged ten to 19 and others. But the, the work that's been done to validate these tests in Australia shows very clear separation between normal and abnormal.

The paper that I think you're referring to that talks about - that talks about a high level of false positives - so, this is a paper from the European Journal of Paediatrics, by Burton and Giuliani, refers to a, a - in, in supporting the statement to an article in the Indian Journal of Paediatrics and - by Mahalingam et al, which I can provide if, if required. In fact, I've--

FURNESS SC: Perhaps, Professor Kirk, you can tell us what reference number you're referring to?

WITNESS KIRK: Sorry. I don't know. That one, yes, exactly. Thank you. So, if you go to page - of the journal article, 636, so it's about five pages in - one, two, three, four, five - that's it. Down the bottom, on the left-hand side, Mahalingam et al, "Quantitative urinary GAG levels in 91 healthy children and 219 children with MPS". That's actually an error. There were 219 children tested, but only 131 had MPS. So--

FURNESS SC: Sorry, you just need to say that again slowly.

WITNESS KIRK: Sorry. There is an error in the - in this paper in front of us, in that they refer to 219 children in the paper by Mahalingam having had MPS, but actually it's a smaller number, about 130. The results of Mahalingam et al are hard to explain and I do wonder whether they had technical difficulties with the assay, because their results were really very poor by Australian standards. They had about a third false negatives and, as I said, we - false negatives are extremely rare in Australian laboratories doing this testing. So, I don't know that we can really draw much from that paper. Although, I would observe that almost all of their false negatives were in mucopolysaccharidoses type III and IV, which we know do have lower levels of urinary excretion of the glycosaminoglycans.

So, I, I don't know why that reference was used in this review article but, really, I don't think it's relevant to the Australian context and I don't think it's got much to tell us about that issue. I'm not sure if I've addressed all the issues now.

MORRIS SC: Okay. And that's subject to the--

WITNESS KIRK: There was one other thing.

MORRIS SC: Yes, please.

WITNESS KIRK: Yeah, sorry. So, there's reference in the Canberra report - and I think you mentioned it yesterday - to deaths of children as young as six months with Hunter Syndrome, and the Canberra report was very well-referenced, thank you, so it was easy to find the, the source of that, and I think it was a misunderstanding. The figure comes from a paper about treatment of people with Hunter Syndrome with enzyme replacement therapy. One of the criteria for giving a person this treatment is that they must not be too severely affected. And in the paper it was stated that there were, I think it was 14 - sorry, in the abstract - there were 14 children who did not receive enzyme replacement therapy and 13 of them had very severe features of the condition, they had very advanced disease that had been progressing for years and so they could not receive it. And one had had a bone marrow transplant and this is a treatment that is sometimes used for Hunter Syndrome.

And the age range of those who died was from six months to I think 19, 20 years and it's very clear from that that the one who received a bone marrow transplant must have been the six month old and I think from that we can draw the conclusion that the cause of death in this child was actually medical, that they died from complications of their bone marrow transplant rather than primarily from the Hunter Syndrome. There's an international registry paper that reviews deaths of 155 children with Hunter Syndrome, over quite a long period and the youngest death in that group was at two years and four months, or maybe three months and that was a child who actually died in 1950s from respiratory features and so it's a little hard to know again how to apply that to the modern context.

But I'm very confident that given that there were no features at all suggesting involvement of any of the organs affected by Hunter Syndrome on the post-mortem examination and given the fact that this is not a condition that causes death in such young children, that this could not have been the cause of Patrick's death.

MORRIS SC: Professor Vinuesa, have you got anything to add to that?

WITNESS VINUESA: No, except I thought I had read some reports that you could find deaths as early 1.5 years or diagnosis, I will need to check that, still I think we would argue what we were arguing yesterday, that you know we just need to find the next mutation that might cause slightly earlier death, when you have very young deaths, I think eight months to one and a half years, or two years, might not be the critical clincher, so again keeping an open mind as to potential variable expressivity but look I take your advice and obviously you're an expert in this area and I am not.

MORRIS SC: Professor Kirk just with respect to your opinion, we're just looking at the Hunter Syndrome gene monogenetically, as a taking that--

WITNESS KIRK: Yep.

MORRIS SC: --variant that we've been talking about, as to the inter-reaction with other genetic variants and so forth, we really just don't have the science yet with respect to--

WITNESS KIRK: I think this is an exception to that, we understand very well how Hunter Syndrome causes disease, some of the fine details on a cellular level are still being worked out, but this is a condition where there is a deficiency of an enzyme that is used by the cell to essentially process used material within a part of the cell called the lysosome and we understand that a deficiency of that enzyme leads to an accumulation of material inside the lysosome and also in other tissues, and this has known consequences which have been observed over decades and which are really well understood. It's not impossible that variation in other genes might affect the severity to some degree of the condition but as to creating a completely different condition, I think we really have enough understanding to say that's highly unlikely.

MORRIS SC: So your ultimate answer is highly unlikely?

WITNESS KIRK: Yes.

MORRIS SC: Now just in relation to phenotypes and Professor Colley in relation to some observations you made that these children were otherwise well and progressing well and so forth, you were aware that Laura had myocarditis?

WITNESS COLLEY: This was a finding on the post-mortem, there wasn't anything about her health in the ten months I think, Laura sorry

MORRIS SC: Laura?

WITNESS COLLEY: Twenty months. There wasn't anything prior to that post-mortem that made anyone think that she had a pathogenic condition of her heart, she didn't present in heart failure, she didn't have episodes to hospital or doctors where she was turning blue and short of breath, children who have a longstanding heart problem don't grow well, so they tend to be small and perhaps less active, so we didn't have any long term data, so yes we can't say what happened in the short term, viral infection at that time, we didn't have any evidence of any long term condition.

MORRIS SC: So you're talking about the fact that there doesn't seem to be suggestive any abnormality of heart structure, which was affecting this child?

WITNESS COLLEY: Or any infectious condition that might have been there long term in her life, this looked like an acute finding and you know, I'm obviously not able to say whether that was the cause of her death or not, that's not my, yeah area.

MORRIS SC: I don't expect you to but I just wanted to clarify, certainly from our side, whether myocarditis would feature as a matter which would cause

you to modify your basic characterisation of the phenotype and I think you've answered that?

WITNESS COLLEY: No.

MORRIS SC: It's fair to say that both teams have undertaken extensive literature reviews and also various search engines to determine pathogenicity and to aid in interpretation of the results, that's?

WITNESS KIRK: Correct yes.

MORRIS SC: To that extent, those search engines that we're talking about rely on people to submit and the literature in order to determine your pathogenicity, you're reliant on other laboratories around the world to submit information about the association between a genotype and a phenotype, is that correct?

WITNESS BUCKLEY: Yes some do, but we are reliant on it, I mean we're only, we can only work with the information that's available, I think that's what you're asking, is that correct.

MORRIS SC: Yes that solves the problem. And Dr Buckley you're saying that some laboratories don't publish?

WITNESS BUCKLEY: No I'm saying that some of the pathogenicity prediction software are based on evolutionary conservation, based on physiochemical properties of amino acids, based on frequencies in a population which have been ascertained independently of whether a particular genetics laboratory has submitted a result about a particular patient and those are still quite useful, in fact they are some of the most useful components I think.

MORRIS SC: But one of the features is that the mathematical modelling and so forth takes into account known science and also reported events and associations, is that correct, in broad terms?

WITNESS BUCKLEY: Certainly we certainly like for some of the resources that we go to, to have reports of patients, in many instances we don't have those reports and we are able to draw conclusions on other bases, yes.

MORRIS SC: Professor Vinuesa, do you agree?

WITNESS VINUESA: Yes absolutely, we rely very heavily on previous reports from other patients.

MORRIS SC: And a lot of those previous reports Professor Vinuesa relate to specific families with specific genetic profiles, is that correct?

WITNESS VINUESA: Yes.

MORRIS SC: And in some ways one of the problems for the geneticist and for

the interpretation is that you might be comparing the genetic profile of one family with its unique gene landscape, against another family which may have a different gene landscape, is that correct?

WITNESS VINUESA: Correct.

MORRIS SC: Do you agree with that Dr Buckley?

WITNESS BUCKLEY: Yes that's a potential problem in comparing between case reports, yes of course.

MORRIS SC: And to that extent one of the issues in the - as these case reports each coming out it can give rise to developments in understanding of genes on particular phenotypes, do you agree Dr Buckley?

WITNESS BUCKLEY: Yes that's true.

MORRIS SC: Professor Vinuesa?

WITNESS VINUESA: Yes.

MORRIS SC: And that is I think as we discussed yesterday, something which is still an unfolding process?

WITNESS VINUESA: Yes.

WITNESS BUCKLEY: Yes I agree.

MORRIS SC: And indeed the ACMG guidelines have indicated that at the tail end and I'm not sure whether we dealt with this yesterday, that in the clinical setting at least, there's a question about the geneticist's obligation to follow up on previous testing, as further information becomes available, you're aware of that Dr Buckley?

WITNESS BUCKLEY: Yes, and we do that routinely.

MORRIS SC: You do that routinely. Dr Vinuesa?

WITNESS VINUESA: Yes absolutely, in fact it's one of the strong criteria according to ACMG, PS1, if you find the same amino acid as previously established pathogenic in a different patient, then that would already be a strong criterion for pathogenicity.

MORRIS SC: Dr Buckley in relation to your discussions with Professor Fahey, you had discussions with Professor Fahey didn't you?

WITNESS BUCKLEY: Yes I have.

MORRIS SC: And you spoke to him about a certain range of genes, a list of 204--

WITNESS BUCKLEY: So Professor Fahey submitted to me 204 genes that he wished me to make sure had been examined in the data that we had available to us both.

MORRIS SC: And to that extent, what was the question you asked him in order to generate that 204, that list of 204?

WITNESS BUCKLEY: I didn't ask him any question, he provided me a list.

MORRIS SC: I see.

WITNESS BUCKLEY: That he wanted to ensure had been interrogated.

MORRIS SC: Okay right. So you didn't speak to him, I just want to clarify something, you didn't speak to him and ask him for his opinion as to what should be interrogated, you had the broad umbrella postulate free or hypothesis-free testing regime?

WITNESS BUCKLEY: Yes, as my recollection is we start with a hypothesis-free approach and then we also went to some cardiac, non-cardiac genes plus just trying to remember exact numbers but approximately 340 that were generated from publications, then Professor Carola suggested another 180 I think, some of which were already there. And then we went on to a list provided by Professor Fahey.

MORRIS SC: Professor Fahey. So I just wanted to clarify, you had your overarching hypothesis-free investigation?

WITNESS BUCKLEY: Mm-hmm.

MORRIS SC: And he suggested to you, well he - was it the fact that he asked for you to look for 204?

FURNESS SC: Your Honour it's perfectly clear from the report and my friend is clearly having some difficulty and the witness is having some difficulty in responding, but it's very clear from team Sydney's report that Professor Fahey asked Dr Buckley to sequence or look at a number of genes that Professor Fahey specified. It's in the report.

MORRIS SC: I understand, am I'm grateful but - just excuse me a moment your Honour I might be able to clarify this. I'll leave it to my friend to clarify this.

JUDICIAL OFFICER: Okay.

MORRIS SC: Because to be honest I'm not making a good job of this.

WITNESS BUCKLEY: I, I'd like to be as helpful as I can but if--

MORRIS SC: I'm not suggesting--

WITNESS BUCKLEY: --till I know--

MORRIS SC: --you're not being helpful. It might be the form of the question and also the understanding of what's taken place, so to that extent I'll leave it to my friend.

WITNESS BUCKLEY: I apologise if any of that obscurity is arising from my--

FURNESS SC: Can we have team Sydney's report on the screen, please? And at page 9 third paragraph in that report it is said that separately, the data was reanalysed using a list of 204 genes associated with childhood neurological disorders provided by Dr Fahey with an emphasis on epileptic encephalopathy and then the studies used a reduced CAD filter stringency of zero. Dr Buckley, you didn't ask for the genes; you were given them?

WITNESS BUCKLEY: Yes, I, I, I have a, not a clear recollection of the conversation I had, your Honour, but the - I think what I almost certainly said to Professor Fahey was that if you, if, if I was, as a clinical molecular geneticist was to just go to any website I could download a list of different genes that had been associated with childhood neurological disorders and every single one of those would be different. And as someone who's not involved in the clinical space, I would not know which was actually the most appropriate to choose. So my view was that it would be preferable that a, an expert who is both a clinical geneticist and a neurologist could generate a list of genes that he would want to have sure had been interrogated in this particular family and that they would be covered. I, I believe that's the origin of it, counsel.

FURNESS SC: Thank you.

MORRIS SC: That solves the problem. Thank you to my friend, and thank you, Dr Buckley. That clarifies things. Profession Vinuesa, there was some discussion yesterday when giving evidence about various calcium channel - I think it was about calcium channel in one of the cardiac genes which caused you to--

JUDICIAL OFFICER: Wasn't me.

MORRIS SC: We may have lost Silverwater. I think--

FURNESS SC: No, I think we've gained. We've got four now.

MORRIS SC: Have we? Right, okay. I don't understand this technology, your Honour. There was some evidence given yesterday which caused you to undertake a search overnight of some literature and, to that extent, you can work on the basis that counsel assisting has been provided with the literature. I'm not sure whether the experts have had time to read it.

FURNESS SC: I think I was provided with two of them this morning, two of

them last night which have been provided to team Sydney, and then a fifth one was provided half an hour ago which I've provided to team Sydney.

MORRIS SC: It's the fifth one that I think is the--

FURNESS SC: The one you're referring to.

MORRIS SC: Yes.

FURNESS SC: Certainly they have had it a few minutes before they gave evidence.

MORRIS SC: I understand but, your Honour, this is the final topic of discussion and--

JUDICIAL OFFICER: We'll take the morning tea adjournment now to give--

MORRIS SC: I was thinking that might be best, your Honour.

JUDICIAL OFFICER: Yes, if Drs Colley and Buckley and Professor Kirk have only just been given it they might need time to read it.

MORRIS SC: Yes, it'll be the most efficient way of dealing with it.

JUDICIAL OFFICER: Yes, so how long do you need?

WITNESS KIRK: I may not need any time, actually.

WITNESS BUCKLEY: Is this paper that we are--

MORRIS SC: I can't see.

FURNESS SC: Yes, it is. It is.

WITNESS KIRK: Because I suspect that I'm going to have say that I would defer to Professor Skinner.

MORRIS SC: Okay.

WITNESS KIRK: So, so, yeah, I mean, I'm happy to look at it in the, in the break but, although I'm aware of these guidelines, I would mainly defer to a cardiologist in interpreting the information that they contain.

MORRIS SC: That may be the issue but, as I understand it, Professor Vinuesa, you've formed the view that this material may have had an impact on some of the discussion that was had yesterday about the calcium channelopathies or something; is that correct?

WITNESS VINUESA: I think it does because most of our points of controversy between the two teams when trying to classify the variants were regarding this

criteria, PP1 and PP4, co-segregation in the family and the presence or absence of phenotypes that are consistent with the presentation in the children and I do think that this does have a bearing on, on those discussion.

MORRIS SC: Just explain to us what are the features about that study which affects your PP1 and PP4, and what was the evidence yesterday that gave you cause to go and have regard to this document?

WITNESS VINUESA: Well, when my colleague, Dr Todor Arsov, put up his family pedigree indicating the different conditions that were present in the family, Dr Skinner's reaction, or Professor Skinner, was a comment that said, "Well, that finding of fainting in a swim race is pivotal. That could really have an impact on the diagnosis." So that's why we went to the classification or to the recommendations for the diagnosis of Long QT syndrome and it does very clearly state that syncope associated with swimming is due to Long QT syndrome until proven otherwise.

Because of that then we do know that the first presentation for some types of Long QT syndrome is typically sudden death so that would also place, give a consistent phenotype in the children and it clarifies, I think, for us some of the key cardiac arrhythmia presentations that we are trying to look into. So I think it is important to consider this. I mean, we can go into - there's a lot of interesting information in these guidelines. It's interesting that - I mean, they have been revised by Professor Skinner so I think it, it would be a useful exercise at least to, to go through some of this information.

MORRIS SC: But primarily it's that information that Professor Skinner gave yesterday about the syncope being pivotal, reference to the guideline and your classification of the arrhythmic-type disorders which have been identified in your tests?

WITNESS VINUESA: Yes, I think it, it mainly tells us that what we are looking for in the children could be very real phenotypes and I think it just eliminates some of the uncertainty regarding some of the phenotypes. I also think that - I mean, it was, it's not just the swimming. That really would make Kathleen affected at the moment, but the criteria for classification also includes syncope with stress. Syncope with stress already alone meets a, the, some type - well, it, it would be already classified as intermedia probability of Long QT and I think this classification really states that it's - this is a probability diagnosis. It's not certainly as black or white diagnosis and it's not based only on ECG, it's based on clinical history, but as it says here, it is essential that there is direct questioning taken of the patient and a family tree being drawn and a family history for this condition.

MORRIS SC: And this of course would be subject to whatever the electrophysiologists come up with today?

WITNESS VINUESA: Well that's interesting. I mean, here it clearly says that Holter syndrome is - Holter, Holter monitoring is not helpful for the diagnosis, and it does say that stress testing may be helpful, but I don't think it clearly

excludes that condition, and - I mean, we have some guidelines here with some scoring system that, that we could go through, but that swimming episode seems to be pivotal as Professor Skinner said.

JUDICIAL OFFICER: Can you clarify one thing for me? Is this Professor Vinuesa giving evidence that a cardiologist would give in the ordinary course of events? It's just an article that she's found?

MORRIS SC: I understand that it was the impact on her classification of PP1 and PP4 which she found in the genetics sphere, the genetics landscape. I don't seek to lead a cardiological opinion from Professor Vinuesa and that will--

JUDICIAL OFFICER: That's what I was asking.

MORRIS SC: --that will be dealt with by the electrophysiologist. But what I wanted to do before we depart for morning tea, or we can deal with it now, now that we've got Professor Vinuesa's opinion on this issue we could ask the others for their opinion, or otherwise--

WITNESS KIRK: Yes.

WITNESS COLLEY: Sorry, could I make a comment about phenotype first, is that okay?

WITNESS KIRK: Yep, sure.

WITNESS COLLEY: Before I hand over to you. I think Professor Vinuesa is quite correct, that obviously phenotype is really important. We all agree on that. The phenotype that you've mentioned is syncope and that's quite right, and that was mentioned by Professor Skinner yesterday. In the notes that I've read, and I think Professor Skinner mentioned also yesterday, that we don't have documentation of syncope. Syncope with stress is really important, but syncope means you lose consciousness, you drop down. We do have episodes of what I would call pre-syncope, dizziness, light-headedness, not feeling well, which comes with dehydration and perhaps fright as I used yesterday is the wrong word, emotional stress. Emotional stress and dehydration, and you will get vasovagal or pre-syncope.

In the case of true syncope you lose consciousness. If someone is swimming and has syncope, like I just read in that article, they usually sink to the bottom of the water and then what happens in a school swimming carnival, clearly it stops, mayhem happens, people dive in and try and rescue the child from the bottom of the pool, they bring them out, they're unconscious. They may well have inhaled water, an ambulance is called and they get resuscitated hopefully and off to hospital.

It was interesting when I took the history from Mrs Folbigg when I mentioned her - met her, she never mentioned any need for resuscitation, losing consciousness, going to hospital, and it's - I think that's quite interesting that if that had happened to someone I think you would have been told or you would

remember, particularly when I'm asking about acute life-threatening events, that that would have come up, and it never did. And we don't have from our genetic counsellor here who went to see her exactly what happened, and I think the phenotype and the history there is so important.

We all know in a school carnival, swimming carnival, you know, it's a long hot day, you go to the municipal pool, there's no shade, you're out in the sun all day, no hats, no sunscreen back then, you're dehydrated. The queue to the kiosk to get water is about ten long. When you get there, there's fizzy drinks and, and lollies, so you spend your money on them. You then line up on the edge of the pool to do your race. You race your little heart out to the other end of the pool. You get there and suddenly realise that Julie next door's beaten you so House Kookaburra's going to lose because you didn't win, and you have a terrible vasovagal event. I think that's probably more likely than actually having a true syncope sinking in the pool and having to be resuscitated and taken off to hospital.

But it's an important distinction as I, I hope that that example just showed you. They are two really different things and one is associated with a common events in teenage girls in swimming carnivals, and one is associated with Long QT syndrome and is a very serious condition. And we really don't have a clear phenotype here.

MORRIS SC: That's a matter that will have to be clarified in order for a greater understanding to be had, is that correct?

WITNESS KIRK: Can I comment as well?

WITNESS COLLEY: Yeah, please do. Please, please be, be more respectful than my..(not transcribable)..--

WITNESS KIRK: So in relation to the statement that fainting during swimming is Long QT until proven otherwise, the purpose of that statement in these guidelines is to ensure an immediate assessment of a child who has just experienced such an event, because of the possibility that that might be the diagnosis, and to ensure that they're adequately investigated, and if a diagnosis is made that management should be, should be instituted.

It's not to say that that is the most likely explanation. It's that you must treat it as that until you have proven that it is not. In this case we've had an ensuing 38 years in which there have been a number of ECGs which we've heard Professor Skinner talk about. There's been one stress test that was normal or I believe there's been more testing today, and so it's that overall context in which the, the phenotype should be considered.

In order to segregate a variant and interpret it you need to have a clear phenotype to start with, and we've got four children but the variants are present in two, and it's not clear on what basis we're selecting which two we think have got the phenotype. If you want to do a segregation test you really need to know in advance what you're going to segregate against. You can't

after the fact say well I've got it in these two, they must have had the phenotype. That just doesn't work.

MORRIS SC: I understand. The fact is, do you agree with Professor Colley that the clinical--

WITNESS KIRK: Professor Skinner's point is, it was well made, that if we had clear knowledge that this was an event of the first type that Dr Colley described, that would be highly suspicious for either Long QT or for CPVT which we've discussed previously.

MORRIS SC: Yes, okay. In relation to that history, if the history was that this girl slipped to the bottom of the pool, is that something that would cause you to reclassify your assessment of these genes, cardiac genes?

WITNESS KIRK: It would make me think very seriously about the possibility that they may have CPVT and I would institute appropriate investigations, and I'd be guided by the results of those.

MORRIS SC: Thank you. Your Honour, I've finished.

JUDICIAL OFFICER: Well done, thank you. I feel like a cup of tea for 20 minutes.

SHORT ADJOURNMENT

JUDICIAL OFFICER: Yes, Ms Furness.

FURNESS SC: Thank you. Dr Colley you were taken earlier to some urine test results of Patrick from the Adelaide Children's Hospital, do you recall that?

WITNESS COLLEY: Yes.

FURNESS SC: And the letter that you were also taken to indicated that there were urine tests done in respect of Patrick at another laboratory, that's right?

WITNESS COLLEY: Yes, in Sydney.

FURNESS SC: In Sydney and the results of those tests are in the genetics tender bundle which you have seen, at tab 4, if you want to be reminded of that or if that's sufficient to inform you that you have seen those results?

WITNESS COLLEY: Yes I'm happy then that we have seen those results, thank you.

FURNESS SC: Thank you. Now Dr Colley, Rett syndrome is a genetic disorder?

WITNESS COLLEY: Yes.

FURNESS SC: That's caused by a mutation of the MECP2 gene?

WITNESS COLLEY: Yes correct.

FURNESS SC: Did you find any mutation of the MECP2 gene?

WITNESS COLLEY: No pathogenic variant was found by my molecular colleagues in the gene and when we looked over the genotyping as a team, we did not find any evidence of a pathogenic variant.

FURNESS SC: Did Rett syndrome cause Patrick's death?

WITNESS COLLEY: I don't believe so no.

FURNESS SC: Professor Kirk?

WITNESS KIRK: I don't believe so.

FURNESS SC: Dr Buckley?

WITNESS BUCKLEY: It's not my area of competence but I would correct the nomenclature just to say it's MECP2, MECP2.

FURNESS SC: Thank you. Professor Vinuesa, yesterday you were given the opportunity to provide further articles and to comment on those if you wish to, you have provided I think four articles, some of which have been the subject of evidence this morning, is there anything further you wish to say about any of those articles?

WITNESS VINUESA: I think it might be worth commenting about cardiac disease in Hunter Syndrome.

FURNESS SC: No no no, my question is in relation to the articles, which article are you referring to?

WITNESS VINUESA: Yes, this is the article entitled, "Cardiac disease in patients with mucopolysaccharidosis presentation, diagnosis and management."

FURNESS SC: Yes, that's from the Journal of Inherited Metabolic Diseases 2011?

WITNESS VINUESA: Yes.

FURNESS SC: Is that right?

WITNESS VINUESA: Yes.

FURNESS SC: What do you wish to say?

WITNESS VINUESA: Well just to, first of all I still think I would like to remind everyone that at least in 5% of exomes from patients, there are two different genetic mutations--

FURNESS SC: I'm going to stop you Professor Vinuesa, what are you referring to in this article?

WITNESS VINUESA: Right. So perhaps in page 1 of this article:

> "Cardiac involvement has been reported in all MPS syndromes and is a common and early feature, particularly for those with MPS I, II and VI. Cardiac disease emerges silently and contributes significantly to early mortality."

And then in page 1185:

> "Nevertheless the prevalence and severity of cardiovascular disease in individuals with MPS, especially MPS I, II and VI is strikingly high, occurring in 60 to 100% of those studied, within a particular type of MPS, cardiac pathology generally develops earlier in life for individuals with more rapidly progressing types of MPS."

And then in page 1187:

> "Conduction abnormalities and sinus tachycardia have been reported in 7% of a subset of Hunter Syndrome for Hunter outcome survey of MPS 2 patients."

There is other types of cardiac arrhythmias, we don't need to go into that. That's all I want to present. I think this is the context also if I may say, that it is probable and possible and very well documented, that two different conditions could be present in individuals and if both have a similar or share some type of organ manifestation, that that could compound in the severity of the presentation.

FURNESS SC: And you've said in your supplementary report or your response to team Sydney, that you defer to a metabolic disease specialist in relation to IDS, that's right?

WITNESS VINUESA: Yes my comment is that there could be interaction between two diseases.

FURNESS SC: I understand that, the answer to my question is yes?

WITNESS VINUESA: Yes.

FURNESS SC: Are they the only articles you wish to give evidence as to?

WITNESS VINUESA: Yes.

FURNESS SC: I asked you yesterday to consider whether if the test results from what's being carried out I think tomorrow, were normal, whether that would affect the ultimate interpretation of CALM2 or MYH6?

WITNESS VINUESA: I still feel uncomfortable performing that exercise because I don't think it will be excluded on the basis of the tests that we are performing, given what we have mentioned this morning, on the criteria for diagnosing Long QT Syndrome, but we have done the exercise and I can comment on that hypothetical possibility, it wouldn't change it--

FURNESS SC: Well it's not hypothetical we'll know tomorrow, it's not hypothetical in that sense Professor, you understand that don't you?

WITNESS VINUESA: I do, I just mentioned that still, right okay. The answer is no because the issues that were borderline for what some of these mutations were about the moderate criteria. For CALM2 we had two moderate criteria. For supporting, one less supporting criteria would bring it down to three so we would still have a likely pathogenic variant and we are not applying BS2 because we cannot assume full penetrance. For MYH6 the issue when we said it was borderline between VUS and likely pathogenic it was in the moderate criteria, whether we had one or two, the issue was whether there was common benign variation and the highest variation we found still occurred in 1 in 4,500 individuals, so for us we would still be more comfortable leaving our classification as it is, likely pathogenic, bringing three supporting criteria to two would not change that evaluation. BS2 would not apply again for the same reason, as I'll come to. For IDS we had two moderate and four supporting, so bringing that to three would not change the valuation.

FURNESS SC: Now your report that you provided us originally was then changed shortly thereafter, that's right?

WITNESS VINUESA: Yes, within 24 hours I saw that I had not changed the actual table, so I submitted the same report but changing the - just the wording of the conclusion.

FURNESS SC: Perhaps we can have the report on the screen, that is the report that you provided on the second occasion and the page dealing with I think it was CALM2 wasn't it?

WITNESS VINUESA: Yes.

FURNESS SC: Page 21. So do you see at the bottom under the heading "Interpretation" you say, "VUS or likely pathogenic"?

WITNESS VINUESA: Yes that is the one that we changed.

FURNESS SC: What did you change it to, that's the report--

WITNESS VINUESA: Likely pathogenic.

FURNESS SC: I beg your pardon?

WITNESS VINUESA: Likely pathogenic.

FURNESS SC: As I understand it, what is on the screen is the document you provided on the second occasion. Do you see on the previous page under the heading "Classification" you have "likely pathogenic", do you see that?

WITNESS VINUESA: So I was nearly convinced I had sent you the revised one so I'm surprised, it must have been a mistake, I did send a second email to Amber--

FURNESS SC: No no no, Professor--

WITNESS VINUESA: Yes.

FURNESS SC: Look at the previous page under the heading "Classification", in the box at the bottom of the page?

WITNESS VINUESA: Yes.

FURNESS SC: That says "likely pathogenic"?

WITNESS VINUESA: Yes.

FURNESS SC: Do you see that?

WITNESS VINUESA: Yes.

FURNESS SC: And then if you go on to the next page the interpretation is "VUS or likely pathogenic"?

WITNESS VINUESA: Yes, so that should have been changed because--

FURNESS SC: So you didn't change the second one but you changed the first one, is that right?

WITNESS VINUESA: Well I was under the impression I had changed both, as I say we had to submit it with a very small timeframe, I was working in the evening doing this and I'm nearly convinced I had hanged it, clearly from here we see we have two moderate and three - I mean we have two colour highlighted with yes so that makes it two moderate and we have four yeses in supporting, one is no yes but that wouldn't change the classification so clearly it says two moderate, four supporting, that would be likely pathogenic.

FURNESS SC: So you're saying this should be amended to remove VUS or in the interpretation section?

WITNESS VINUESA: Yes.

FURNESS SC: Now can I turn to team Sydney, there has been discussion over the last few days about the ACMG standards and guidelines and whether and if so how they should apply, either Dr Buckley, Professor Kirk or Dr Colley, why do you say the ACMG guidelines and standards should apply to the exercise you've carried out for the Inquiry?

WITNESS BUCKLEY: Because the rationale for that was that the investigation of sudden death of a child is intrinsically a clinical matter and therefore as the ACMG guidelines are developed to guide clinical understandings we thought they applied in this instance.

FURNESS SC: Professor Kirk do you want to add anything?

WITNESS KIRK: No, no I agree with that, I think it's reasonable.

FURNESS SC: Dr Colley?

WITNESS COLLEY: I agree.

FURNESS SC: I have nothing further. Perhaps if Professor Vinuesa and Dr Arsov can be excused.

JUDICIAL OFFICER: Yes I think they can be excused. Thank you very much for coming and thank you for taking part in the investigations.

WITNESS VINUESA AND WITNESS ARSOV WITHDREW

FURNESS SC: Now your Honour, I call - two of whom are on AVL, Associate Professor Michael Fahey and Professor Ryan.

AUDIO VISUAL LINK COMMENCED AT 11.54AM

JUDICIAL OFFICER: Thank you. We have on the screen - this is?

FURNESS SC: Associate Professor Fahey.

JUDICIAL OFFICER: Professor Fahey, can you hear us Professor Fahey?

FAHEY: Yes sir.

JUDICIAL OFFICER: And the other?

FURNESS SC: Professor Ryan.

RYAN: We seem to have an issue with the camera, I'm sorry I'm not sure what the problem is exactly.

FURNESS SC: Is that you Professor Ryan?

RYAN: Yes can you hear me now?

FURNESS SC: I can, but I don't know your voice, so it is Professor Ryan who is now speaking?

RYAN: Yeah I am speaking, my name is Monique Ryan. I'm sorry the camera was working and it seems to have stopped for reasons which are unclear.

FURNESS SC: Your Honour we can proceed without vision.

JUDICIAL OFFICER: Yes we can proceed without vision.

FURNESS SC: Unless your Honour needs it to swear the witness.

JUDICIAL OFFICER: Well we can do that by way of video link as well.

LTS:DAT

<MICHAEL COLLINGWOOD FAHEY AND MONIQUE MAREE RYAN, SWORN(11.56AM)

FURNESS SC: Professor Ryan would you tell the Inquiry your full name and professional address?

WITNESS RYAN: Monique Maree Ryan, I'm Director of Neurology at the Royal Children's Hospital in Parkville, Victoria.

FURNESS SC: What are your qualifications Professor?

WITNESS RYAN: I have medical degree from Melbourne University, I'm a fellow of the Royal Australasian College of Physicians, I have a Masters in Medicine from the University of Sydney and advanced training in paediatric neurology and neurophysiology accredited by the Australia and New Zealand Child Neurology Society.

FURNESS SC: Do you have any qualifications in clinical genetics?

WITNESS RYAN: I do not.

FURNESS SC: Have you worked in that area?

WITNESS RYAN: I see many patients with genetic disorders because my area of particular specialty, neuromuscular disorders is one in which most patients actually do have genetic conditions, so I have a lot of expertise I guess in dealing with children and with these sorts of conditions but I don't have any formal qualifications in that area.

FURNESS SC: When you have patients who you believe may have a genetic condition, do you get that dealt with by a geneticist or do you diagnose it yourself?

WITNESS RYAN: That's a bit variable, so it it's a neuromuscular disorder I think my expertise would probably trump that of a clinical geneticist but in other areas I might seek the assistance of advice of a clinical geneticist and in areas where there's questions I guess we would probably work together.

FURNESS SC: Did you say neuromuscular?

WITNESS RYAN: Neuromuscular yes.

FURNESS SC: Sorry we're not familiar with some of these terms so we might just need you to speak slowly when you use terms that we're not familiar with so thank you for clarifying that.

Now Professor Fahey, your full name and work address?

WITNESS FAHEY: Michael Collingwood Fahey, I'm Director of Paediatric Neurology at Monash Children's Hospital and head of neurogenetics here.

FURNESS SC: What are your--

WITNESS FAHEY: My qualifications.

FURNESS SC: What are your qualifications?

WITNESS FAHEY: Bachelor of Medicine, Bachelor of Medicine, Bachelor of Surgery with Honours from Monash University, PhD from Melbourne University and I've trained through the RACP in Child Neurology, Paediatrics and ..(not transcribable)..

FURNESS SC: Do you hold any other positions Professor Fahey?

WITNESS FAHEY: I'm the neurologist to the Paediatric Rehabilitation Unit at Monash Children's hospital and I'm a neurogeneticist to the neurogenetics clinic at Royal Melbourne Hospital.

FURNESS SC: Can I come back to you Professor Ryan, you were asked to provide a report by solicitors Cardillo Gray partners?

WITNESS RYAN: Yes.

FURNESS SC: And you were provided with the material that you set out on page 1 of your report?

WITNESS RYAN: That's right.

FURNESS SC: In addition the Inquiry provided you with a bundle of further documents?

WITNESS RYAN: Yes.

FURNESS SC: That's right?

WITNESS RYAN: That's right.

FURNESS SC: The report you provided prior to receiving those further documents is dated 15 March 2019?

WITNESS RYAN: That's right.

FURNESS SC: I tender that report.

EXHIBIT #AJ REPORT BY PROFESSOR RYAN DATED 15/03/19 TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: Having received the additional documents from the Inquiry, Professor Ryan, is there anything you wish to add to or amend your report?

WITNESS RYAN: Not substantially but I guess that in my original report I had suggested that Patrick's case might be better understood with the benefit of additional genetic testing--

FURNESS SC: Yes.

WITNESS RYAN: --and I'd suggested that that be undertaken by means of Whole Exome Sequencing or ideally by Whole Genome Sequencing, and the documents which were subsequently forwarded to me contained results of that testing, and my conclusion on, on reviewing those documents was that a causative genetic condition for his presentation, of course, was not identified on the basis of that genetic testing. That did not, however, change my substantive view that the, that his presentation was potentially consistent with an as yet identified undiagnosed genetic disorder.

FURNESS SC: When you say "as yet identified undiagnosed genetic disorder", what do you mean by "identified"?

WITNESS RYAN: Well, the genetic testing that's been undertaken and the other extensive investigations which have been undertaken to date have not identified a diagnosis for his, accounting for his clinical course, but my, my feeling is that, that that course is potentially still consistent with an underlying genetic condition. What I can't do is give you a name for that condition.

FURNESS SC: What's the basis for your view that there's an underlying genetic condition that hasn't been identified, Professor?

WITNESS RYAN: I guess my, my, my underlying view was based on the fact that his, I felt that there are aspects of his clinical course which were atypical or unexplained and which were, which remained poorly understood at the time of his death and which I think remain poorly understood now, and that one of the potential causes for that course and that, for his condition was an underlying genetic disorder. Obviously the, the concern is that a, a, an alternative explanation is inflicted injury but there were things about his course which I felt to be atypical or inconsistent with a single inflicted injury at the age of four and a half months and, and that was why I suggested that a genetic condition was a possible alternative diagnosis.

FURNESS SC: All of the alternative diagnoses you provided have been the subject of testing; do you understand that?

WITNESS RYAN: I do.

FURNESS SC: So are you suggesting from the base of your expertise that there is a genetic disorder that is potential in Patrick's case that was not the subject of testing?

WITNESS RYAN: The, the issue with the genetic testing is that, even in the very best of hands and with the very best genetics, geneticists using the most up to date databases that in children with unexplained genetic disorders and,

and only undertake Whole Exome Sequencing or Whole Genome Sequencing we identify a causative mutation or a genetic cause for their presentation in only about a third of cases. So in, in instances where it's very, very clear that there's a, an underlying genetic disorder by virtue of the family history or the clinical presentation, we, we still are unable to identify the genetic cause of that in the majority of instances and my concern is that this is one of those instances in which there, there might be an underlying genetic problem but we haven't been able to identify it with the knowledge that we have in 2019.

FURNESS SC: I don't understand, Professor, why you're assuming that there is an unexplained genetic disorder; can you help me there?

WITNESS RYAN: I think that the, the - in my report I laid out a number of things about Patrick's presentation and course which I felt were atypical, things about, the, the specific things which I can go through if, if you'd like me to do that which didn't go along with the expected trajectory of a child who has a, a, an acute hypoxic ischaemic insult at the age of four and a half months and then has neurological residua of that insult. There were other thing that, there were things at the time and subsequent to that initial presentation which appeared to me to be atypical of the course of, of a child having sustained that sort of insult and so my question was whether he, in fact, had a different condition, a different diagnosis and, in children with progressive neurological disorders in the first 12 to 18 months of life, a genetic cause would be one of the top two or three things that you would consider in that instance.

You would consider things like infection, but they were excluded. You would consider those metabolic disorders which are easily excluded but they were excluded as best they could do at the time, and then you would consider things like genetic disorders as well, and so that's how I came to that suggestion.

FURNESS SC: And the genetic disorders that you considered have been the subject of testing and the result of that testing is that those genetic disorders were not found to be present in Patrick; do you understand that?

WITNESS RYAN: I do understand that the testing that has been undertaken has included, as best we can in 2019, those known genetic causes of those presentations, but if I, for example, took patients - I, I, I suggested a number of alternative possible diagnoses in my report. One of them, just for, as an example, is a condition known as alternating hemiplegia of childhood in which children have developmental delay, fluctuating movement disorder, fluctuating feeding issues and changes in their tone over time. If we took all children with that clinical diagnosis in 2019 and subjected them to genetic testing, we would not find a genetic cause in all of those patients and that's because there are unknown genetic causes of that presentation at that time - at this time. So the genetic tests that we have, I guess, I'm suggesting is, it, it does not identify all of the neurological - the cause of all of the genetic neurological disorders that we see in infancy.

FURNESS SC: Initially I asked you to clarify whether you were referring to genetic disorders which are known but were not captured by the testing and I

understood that to be your answer. However, your answer you've just given now suggests that you're referring to unidentified as yet genetic disorders. Can you clarify that for us?

WITNESS RYAN: Sorry, I'm a little bit confused. What I, what I'm talking about is genetic disorders for which the genetic cause or basis is not yet known and there are, every, every year in the - every week in the medical literature the, the cause of genetic disorders is better delineated by the finding of new genes that cause recognised or novel clinical syndromes.

FURNESS SC: So are we to understand your position is that you are not convinced that Patrick's clinical history is consistent with him having neurological deficits resulting from a single hypoxic ischaemic episode on October 18 and the possible cause of that episode is an as yet identified genetic disorder; is that--

WITNESS RYAN: That's right.

FURNESS SC: --how we're to understand your evidence?

WITNESS RYAN: That's right.

FURNESS SC: You understand that when Patrick arrived at emergency he was hypoxic?

WITNESS RYAN: Well, I'm not, I'm not sure that I, I do understand that. So my, the information that I was given that was when he arrived at the emergency department he was found to have a, a low blood oxygen on oxygen, oximetry, which is when put a, a probe on the finger or on the toes and measure the blood oxygen in a, a somewhat indirect fashion.

FURNESS SC: It was 88%, wasn't it, Professor?

WITNESS RYAN: On the oximetry, yes, so, which is low but not terribly low and--

FURNESS SC: But it's hypoxic, isn't it?

WITNESS RYAN: Well, no, well, a hypoxia is a slightly different thing. Hypoxia is when you have a measured low oxygen level in the blood and he didn't have a - and, and we would measure that by, by means of a blood gas. As far as I could determine he didn't have a blood gas and oximetry where you put a probe on the fingers or the toes can be inaccurate. It can misread the blood oxygen levels, especially in a child who's got, who has what we call shut down, who's, who doesn't have the normal blood flow to the extremities and it's an indirect measure of the blood oxygen level.

So I wouldn't say that a child who had an oxygen level measured by oximetry on a single occasion of 88%, I wouldn't infer that that child was hypoxic. I would like to know, have a, a formal measurement of their blood gases

demonstrating, you know, with a little bit more, more definitively that the blood oxygen level was low.

FURNESS SC: So you describe Patrick based on the medical records that you've read as a vigorous normal baby who was behaving normally and, apart from a snuffly nose, was otherwise well; that's right?

WITNESS RYAN: Well, yes and no. I think it's a little bit hard to be sure. There are, there, there are some descriptions of him in the, in that where he's described in the, in that sort of matter. In his infant health book, for example, it says that he's, he's strong in the legs, he's trying to roll over when he's three months old. He's, is very, he's visually responsive but, and by 15 weeks when you, and by 20 September he was reaching for objects and, and grabbing at them, so he was doing quite well developmentally at that point, but there are some, some things which are a little bit at odds with that. So, for example, on the day that he presented very unwell on 18 September (as said) and where his time was variously described as being normal or decreased and there was some arching of his neck, there was also--

FURNESS SC: Can I just stop you there, Professor? Can I just stop you there and ask you to direct your attention to before Patrick's event on 18 October.

WITNESS RYAN: Yeah.

FURNESS SC: Before his event he was--

WITNESS RYAN: Yes.

FURNESS SC: --invariably described as a normal, well, otherwise healthy baby; that's right?

WITNESS RYAN: Except that on the, on the day that he presented he was, he was moving in an abnormal fashion and he was neck arching and there was a note in the notes that he always did this.

FURNESS SC: I understand that but are you taking issue with the description of Patrick as a well, behaving normally baby before the event on 18 October? Do you take issue with that?

WITNESS RYAN: I think, I think there's, there's just a couple of things which are at odds with that and those two things are the fact that he had torticollis, which can be a benign phenomenon but not, is not always a benign phenomenon, and because there was this description that he always tended to arch his back at times. Now, I don't know what to make of those but they, they suggested to me a possibility that he was not entirely normal prior to 18 October.

FURNESS SC: And you know from the genetic testing that was done that various epilepsy encephalopathy and other matters referred to in your report and Professor Fahey's report ruled out any of those genetic conditions, don't

you?

WITNESS RYAN: To the extent that we're able to do that by genetic testing, yes.

FURNESS SC: Now can I come back to your conclusion that you were not convinced that his clinical history was consistent with him having neurological deficits resulting from a single hypoxic ischaemic episode? I take it you accept that it is possible that, indeed, he did have a single hypoxic ischaemic episode on that day?

WITNESS RYAN: It's possible, yes.

FURNESS SC: It's probably, in fact, reasonably possible, isn't it, Professor, given the results of the genetic testing?

WITNESS RYAN: I don't think I, that I would infer from the genetic testing - I, I wouldn't feed that back onto my interpretation of the descriptions of an event on a, in a patient's life. I think, you know, absence of evidence is not evidence of absence. It's, I, I think it would be inappropriate to say all the genetic testing is negative at this point so that must be what had happened.

FURNESS SC: So you're preferring a diagnosis that you are not convinced of the single hypoxic ischaemic episode as against a yet to be known genetic disorder that he may have suffered from; is that right?

WITNESS RYAN: I think that there's sufficient doubt about his presentation and his clinical course to - that I, I would not feel, you know, as I said in my report, I don't feel comfortable ascribing his findings and his subsequent course to the after effects of a single hypoxic ischaemic episode.

FURNESS SC: That was primary because of the variability of his presentation, if I can put it in a shorthand form?

WITNESS RYAN: The variability of his presentation, the apparent progression of the imaging changes on his CT scans, in as far as we are dependent on the reports of the CT scans, having not been able to review them, the evolution of his seizure disorder, and some, some aspects of the way in which he was described during seizures or other sorts of episodes. Also, the apparently late recognition of visual loss, which it's not quite clear at what point he sustained, what point he lost his vision.

FURNESS SC: Can I turn to you Professor Fahey.

WITNESS FAHEY: Certainly.

FURNESS SC: You were asked to provide a report to the Inquiry--

WITNESS FAHEY: Yes.

FURNESS SC: --after the genetic testing results were available. That's right?

WITNESS FAHEY: It was, it was concurrent with the genetic testing becoming available, so Professor Buckley's report was, was happening in a similar time.

FURNESS SC: You asked Professor Buckley to consider a list of 204 genes explicitly relating to epilepsy, metabolic conditions and dystonia?

WITNESS FAHEY: That's correct. I heard some of the discussions this morning, and if I could take the opportunity just to explain the process as Dr Buckley was asked about it?

FURNESS SC: Certainly.

WITNESS FAHEY: If that's okay. So I had Professor Ryan's report and I, I spent some time going through the conditions which she had mentioned, and including those in the article of Ng, but also those relating to the, the differentials that she'd provided. I then went to see as many different variations on those conditions, not just the genes in the, in the Ng articles, but as many variations from a number of different sources to provide what I'd consider to be an extensive list, and provided that in discussion with Dr Buckley, including other genes of conditions which, which may be missed, may be mimics of, of childhood epilepsy, with the knowledge and the discussion that really we were - we had had a hypothesis-free analysis undertaken already and then - but if I was to have a discussion with him about which genes I'd want to make sure we absolutely had excluded, this was the 200 or so genes involved in that.

So I acknowledge that they had already been looked at, but, but often times in the clinic this is a, this is a discursive process, it's an iterative process where a clinician will have a hypothesis, and I looked at Professor Ryan hypotheses and I made some of my own and I discussed those with Professor Buckley about what we might find. So these genes were - a gene list was provided.

FURNESS SC: Then you prepared your report taking into account the results of those tests?

WITNESS FAHEY: Correct.

FURNESS SC: You had Professor Ryan's report obviously at the time you prepared your report?

WITNESS FAHEY: Correct. I was asked to comment as you'll see in my instructions on Professor Ryan's report.

FURNESS SC: Is there anything you wish to alter in relation to your report?

WITNESS FAHEY: Thank you. There is. There was some sloppy, slopping writing that I apologise for, on page 8, one - 143, I'd like to rewrite that and to read "Professor Ryan has not described the oxygen saturation on presentation

of 88% as hypoxic. All this hypoxia is a differential diagnosis at this clinical state at that time."

FURNESS SC: So by making that amendment you recognise that Professor Ryan recorded an oxygen saturation on presentation of 88% and that he was poorly responsive to painful stimuli and had glycosuria, and you wish to refer to her not referring to that presentation as hypoxic, is that right?

WITNESS FAHEY: Correct.

FURNESS SC: I tender the report.

EXHIBIT #AK REPORT OF PROFESSOR FAHEY TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: Just continuing on the genetic basis for the moment Professor, you conclude under the heading of "Genetic Testing" on page 4 of your report, that:

> "No genetic variants were identified which could be considered pathogenic as is understood in 2019, using standardised interpretive methods in Patrick, his mother and his siblings."

Do you see that?

WITNESS FAHEY: Yes.

FURNESS SC: Then further on you consider that the "investigations are comprehensive and they virtually eliminate a recognised genomic cause". Do you see that there?

WITNESS FAHEY: That's correct.

FURNESS SC: So you're satisfied that of the genes that could be identified in 2019 related to your area of expertise, there is no variant that was identified in respect of these individuals, that's right?

WITNESS FAHEY: If I could add a word counsel, no pathogenic variant was identified.

FURNESS SC: Thank you. When you say "they virtually eliminate a recognised genomic cause" why do you use the qualification "virtually" there?

WITNESS FAHEY: Because I, I think that an absolute is not a reality in, in medicine, or in, in genomics, and - but as far as we can do so in 2019, and as far as the genomic causes are recognised we, we have not, we have looked hard - not just in Patrick, but in comparative genomics, at him and his siblings and his mother, and we haven't identified anything which is a, a consistent finding or indeed a pathogenic disease cause finding in Patrick.

FURNESS SC: At page 16 of your report you repeat that using slightly different language, that all recognised pathogenic changes are now excluded. Do you see that?

WITNESS FAHEY: Yeah, I, I agree with that statement.

FURNESS SC: So by inserting the word "recognised" do you accept that that's the case as at today, but it may not be the case tomorrow?

WITNESS FAHEY: Correct.

FURNESS SC: Dr Buckley, is there anything that you wanted to say about the genetic testing?

WITNESS BUCKLEY: No, I believe that genetic testing has been comprehensive, has been diligently done. It's been done in two separate laboratories. It's been done to international best practice standards. It's had a diversity of people looking at the data from different cultures in a sense, a research culture and a diagnostic culture, and I think we are all in agreement that there is no likely pathogenic or pathogenic variant in a known disease causing - a gene that causes a significant disorder in children, as knowledge stands in April 2019.

FURNESS SC: Thank you. Professor Fahey you are of the opinion that when Patrick presented at the emergency on 18 October he was hypoxic?

WITNESS FAHEY: I, I accept that Professor Ryan said, but I think that the face value is that Patrick was hypoxic at that time. He responded to oxygen at that time, and I think that at the end of the day his pathology shows that he had ischaemic changes.

FURNESS SC: The relevance of those ischaemic changes are what?

WITNESS FAHEY: That he had hypoxia at some stage.

FURNESS SC: Are there any other areas that you're aware from the documents you've received, including any tests undertaken on Patrick that support hypoxia?

WITNESS FAHEY: So, so I, I suppose the question of whether or not his brain scans, and I was alerted to just recently by Professor Ryan, are consistent with hypoxic damage, a so-called watershed damage, and whether or not his EEG and the evolution of those changes could be consistent with that seen after an hypoxic event, and I, I tried to mention that in my report as well.

FURNESS SC: So you're saying they're supportive as well, is that what your evidence is?

WITNESS FAHEY: I, I think, I think that they are supportive of that. I think that their - the changes that we see before the - in my opinion, before the 18th he

was a typically developing child, and after the 18th he had an evolution of changes and I think we need to be careful about the wording of evolution versus progressive, because we're not finding anything suggestive, either pathologically, biochemically or genomically, that suggest that he had a, an underlying progressive disease.

FURNESS SC: Thank you. Can I turn to you Dr Colley. You have had regard to the medical records available to you of Patrick?

WITNESS COLLEY: Yes.

FURNESS SC: Tell me whether this is an area that you have relevant expertise in, but from your review of those records, and I think you've had the opportunity to see Patrick - Professor Fahey and Professor Ryan's report, your view is that Patrick was a healthy, well-developed normally progressing baby before the ALTE?

WITNESS COLLEY: Yes, correct.

FURNESS SC: The torticollis (as said)--

WITNESS COLLEY: Torticollis.

FURNESS SC: Torticollis, thank you, that was referred to by Professor Ryan, you were aware that there was evidence to some extent of that in the notes?

WITNESS COLLEY: Yes. It's a not uncommon condition which is often quite benign, and so I think adding it into a life-threatening, acute life-threatening event, is not necessarily what I would do. I'd say it's a standalone, and on its own doesn't make a diagnosis of a neurogenetic condition.

FURNESS SC: What about the presence of back arching to the extent that the notes said he always does this?

WITNESS COLLEY: It's, it's hard to know what to make of that. Children do back arch when they're a bit irritable, they're unhappy, they're crying. They might have some indigestion, some reflux. One of the things I guess as a doctor, as a paediatrician or geneticist will always note, that when a baby's healthy and well what can be normal behaviour or things just go unnoticed, they're just part of a normal baby behaviours. When a catastrophic event happens, obviously mothers, families and doctors try to go back into the history and say is there anything, anything possibly that could give us some clues, and so you often have an overzealous natural wanting to find something beforehand, and something that might not really be relevant suddenly perhaps can assume a greater importance than what it should.

And so it's, it's very hard in retrospect to know whether that was really relevant. If his paediatricians, GPs, nurses, someone had written beforehand actually objectively in the notes "This child is back arching", then that would be more relevant.

FURNESS SC: Is it your view that he was hypoxic when he presented at the emergency centre based on the 88%?

WITNESS COLLEY: Yeah, I mean obviously as Professor Ryan said a blood gas would have been ideal and it would have been good, but we don't have it, and so my opinion is that yes, he was hypoxic when he presented. I make one comment that in the notes it did say that obviously when he was found at home in this state the ambulance was called, the paramedics came. The paramedics put oxygen on him and - so he had oxygen. I don't know whether that oxygen was continued, it probably was, in the ambulance to hospital, and I don't know whether that oximeter at 88% was actually while he was on oxygen or not, and perhaps Professor Fahey could make a comment about whether that would be relevant.

FURNESS SC: Professor Fahey?

WITNESS FAHEY: I suppose we need to wonder about, about whether or not he has a drive to breathe at that point, so it's, it's a problem with breathing or it's a problem with the oxygen getting through to his lungs. We, we don't have too much evidence that he had a direct lung condition, aside from the X-ray that mentioned maybe bronchiolitis, but that seems to have disappeared through, through the notes. So I, I couldn't find those - I agree with Dr Colley but I couldn't find those - the reference to the oxygen in the ambulance notes or, or the saturations taken en route.

FURNESS SC: Professor Kirk, do you want to add anything to this?

WITNESS KIRK: No, I don't think I've got anything to add.

FURNESS SC: Coming back to you Professor Fahey, you considered the evidence as to his presentation on the 18th and then his presentation or how he appeared over that day and the night into the 19th.

WITNESS FAHEY: Yeah.

FURNESS SC: What opinion did you form about that change in presentation from when he was hypoxic, in your opinion, at emergency to when he began having seizures the following day?

WITNESS FAHEY: So, so remembering that my, my brief was to think about Professor Ryan's notes and, particularly, refer people to Professor Ryan on page 14 in the second paragraph from the bottom, which was about if, if he had a severe hypoxic episode then why was he - so, Professor Ryan's notes, not my notes, sorry - if he had a hypoxic episode, why did he return to being a feeding baby who through, through some stage of the afternoon was, was said to be relaxed, and his EEG on that first day of presentation was normal?

And so, I, I went back over the literature and - to address this, and looked at the literature of..(not transcribable)..presenting with hypoxia and, particularly in

regards to when seizures emerge after hypoxia and, second, in relation to his clinical state and whether or not it had been reported of children who, after an apparent hypoxic event, life-threatening event, became then near normal before, before progressing. And it was difficult to find the literature, partly because the ALTE literature excludes those with hypoxia or an alternative diagnosis and the BRUE literature, or the BRUE literature certainly excludes children who, who may have something else going on.

And so - but there are reports going back into the - into the 90s - 1989, sorry, rather - Constantinou, who was a colleague of Professor Ouvrier's, who, who described a group of 14 children who presented similarly to how Patrick presented and, of those, half of them were comatose and remained comatose, but half of them had a period of apparent lucidity and, and they say that they were striking an interval of near normality before neurological deterioration, with an evolution of seizure disorders in some instances over days. And that was echoed in the - in some of the older drowning literature, which, which reflected the evolution of the EEG changes that would happen from early on to evolving with time over the, the 72 hours up to a week, with progressive changes of slowing and then electrical discharges.

So, I was satisfied from that that this was a possibility after hypoxia and that it had been reported, in fact remarkably similar to how Patrick presented. I then took a - again, a hypothesis-free result approach in the - in the clinical side of things about, well, what, what does the literature say if this was a seizure and this was the beginning events of, of the epilepsy? And, the Bonkowsky article, which I, I mentioned there and it's, it's associated editorial, shows that in about 3.5% of the ALTE children it's the first presentation of seizures and, in fact, those seizures also can be - can be initially normal and evolve with time.

But they make some points about that in Farrell and that is that there's a strong family history, in many if not all, in those who evolve to seizures. And so, I thought that that was a possibility, but less likely, maybe, than the first option.

FURNESS SC: So, by this stage, Professor, is it the case that you had excluded the theory of unrecognised seizure on presentation? Is that how I'm to understand your evidence?

WITNESS FAHEY: I, I thought that was less likely. I thought that was less likely and, and there were some other points about that that aren't in my report but I'm happy to talk about, and that was the - if he'd had a, a seizure that was one which led him to have a low oxygen saturation, if not be hypoxic, and be unresponsive, that first seizure was very different from any of the other seizures he presented with across his life. He never showed that semiology again, the seizures seemed to be stiffening seizures or soaking seizures, or even eye-rolling seizures potentially later. And, and so that would make the first event different from the other events, which I would consider unusual.

FURNESS SC: So, as you've said, you have considered it less likely that it was an unrecognised seizure on presentation. You've also indicated, by reference to the literature, particularly Constantinou, that it was not

inconsistent with hypoxia on presentation, the variability in his presentation. Are there any other matters that you took into account, leaving aside the genomics, in coming to the view that you ultimately do?

WITNESS FAHEY: I, I think the visual loss is important and that was commented on in Professor Ouvrier's original report. And one, one interesting annotation of that is that the visual loss is, is noted on his ophthalmological review, but when - which was on 20 November in that year, 1990 - but when asked, the history documents very well that it had been present for about a month, according to Patrick's mother. So, she, she dates it back to at or around the time of - I can - I can join the dots on that of a - of his life-threatening event or his presentation on 18 October, about a month earlier.

FURNESS SC: Can I come then to page 15 of your report?

WITNESS FAHEY: Yeah.

FURNESS SC: You deal, at the top of the page, with the changes on post-mortem, which I think you've already given evidence about.

WITNESS FAHEY: Yeah.

FURNESS SC: Then, coming down to the next paragraph, you refer there to, Professor Ryan's, as you say "speculation about genetic causes of the tonic upward eye deviation"--

WITNESS FAHEY: Yeah.

FURNESS SC: --and you note there that the Whole Genome examination didn't see anything to that effect. That's right?

WITNESS FAHEY: That's, that's correct, it didn't identify pathological changes.

FURNESS SC: And then further, you go down to the physiotherapy assessment of Patrick, and your opinion as to the meaning of that differs from Professor Ryan. Can you explain that to us?

WITNESS FAHEY: Sure. So, it's a - it's an interesting physiotherapy report because the, the body of what she's written I think differs slightly from her conclusion, and so, as a - as a developmental neurologist, I describe myself as, and someone who's, who's been heavily involved in the diagnosis of cerebral palsy and, and guidelines on the diagnosis of cerebral palsy, I would consider that this examination, as she describes, is atypical and warrants further investigation. And I've highlighted the, the bit there, it's on the next page on your screen.

So, specifically, I'm concerned about him being - going up on his toes, the tone being increased, some asymmetry in his, his increased tone, decreased control on his left side, but that being improving. So, so I, I consider the, the -

that that may indicate an underlying brain damage and, as I say, "investigate for brain abnormality", but specifically for ischaemic brain changes. And, as I've mentioned there, there are - there are notes to the same, that Dr Wilkinson shared some concerns, although it maybe wasn't as, as highly ..(not transcribable)..in 1990 as it would have been in 2019.

FURNESS SC: And the genetic sequencing that was done in relation to Patrick indicates that there was no, what could be described as a, brain abnormality, is that right?

WITNESS FAHEY: So, so, we, we put together on - there's been lots of discussion about the phenotype. We, we put together a range of things to, to have us - for the phenotype, including the neuroimaging, the, the pathologies in Patrick's case and then - and then whatever other information we have available. I, I - we had not identified any genomic changes in 2019 which would explain, in my - his presentation to explain the episodes of eye-rolling or explain this particular examination as laid out by the physiotherapist on that date.

FURNESS SC: Now, you refer to the question asked of Professor Ryan--

WITNESS FAHEY: Yeah.

FURNESS SC: ---whether Patrick's condition is consistent with a single hypoxic episode on 18 October? What's your answer to that question?

WITNESS FAHEY: I, I believe that he had a presentation consistent with a severe hypoxic event on 18 October and I - and I don't - I, I don't believe we've found alternative diagnoses and I think we have a - sorry, we have pathology at post-mortem which is concordant with ischaemic changes, from the reports I've read.

FURNESS SC: Thank you.

WITNESS FAHEY: And I, I didn't see any of the pathologists disagreeing with that - with that. And, and furthermore, we're not seeing evidence on pathology of there being a progressive bone abnormality, as, as might have been described, and, and I think his brain changes explain his visual loss and, and his clinical examination findings.

FURNESS SC: Your reference to "the pathologists" is a reference to the evidence that was given a few weeks ago by a number of forensic pathologists to the Inquiry, is that right?

WITNESS FAHEY: That's correct. That's correct.

FURNESS SC: And the evidence that they gave that they saw no degenerative disease in the post-mortem?

WITNESS FAHEY: Correct. Correct.

FURNESS SC: Just coming back to you, Dr Colley. Is there anything that you want to say about the process from presentation to the seizures that were observed, perhaps in the early hours of 19 October, in relation to the variability as has been described by Professor Ryan and Professor Fahey?

WITNESS COLLEY: Can I just clarify, counsel, do you mean from the time when Patrick had his life-threatening event to the time - during the time subsequently to his demise?

FURNESS SC: No. There has been evidence about the variability of his presentation. He seemed well, initially, his EEG - ECG was normal and he was feeding well and the like, and then he had the seizures overnight.

WITNESS COLLEY: I see, the first - no, I defer to Professor Fahey and I agree with everything that he has just said about that. Just to again make the point that, up until the time when Patrick was found in his bed at home, there was none of these features noted by any of the health professionals who saw him. So, there was a, a sudden onset.

FURNESS SC: When he was "found in his bed", do you mean on 18 October?

WITNESS COLLEY: Yes, yes.

FURNESS SC: Yes, thank you. Professor Kirk, is there anything you wanted to add to that?

WITNESS KIRK: No, I mean, like Dr Colley, I would defer to Professor Fahey on this.

FURNESS SC: Coming back to you, Professor Ryan--

WITNESS RYAN: Yes.

FURNESS SC: --now, you've heard the evidence that's been given by Professor Fahey in relation to his theory that he assumed an unrecognised seizure on presentation and the reasons he gave for not accepting that as a theory that applied in this case. Do you agree with that?

WITNESS RYAN: I'm sorry, can I ask you to, to rephrase that?

FURNESS SC: Certainly. Professor Fahey's been giving evidence as to assuming a theory of unrecognised seizure on presentation, which is set out in page 13 of his report, and he concluded that that was unlikely to be the case. Do you agree with that?

WITNESS RYAN: No, not entirely. Because I, I guess - I mean, there's, there's a few things about that. I mean, the first thing is - that I would - will comment in response to Professor Fahey's report is that I don't think that the literature on near drowning is relevant in this setting.

FURNESS SC: Can I just leave near drowning for the moment--

WITNESS RYAN: Okay. All right.

FURNESS SC: --and just ask you to address my question?

WITNESS RYAN: So, if we just talk about the seizures, so, I mean, a single unrecognised seizure, if it were prolonged, can result in hypoxic ischaemic injury to the brain. It can result in the sort of pathological changes that were subsequently seen on Patrick's post-mortem evaluation and, and, and I'm not sure on what grounds it - that could be - I, I don't feel that that could be confidently excluded as a, a cause for his acute episode on that date.

FURNESS SC: Now, he - that is Professor Fahey -refers to various literature--

WITNESS FAHEY: Yes.

FURNESS SC: --in relation to near drowning. What did you want to say about that?

WITNESS RYAN: I just don't think it's relevant. I think near drowning the, the, the circumstances are, are different, the pathology is different, there are other variables related to things like body cooling and time of submersion and things like that, which would - I think would - I mean, this is a very poor way to put it but, it would muddy the water to bring in the drowning literature in this instance.

FURNESS SC: Professor Ryan is there's anything you've heard from Professor Fahey or Dr Colley that causes you to alter your ultimate opinion, that is that you're not convinced as to a single hypoxic ischaemic episode on that day?

WITNESS RYAN: No there's nothing that causes me to substantially alter my opinion in that regard.

FURNESS SC: What about less than substantially Professor?

WITNESS RYAN: No I mean I think that the sorts of points that Michael and Alison raised you know were things that I'd considered myself and taken into, into consideration in making the - in coming to the conclusions that I came to. I think I would just make the point you know, there's a suggestion that with acute life-threatening events and epilepsy that there always has to be a family history, that is not my experience and I don't believe that's borne out by the literature, I think there are instances in the literature of children presenting with a first presentation seizure and sustaining a significant hypoxic ischaemic insight related to that and in some of those instances a genetic cause for that syndrome, for that presentation has subsequently been identified. These are conditions which were not known of in 1990. So you know I think, not taking into account the opinions of Professors Colley and Fahey, that doesn't cause

me to substantially change my conclusions.

FURNESS SC: Or at all from what you're saying Professor, is that right?

WITNESS RYAN: No.

FURNESS SC: Professor Fahey there was evidence earlier about whether or not the ambulance officers applied oxygen en route to the hospital and there is evidence and I can take you all to it but perhaps if you can assume for the moment there's evidence in the trial as well as before this Inquiry, that indeed oxygen was applied by Mr Hopkins on the way to hospital, does that affect any evidence you've given Professor Fahey?

WITNESS FAHEY: I suppose that it just makes me wonder why the saturations, albeit the potential for a spurious result, but I'm taking on face value that the saturations were 88% and that we didn't have a blood gas and I accept that, but the baby was not, at that stage Patrick was not breathing up enough to allow oxygen to get to his body. If I can just, if I can just talk about the drowning literature and why I went to that, and notwithstanding body temperature and downtime and potential cooling and all those things, the reason I brought that in was because it's one of the times that we know that there's hypoxia and my question was not you know, how similar drowning is to ALTE but if you've got a hypoxic event, what does the EEG do with time and I'm satisfied myself that the EEG evolves with time after such a hypoxic event and so I remain different from Professor Ryan on that.

FURNESS SC: Professor Colley if I can more precisely tell you the evidence before the trial of the ambulance officer. He was asked, "Did you place the baby and mother in the back of the ambulance", this is at transcript 436 line 48, the answer "We did, we sat the baby on the mother's lap, and the mother on the stretcher, and administered oxygen therapy en route to the hospital." Next question:

> "Q. Did you notice anything about the condition of the baby during the time that you were going to the hospital?
> A. Upon the use of oxygen therapy, its level of consciousness did rise, its respiratory effort did remain impaired."?

WITNESS COLLEY: Yes I would defer to Professor Fahey but my thinking on that was we have a saturation of only 88% and oxygen was applied, so--

FURNESS SC: From which you draw what conclusion?

WITNESS COLLEY: That it's more likely that there was indeed a problem with delivering oxygen to the brain, and that the oxygen desaturation was in my mind more significant but I'd defer to Professor Fahey.

FURNESS SC: Do you accept that Professor Ryan?

WITNESS RYAN: Look I think if you've gone - I'm not an ambulance driver,

but if an ambulance driver is called to a situation where a child or an adult are acutely unwell, first thing they do is put oxygen on the child or the adult, it's the sort of thing that they do, we don't know if they were measuring oxygen saturations at that time but it's one of the very first, you know, airway, breathing, circulation, oxygen pretty much, so I just don't think you can read too much into it. I mean the oxygen saturation was 88% which is low, but you can have a low oxygen saturation just because of technical issues with monitoring which can relate to things like poor peripheral circulation and things like that, I don't think you can read too much into a single oxygen saturation measurement.

FURNESS SC: Well the fact that the baby had oxygen from when the ambulance arrived and had it during the ambulance trip and his respiratory effort did remain impaired and you had a reading of 88%, doesn't that tend towards hypoxia Professor Ryan?

WITNESS RYAN: I think, yeah hypoxia is a low arterial oxygen level, as I said I don't think you can read too much into a single measurement of oxygen saturation levels from the periphery, I'm not arguing that Patrick was very unwell when he came to the emergency department and I said that in my report but I think we have limited evidence in this instance as to exactly how unwell he was and I think it's kind of inappropriate to extrapolate too much from that. And if I could just - one thing that happens when children or adults have a severe hypoxic ischaemic injury, and it's mentioned at some length in the Constantinou paper to which Professor Fahey referred is, that you get evidence of other end organ injury after the fact, so if you had a very low oxygen level in your blood for any period of time, sufficient to cause brain injury, then you'll usually go into kidney failure and you'll have other abnormal blood tests identified.

You'll have blood gases measured that will show significant abnormalities, you may have other end organs, such as the liver and the bone marrow might also be affected as well but we don't have any evidence that those things were found in this instance and if we had further supporting evidence of that kind I think that would be supportive of him having had a significant hypoxic ischaemic insight but that evidence is just it doesn't exist.

FURNESS SC: So when you say it doesn't exist, is that because the tests weren't done, for example the blood gases and therefore we don't know one way or the other, or the tests were done and the conclusions were reached contrary to the ones that you indicate should have been there if indeed he had a severe hypoxic ischaemic event?

WITNESS RYAN: As far as I can determine, the tests weren't done.

FURNESS SC: So we don't know one way or the other.

WITNESS RYAN: Well the blood counts and things and the electrolytes and things that were done during that admission were essentially as normal as far as I could tell. But if a child is unwell enough to present after an acute hypoxic

ischaemic insight, you'd expect that additional blood tests would be done, other than showing the one, there was a urine test that showed glycosuria but the other blood tests were essentially normal, he didn't have a whole battery of things done but the limited testing, the subset that was done was normal.

FURNESS SC: Professor Fahey is there anything further that you want to say?

WITNESS FAHEY: So I wondered about this issue and I read the Constantinou paper back and forth as recently as this morning, thinking about this, they've got an inclusion criteria of, "or" so it's not a "and" liver failure "and" kidney failure, is my first point, and one of the ors is neurological impairment presenting with seizures, so they included people just like Patrick and the other support for that is Professor Ouvrier who gave evidence in the initial hearing, is the co-author on that paper and makes the point that Patrick was the very sort of person that they would've included in his series.

FURNESS SC: Dr Colley does anything arise for you from that exchange?

WITNESS COLLEY: Not the immediate exchange, is it possible to go back to Professor Ryan's comment on the first serious epileptic event doesn't necessarily - and to be the first event of an epileptic encephalopathy, and she commented that you don't need to have a family history to have the first episode of an epileptic person to be that severe, which I would agree with. The only thing is in this family we have three other children who died young and one would think if there was an epileptic encephalopathy in the family causing early death, we don't have any evidence of epilepsy or seizure in the other three children as far as I'm aware.

FURNESS SC: Anything further?

WITNESS COLLEY: No thank you.

FURNESS SC: Professor Kirk?

WITNESS FAHEY: Can I also add to that that the presentation, although I agree with Professor Ryan about people with severe epilepsy having potential hypoxic events with potential brain damage, he wasn't fitting in that way when he was discovered, there's no history from either the notes or the ambulance officers or the emergency department that he was in status fitting and so we're extrapolating his found state to be an unwitnessed seizure before that. And while that's possible I think it's less likely.

FURNESS SC: Professor Kirk?

WITNESS KIRK: I guess I'd just say that in my experience of epileptic encephalopathies I haven't seen hypoxic injury of this nature, I'm sure I've seen a lot less of those conditions than either of my colleagues on the line but, and I accept that it may be possible for it to happen, it does seem that the pathology at post-mortem is consistent with a hypoxic event, I actually agree

with Professor Ryan that if there is a severe hypoxic event there is other end organ damage, but most of my experience in that regard relates to newborn babies and I'm not sure that it's entirely relevant to this situation.

FURNESS SC: With a four and a half month old baby?

WITNESS KIRK: Yeah I think things change, there are some special circumstances around the time of birth that don't apply to a four month old.

FURNESS: Thank you. Your Honour, other than to tender the Neurology Tender Bundle, which I do--

EXHIBIT #AL NEUROLOGY TENDER BUNDLE TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: I have nothing further.

JUDICIAL OFFICER: Mr Morris, it's a couple of minutes to 1.

MORRIS SC: We've got a choice, I don't think I'll be longer than 20 minutes, I might be half an hour. We can proceed now, I'm mindful that everybody is here, or we can take the luncheon adjournment, whatever suits your Honour's convenience and that of the witnesses.

JUDICIAL OFFICER: Might be some re-examination.

FURNESS SC: I suspect that the luncheon adjournment is appropriate, your Honour.

JUDICIAL OFFICER: Yes, well I'm sure everybody wants to get away and I'd give in to that, but it's a little bit difficult to know, after the cross-examination - Mr Morris has been very accurate in his estimates about how long he takes, so I'm believing him when he says he - normally judges don't believe barristers when they give estimates, but Mr Morris has been very good. But then there could be re-examination, so it's unknown. We'll take the lunch adjournment, resume at 2.

LUNCHEON ADJOURNMENT

JUDICIAL OFFER: Yes, Mr Morris.

MORRIS SC: Professor Ryan and Professor Fahey, I act in the interests of Ms Folbigg in this matter, who is the mother of Patrick. We've had some discussion about the oxygen saturation issue of 88% and that it was 88% not on room air but with oxygen therapy; is that correct?

WITNESS FAHEY: That's our understanding.

MORRIS SC: Professor Ryan?

WITNESS RYAN: I'm sorry, yes, that's our understanding.

MORRIS SC: To that extent it seems that that oxygen therapy had been maintained by the ambulance officers and then again at hospital; is that correct?

WITNESS RYAN: That's right.

WITNESS FAHEY: I agree with that.

MORRIS SC: In general terms oxygenation like this would be managed by the emergency physicians at the hospital; do you agree with that?

WITNESS RYAN: Yes.

WITNESS FAHEY: True.

MORRIS SC: To that extent the reason why it is that the oxygen saturation at 88% while being administered oxygen would really be a matter, would it not, for the opinion of somebody who has day to day experience with managing oxygen balance levels in an emergency room; do you agree?

WITNESS FAHEY: I don't actually agree with that. I think that any doctor would be, or ambulance officer or nurse would be appropriate to manage that.

MORRIS SC: Okay, can I just rephrase it then? The management would be undertaken by ambulance officers or doctors in the emergency department but an explanation for the 88% oxygen saturation, and that's peripherally monitored, in the fact of oxygen therapy would be something that they would be able to comment on, do you think?

WITNESS RYAN: Yes.

WITNESS FAHEY: I think they'd be able to comment but I don't think that means that they're the exclusive holders of comments in that regard.

MORRIS SC: Do you say that the oxygen level of 88%, given that the child was being administered oxygen directly by a facemask, is an out of the ordinary experience and in how long would you expect it to recover?

WITNESS FAHEY: So it depends on the cause and I think that's what we're discussing here. So, but I suppose pertinent to this is that we don't have a cardiac condition. We don't have a recognised respiratory position - condition and that the ambulance officers noted that he had poor respiratory effort, that is that the drive to take breaths was reduced, which can signify it being related to the brain rather than anywhere else. If you've got an obstruction of your airway you tend to work against that obstruction and choke. That's not how baby Patrick was described by the ambulance officers.

MORRIS SC: You're referring to when, on arrival, he was experiencing stridor

and difficulty breathing?

WITNESS FAHEY: I'm referring to the, to the documents that, that counsel Furness, led us to this morning.

MORRIS SC: Right, okay. The brain changes on EEG and the CT scan, and we don't have the scan but we've got the report, Professor Ryan, could they have occurred by reason of some neurological difficulty other than a hypoxic event?

WITNESS RYAN: Well, the, the EEG that was recorded on 18 October 1990, which is the day Patrick first presented, was felt to be normal. The CT that was recorded on that day showed some changes which were quite extensive which affected the temporal, occipital and frontal lobes which were felt at that time to be or they were reported as being potentially consistent with encephalitis or a, a cerebral infection and I think they probably were, in retrospect, also consistent, potentially consistent with residual of a hypoxic ischaemic insult, but there's other sorts of things that could also cause the same changes. So those, those findings are not specific in any way.

MORRIS SC: What are the other things that could cause those changes, Professor?

WITNESS RYAN: Well, we, we discussed this morning whether or not you can sustain a hypoxic ischaemic injury as part of a seizure and certainly, you know, the, the changes there they were potentially consistent with epilepsy. They are consistent with a, a white matter developmental disorder, although that wasn't, that, that's not--

WITNESS FAHEY: Can't have that on--

WITNESS RYAN: That diagnosis is not consistent with his other findings as far as we understand them but the, the - any sort of acute injury, I guess, potentially could cause the sorts of diffuse changes seen on the CT scan. CT scans are - in, in, in 1990 in particular but even now CT scans give very poor tissue definition and they don't distinguish well between different pathologies.

MORRIS SC: Professor Fahey?

WITNESS FAHEY: I agree with that but I think that my feeling of the CT scan is that, regardless of what we're postulating, we didn't find any evidence of infection and we, on pathology, have not found any other, any other mechanisms of brain damage except for the ischaemic changes that have been mentioned before, and so I find, I find that very difficult to, to walk away from, that, at the end of the day, we've got a pathologist's reports that, that indicated that there's been ischaemia at some stage and we've got a, a, a sentinel event occurring on 18 October with, with emerging CT changes from that time, albeit they're nonspecific. It, it doesn't matter that they're nonspecific to me because at the end we discover what they are, which is ischaemic.

MORRIS SC: Yes, okay. Professor Ryan have you got anything to add to Professor Fahey's comments there?

WITNESS RYAN: I guess what I, what I would add is, that there are instances in which children, in particular young children, have genetic epilepsy. There was one that's, that's called Dravet syndrome and the gene for it is, is well recognised now. That wasn't the case in 1990. And children with that condition can have prolonged seizures with or with fever, so in the context of a febrile illness or after vaccinations and things like that, and in the context of that long seizure they can sustain hypoxic ischaemic brain injury that can result in laminar necrosis and the sorts of changes that were seen on Patrick's post-mortem.

Now, SCN1A is not the only genetic cause of that presentation. There are other children in whom a similar clinical presentation is seen for which a genetic cause cannot be found and for, for me that would be a potential alternative explanation for his presentation on that date and his subsequent course and findings.

MORRIS SC: Professor Fahey, what have you got to say about that postulate?

WITNESS FAHEY: So, so I agree with, agree with Professor Ryan about Dravet and my comments are that that would have to have us accept that he was hypoxic on presentation, number 1, and number 2 is that, as I said this morning, he was not fitting when he was found and Dravet syndrome frequently presents with, with seizures that are recognised as movements of the body rather than a, rather than a, a child who has low tone and making poor respiratory effort.

MORRIS SC: Could he have been in a post-seizure condition when he was found?

WITNESS FAHEY: I think that's a, that's certainly possible but it's, it's one, one explanation but we'd have to accept that this post-seizure condition represented that he was hypoxic at that time and that there was an evolution of events from the 18th on.

MORRIS SC: Professor Ryan, you mentioned this condition in the context of fever. I want you to assume that when he was put to bed about 7 o'clock the evening before, he was said by his mother to be suffering a fever and be swearing, crying and clingy. Is that a piece of evidence which may be of assistance to this Commission? That by itself, could that be of assistance to the Commission in understanding what might have gone on?

WITNESS RYAN: Yeah, I think it is relevant, not only in that particular instance of which I spoke with Dravet syndrome associated SCN1A mutations but, in general, children who have a genetic or other predisposition to seizures are more likely to have them when they have an intercurrent illness, especially

one that's associated with a significant fever. So I think it is relevant.

MORRIS SC: Professor Fahey, what have you got to say about that?

WITNESS FAHEY: I think that, I agree that seizures are, the seizure threshold is lowered by having a fever but, but he was not noted to be fitting - I'll say it again - and he has been proven not to have an SCN1A mutation, albeit it that there are other genetic causes as yet unrecognised with the Dravet phenotype.

MORRIS SC: When you say that, Professor Fahey, what you're saying is that there are genes that have not yet been discovered which are thought to explain the phenotype; is that right?

WITNESS FAHEY: So, so I think we, we've covered some of this already. There are not - not specifically, so we're talking about - Professor Ryan has raised Dravet syndrome and has made the point that in some instance with Dravet syndrome we do not find a genetic change and I agree with that statement in, in principle. I agree with the statements in principle that the, it is possible that he is in a post-seizure state and I agree with the statements in principle that a, a seizure threshold is lowered by having a fever. So, so all of those things are, are, are potentials but I, I come back to him not being witnessed to have a fit, him being, us accepting that he's hypoxic on presentation and us accepting that his pathology is consistent with ischaemic events at some stage.

MORRIS SC: Okay. Just in relation to his subsequent hospital admissions, Professor Ryan it seems that when one looks at the hospital records, it seems that the observations of the hospital staff on a number of these admissions was that he was suffering from some sort of seizure associated with a mild fever. Do you recall seeing that in the clinical records?

WITNESS RYAN: During this admission or?

MORRIS SC: No, subsequent--

WITNESS RYAN: During subsequent admissions?

MORRIS SC: Subsequent admissions.

WITNESS RYAN: Yeah. I do, yes.

MORRIS SC: Is that evidence, those observations by the hospital staff recorded in the hospital notes of any use to this Commission and could you please explain why?

WITNESS RYAN: Well they are to some extent, but I think that that usefulness is limited, because regardless of the cause of the acute event of 18 October, I think everyone agrees that a brain injury was sustained at that time. Subsequent to which Patrick did develop an epileptic syndrome which evolved over time, it changed over time, which is the natural - consistent with the

natural history of epileptic encephalopathies of early infancy, and so any child with an epileptic syndrome in early infancy will be more likely, as I said earlier, to have breakthrough seizures at times when they have intercurrent illness with or without fever.

MORRIS SC: Professor Fahey, have you got any comment?

WITNESS FAHEY: I agree with Professor Ryan that, you know, we've got a - by the time he left hospital after his admission beginning on 18 October he had established epilepsy, and any time after that that he got a fever he would be at more risk of having a seizure from that point. So I don't think it's, I don't think that's contributory as such. I think thought that it's - one comment I made this morning, and I'll say it again, that none of his other fevers - none of his other seizures were associated with a period of hypoxia.

MORRIS SC: A lot of those seizures had occurred in the face of anti-epileptic medication having been administered to the young boy.

WITNESS FAHEY: Sure, so he had refractory epilepsy as I think we all agree. Refractory means that in spite of efforts for therapy, he was continuing to have fits, although they were, they were not everyday fits as sometimes we see, as far as we recognise from the notes.

MORRIS SC: I'm sorry, when you say every day, do you mean--

WITNESS FAHEY: So they weren't occurring on a daily basis, they were occurring spaced out.

MORRIS SC: I understand. Professor Ryan, have you got anything to add to that?

WITNESS RYAN: No, I agree with, with what Professor Fahey said.

MORRIS SC: Professor Ryan, you gave us a statistic this morning when giving evidence about the number of cases of what appeared to be brain abnormality with a probable genetic cause when no gene could be identified. What was that statistic again?

WITNESS RYAN: I think the, the number that I quoted to you is that in cases where we undertake Whole Exome or Whole Genome Sequencing in children with presumed genetic aetiology, neurological conditions, an answer is found in only approximately one-third of cases overall.

MORRIS SC: Professor Fahey, have you got anything to add to that?

WITNESS FAHEY: I, I think there's two things. One is that we'd hope that we start to push it over 40%, although we are still endeavouring to do that. But I think it's pertinent to add that not every case of children presenting with seizures has a genetic cause, and so we're not aiming to get to the hundred per cent, the hundred per cent level, and, and so if we find an answer in, let's

say conservatively 25% of children with an epileptic encephalopathy, that's - our maximum that we might find of all cases which are genetic may be up to 70%. There's still some who, who have different causes.

MORRIS SC: Are we to understand from that, that a certain percentage of epileptic conditions in young infants such as this may be, the cause by be idiopathic?

WITNESS FAHEY: Well maybe, maybe non-genetic I think is a safer way to put it.

MORRIS SC: But it may not necessarily be associated with trauma or--

WITNESS FAHEY: No, I didn't postulate a cause.

MORRIS SC: Just in relation to an observation Professor Fahey that you made at page 16, and I just want to clarify it.

WITNESS FAHEY: Yep.

MORRIS SC: And I'll read it to you. Specifically I'm concerned with the description, "Patrick tends to go up on his toes", that bit, and I won't read the rest of it, and then you say, "In my clinical experience as a developmental neurologist with expertise in cerebral palsy, these clinical findings are concerning as it would prompt me to investigate for a brain abnormality." I wasn't quite clear on your evidence this morning. Are you suggesting the potential for a brain abnormality other than ischaemic damage?

WITNESS FAHEY: No, no, not at all. I'm suggesting that there was - this is evidence of ischaemic damage and this is the sort of changes that we recognise during formalised assessments of infants who have injury before 12 months of age, and if I examined Patrick and had these findings I would be looking for a cause in the brain or the spinal cord, probably the brain, and ischaemia would be, would be high on my list of differentials.

MORRIS SC: What would your other differentials be?

WITNESS FAHEY: Things that we haven't found in Patrick, like abnormalities of brain development, cortical migrational abnormalities, metabolic conditions, things that we found no evidence of.

MORRIS SC: When you say no evidence, are you talking about--

WITNESS FAHEY: Pathologically.

MORRIS SC: I'm sorry?

WITNESS FAHEY: So metabolically, pathologically, genetically, we have not found any evidence for those conditions.

MORRIS SC: Professor Ryan, have you got anything to add to that?

WITNESS RYAN: Well no, I agree with Michael. I mean, based on the description of the child at that time, he clearly had some neurological problems and if they were seen in isolation they would have prompted, or should have prompted investigation. He'd been extensively investigated up to that point. But the cause of that constellation of symptoms and signs as described on that date is protean and it's all of the things that both Michael and I have referred to in our reports.

MORRIS SC: There's no doubt I take it that at the time of his death this boy had an encephalopathy?

WITNESS RYAN: No.

MORRIS SC: Professor Fahey?

WITNESS FAHEY: Well I think that he had, he had a progressive seizure disorder. He had brain changes and he had upper motor neuron signs. I, I think that he had, whether or not he was actively fitting at or around the time of his death in February, I don't think we know.

MORRIS SC: Professor Fahey, am I to take it from that, that when you look at this clinical picture between October and February, and let's be clear, I mean we don't know what necessarily happened immediately before the ambulance was called, but from 18 October through to the time of his death is it fair to say that this young man had a progressive encephalopathic condition?

WITNESS FAHEY: No, I don't, I don't think that's fair. I wouldn't, I wouldn't use the word "progressive" because it implies to me something which is deteriorating and changing, and I don't think we know that sir. I think that he had an insult and there were evolving changes as a result of that insult, but I, I don't think that we can state that this was something which was, which was developing or progressing on the evidence that we have.

MORRIS SC: On the evidence that we have, and I know we're dealing with possibilities, but is it a possibility that he had a deteriorating condition?

WITNESS FAHEY: Well against that is that we didn't see signs of that on his brain pathology, and I, I think that that's a, that's a material fact that we have..(not transcribable)..ourselves to in my opinion, that, that we're not seeing from - leaving aside the genomic evidence that we have, that we're not - we didn't find any of those conditions and - but, but on brain pathology what we saw was, was old ischaemic changes, not changes which were active, not changes where the cells would deteriorate, and so I don't, I don't agree with the premise or the use of the word "progressive".

MORRIS SC: It's a word that's used in the hospital notes. That's where the--

WITNESS FAHEY: Sure, but it's - I, I just hope you understand the nuances in

my objection to that word.

MORRIS SC: No, no.

WITNESS FAHEY: I think evolving implies something, implies something different.

MORRIS SC: I fully appreciate the reservation you wish to place on it, and I thank you for that clarification. Professor Ryan what's your view?

WITNESS RYAN: I think it's difficult to be entirely sure whether or not this was a progressive neurological condition. One of the things that did worry me on reviewing the notes was that when Patrick was seen by Dr Wilkinson, his neurologist, on 30 October, 12 days after this acute event, he was felt to be active and interested and Dr Wilkinson noted that "On examination I could not find any neurological problem". And yet in - by the - by November when the child was readmitted to hospital it was apparent to people that he was blind, and that changed - that seemed like quite a significant change, and I think it's very problematic to - in - if one is postulating that this is not a progressive disorder.

The visual loss, having said that, there was a comment later on just before Patrick died that his vision had perhaps improved, so it was potentially fluctuating during that time. But that in and of itself would also be inconsistent with the sequelae from a single hypoxic ischaemic insult on 18 October.

MORRIS SC: Professor Fahey, have you got anything to say about those observations?

WITNESS FAHEY: Yes, so, so I bring back to the ophthalmological consult from 30 November when Mrs Folbigg was questioned about how long the visual loss had been there for, and the notes clearly state for about a month, and I just, I just add into the complexity of this child his - the fact that he is having seizures and he is likely to be at a potentially different clinical state depending on how his seizures are going at the time and his therapies that he's on. I don't think we necessarily need to expect him to be static in place if he's having active, active epileptic events.

MORRIS SC: What about the observation made by Professor Ryan about the fact that at the physiotherapy assessment it was thought that his vision had improved?

WITNESS FAHEY: I take that on board. I wonder about, as I say, whether or not how closely related his physiotherapy assessments are to an epileptic event, and as we've discussed these were not infrequent, but not all the time, as noted by people, and it's possible that he was less attentive on one occasion compared to another because of, because of something which had - something epileptic which had occurred around the time of his assessment.

MORRIS SC: That observation by Professor Fahey, Professor Ryan, those

observations about the proximity to the epileptic event and the ophthalmological status of this boy, from time to time, have you got anything to say about that?

WITNESS RYAN: Well, I mean I think the episodes that Patrick had in which he was felt to either be having a seizure or a different sort of acute neurological event such as an ocular crises, and there was some confusion with various presentations as to exactly what sort of neurological event he's experiencing. They seem to be fairly overt. I'm not sure that he was - it doesn't sound as though he was having seizures at home, or that people were concerned that he was having unrecognised seizures. It seemed to be - the impression I got from reading the notes was that it was fairly much apparent to people when he did have events. So I'm not sure that - postulating that he was less responsive because he'd had a seizure in the day or two prior to his ophthalmological assessment is valid. I'm not sure about that.

WITNESS FAHEY: But they still thought he was cortically blind at the ophthalmological assessment.

WITNESS RYAN: So, cortical visual loss is when children have a, a neurological injury to the optic lobes or the posterior part of the brain that results in loss of vision while they still have structurally normal eyes and have a normal ophthalmological examination, and that's - that is what the ophthalmologist felt that Patrick had, that he had cortical visual loss. But that's not something which would usually fluctuate, and it wouldn't usually vary temporally in association with epileptic seizures.

MORRIS SC: Professor Fahey?

WITNESS FAHEY: No, cortical visual loss would not - would not - would not vary in association with seizures, but visual attentiveness is, is described by a physiotherapist..(not transcribable)..

MORRIS SC: I think, just finally, there was reference, I think, in one of the hospital records in November - so that's after the initial discharge and I think it may have been the ophthalmological assessment - that there was some blue tingeing in the eyes, or to the edge of the eyes. Do you recall reading that piece of material?

WITNESS FAHEY: I do, I think it was around Rob(?) Smith's notes. But, to anticipate your question, I, I don't know what to make of that.

MORRIS SC: I see. Just to draw your attention, Professor Ryan, to your observation here, it's at page 8 of your report, in which it was observed "his face moved symmetrically" - these are your words, not the doctor's, Professor Ryan:

> "Dr Smith noted that Patrick did not fix or follow that he reacted to sound. His face moved symmetrically, but Dr Smith wondered if he had a ? droopy left lid. Dr Smith felt that Patrick's optic discs

possibly had a blueish tinge"?

WITNESS RYAN: Yes.

MORRIS SC: And, to that extent, Professor Fahey, you say you're not quite sure what you could make of that. Professor Ryan--

WITNESS FAHEY: Which, which part of it?

MORRIS SC: I'm sorry, "Patrick's optic discs possibly had a blueish tinge"?

WITNESS FAHEY: No, I'm, I'm not sure what to make of it.

MORRIS SC: Okay. Professor Ryan?

WITNESS RYAN: No, I don't know what to make of it either. I think it's, it's, it's kind of immaterial because Patrick was subsequently seen by a consultant ophthalmologist who felt that his discs were normal.

MORRIS SC: Okay, thank you. Could I thank you both for your time and assistance? I have no further questions for you, thank you. Thank you, your Honour.

JUDICIAL OFFICER: Yes?

FURNESS SC: Nothing arising, your Honour, thank you.

JUDICIAL OFFICER: Nothing from the panel?

FURNESS SC: Unless there is something from the panel?

WITNESS KIRK: No.

FURNESS SC: No.

JUDICIAL OFFICER: No comments from the panel? Well, thank you. Thank you for appearing on television for us. Your evidence has been helpful, and you're excused now.

WITNESS RYAN: Thanks a lot.

WITNESS FAHEY: Thank you, your Honour.

WITNESS RYAN AND WITNESS FAHEY WITHDREW

AUDIO VISUAL LINK CONCLUDED AT 2.33PM

FURNESS SC: Your Honour, there's one matter which I'd like to raise while team Sydney is here. There was some evidence as to the family tree that Dr Arsov took and also the notes that Dr Colley took in relation to Craig's

nephew. We've since had Craig Folbigg in contact with us and a short statement will or is being prepared. But to the extent that we have these witnesses here, as I understand it, he says that the baby was born premature, five and a half weeks premature, and died after seven hours and that there have subsequently been children and grandchildren in the family. Given that it was an important issue, I don't know whether that makes any difference. Dr Colley?

WITNESS COLLEY: Well, I, I - it's very good extra information to have, isn't it, 'cause we were querying whether there was - a SIDS or SIDS-like episode had been queried. But to know a baby was born so prematurely and lived a few short hours points to demise due to the prematurity and probably complications thereof, yeah.

FURNESS SC: Thank you. Thank you, your Honour.

JUDICIAL OFFICER: We don't need the panel any longer?

FURNESS SC: No, your Honour, thank you.

JUDICIAL OFFICER: Thank you, it's been a great pleasure to have you here, I must say and we really do appreciate the fact that you've taken so much time out of your lives to come here and help us with what is, you can well imagine, for lawyers a fairly difficult area to understand.

WITNESS BUCKLEY: Thank you, your Honour, it's, it's been a privilege.

WITNESS COLLEY: Thank you. Thank you, it's been a privilege.

<THE WITNESSES WITHDREW

FURNESS SC: Now, your Honour, there are a number of matters I have to deal with.

JUDICIAL OFFICER: Yes.

FURNESS SC: Firstly, there was reference in the forensic pathology hearing to haemosiderin in Caleb and Dr Berry's statement that he had seen slides showing that, the staining. Inquiries have been made of the relevant people and no such slides remain in existence.

Secondly, in relation to the forensic pathology documents to be tendered, I referred with Professor Cordner to a report of seven or so colleagues of his at the Victorian Institute of Forensic Medicine and I did not tender those seven reports, and I tender them now.

EXHIBIT #AM SEVEN REPORTS FROM VICTORIAN INSTITUTE OF FORENSIC MEDICINE TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: I referred, during that hearing, to a bundle of literature being

prepared of the material that was the subject of evidence and I tender that bundle.

EXHIBIT #AN BUNDLE OF LITERATURE TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: And there were three MFIs that, for one reason or another, haven't been tendered and I tender those. The first is MFI 24, which is a policy statement from the American Academy of Paediatrics entitled "Distinguishing sudden infant death syndrome from child abuse fatalities".

JUDICIAL OFFICER: Are you tendering those individually?

FURNESS SC: I think I will, your Honour.

EXHIBIT #AO FORMERLY MFI 24 TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: MFI 39, "Summary of prosecution medical evidence concerning the deaths and the ALTE".

EXHIBIT #AP FORMERLY MFI 39 TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: MFI 40, "Crown chronology of deaths and the ALTE for each of the Folbigg children".

EXHIBIT #AQ FORMERLY MFI 40 TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: And, I'm sorry, there's a fourth, MFI 41, "Crown coincidence evidence: similarities relied on by the Crown to disprove mere coincidence".

EXHIBIT #AR FORMERLY MFI 41 TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: And MFI 42, "Written directions and list of questions to assist the jury". I'm sorry, your Honour, addition is not my strong point.

EXHIBIT #AS FORMERLY MFI 42 TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: Now, in addition, your Honour will recall that I invited Professor Clancy to respond in relation to the connection between SIDS and ALTEs. He did, at length, and some of that material is relevant and some of it is not relevant. I tender a redacted statement of Professor Clancy.

EXHIBIT #AT REDACTED STATEMENT OF PROFESSOR ROBERT CLANCY TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: Your Honour will recall that a report from a Professor Goldwater was provided those assisting Ms Folbigg and, similarly, that report has been redated for irrelevant material and I tender the redacted version.

EXHIBIT #AU REDACTED REPORT OF PROFESSOR PAUL GOLDWATER TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: As indicated at the directions hearing, a report was received from Dr Waddell-Smith and my friend indicated on Monday that there was to be no additional report, although it was foreshadowed. So I tender her report dated 29 March 19.

EXHIBIT #AV REPORT OF DR KATHRYN WADDELL-SMITH DATED 29/03/19 TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: That deals with the forensic pathology matters. Coming back to the genetic matters, there was a gene list generated by team Sydney and a gene list generated by team Canberra which are very similar in nature but I tender each of those gene lists which could be one exhibit.

EXHIBIT #AW GENE LISTS GENERATED BY TEAM SYDNEY AND TEAM CANBERRA TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: And, as has become clear during the evidence over the last few days, Professor Kirk and Dr Buckley provided a written response to team Canberra and that response I tender.

EXHIBIT #AX WRITTEN RESPONSE FROM PROFESSOR KIRK AND DR BUCKLEY TO TEAM CANBERRA TENDERED, ADMITTED WITHOUT OBJECTION

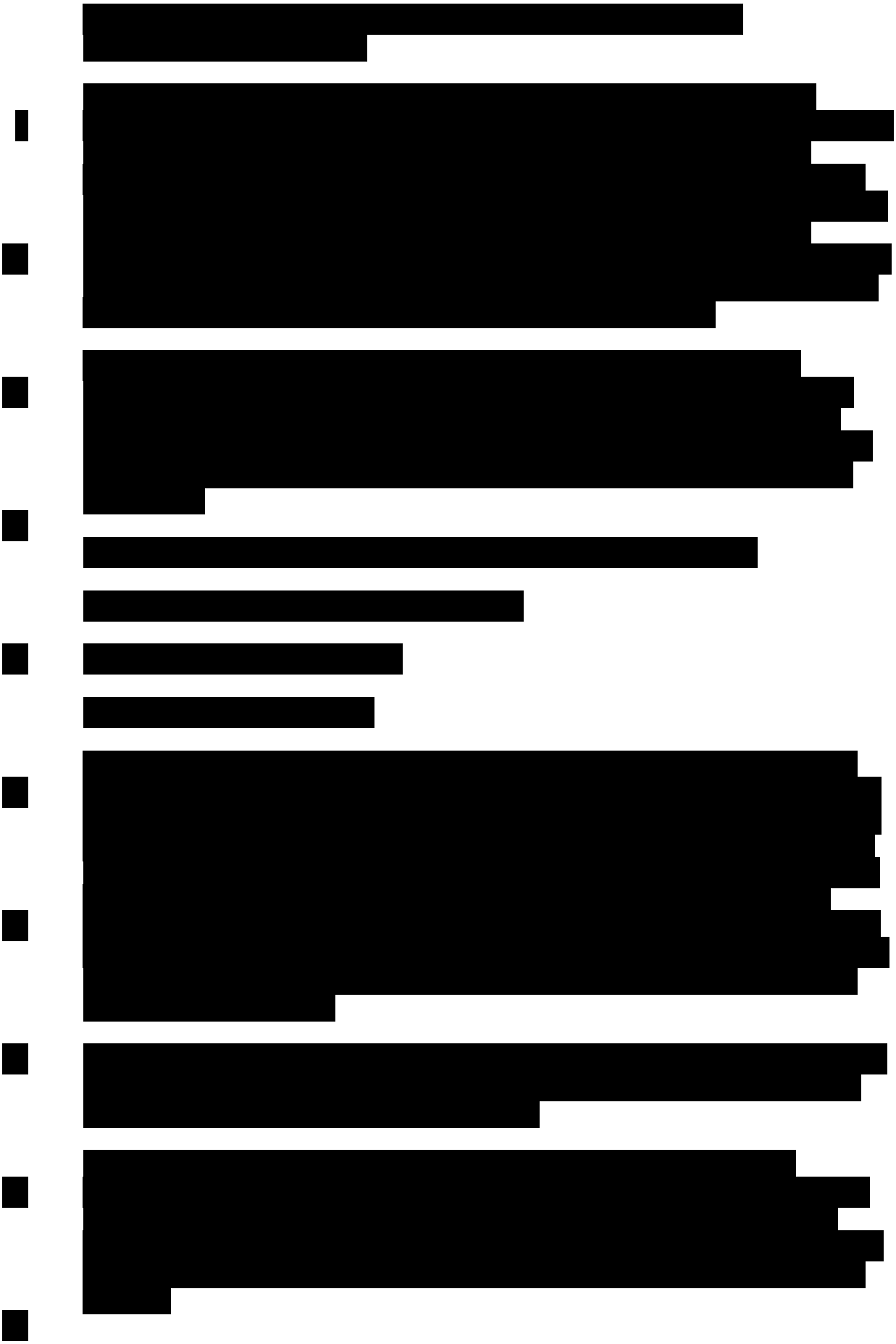
FURNESS SC: And Professor Cook and Professor Vinuesa responded to that response and I tender that response.

EXHIBIT #AY WRITTEN RESPONSE FROM PROFESSORS COOK AND VINUESA TO RESPONSE FROM PROFESSOR KIRK AND DR BUCKLEY TENDERED, ADMITTED WITHOUT OBJECTION

FURNESS SC: The only matter outstanding is there is a literature bundle which is to be finalised arising from the matters that were the subject of evidence today. So that will be tendered on the next occasion.

JUDICIAL OFFICER: Thank you.

[redacted]



[redacted]

JUDICIAL OFFICER: Ms Furness?

FURNESS SC: Your Honour, the next hearing is on the 29th, which is Monday week, here to hear evidence from Kathleen Folbigg in respect of the diary entries and the possession and dispossession of the diaries.

JUDICIAL OFFICER: Yes. All right, we'll adjourn then to the 29th. Thank you.

ADJOURNED PART HEARD TO MONDAY 29 APRIL 2019

[redacted]