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TRANSCRIPT OF PROCEEDINGS

INQUIRY INTO THE CONVICTIONS OF KATHLEEN MEGAN FOLBIGG

MEETING OF DATA INTERPRETATION PANEL

MONDAY, 4 FEBRUARY 2019 at 9.30am

PRESENT:

Legal representatives
Gail Furness SC, Senior Counsel assisting the Inquiry
Sian McGee, counsel assisting the Inquiry
Amber Richards, solicitor assisting the Inquiry on behalf of the Crown Solicitor
Isabel Reed, counsel for Ms Folbigg
Rhanee Rego, solicitor for Ms Folbigg
Ian Fraser, counsel for NSW Health and Dr Alison Colley
Blaise Lyons, solicitor for NSW Health and Dr Alison Colley

Data interpretation panel
Dr Michael Buckley, Genetic pathologist
Dr Alison Colley, Clinical geneticist
Professor Jon Skinner, Paediatric cardiologist and electrophysiologist (by AVL)
Professor Matthew Cook, Director of Immunology at Canberra Hospital (by phone)
Professor Carola Vinuesa, National Health and Medical Research Council Principal Research Fellow (by AVL)

Observers
Professor Johan Duflou, Forensic pathologist

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MS FURNESS SC: If I could just ask who we have on video first. Is that you, Professor Vinuesa, at the top? Hello, can you hear me?

PROF VINUESA: Yes, this is Professor Vinuesa. I can hear you well.

MS FURNESS: Thank you very much. I am--

PROF VINUESA: Good morning.

MS FURNESS SC: Good morning, and we have as well - who do we have as well?

PROF SKINNER: Professor Skinner.

MS FURNESS SC: Hello, Professor Skinner.

PROF SKINNER: (Indistinct)

MS FURNESS SC: I haven't met you, although we've spoken on the phone. My name is Gail Furness, I'm senior counsel assisting the Inquiry. Are we expecting anyone else by video?

MS RICHARDS: (Indistinct) Professor Cook has called in by phone, so he can hear us.

MS FURNESS SC: Professor Cook, can you hear us?

PROF COOK: Yes, good morning.

MS FURNESS SC: Good morning. Now, I think that of the people who are here today nobody is new, with the exception of Professor Skinner, but for your benefit Professor Skinner, we might just indicate who is who, leaving aside the lawyers. Professor Duflou?

PROF DUFLOU: I'm Johan Duflou, yeah, I'm - I think we know each other, Jon.

PROF SKINNER: Yes (indistinct)

PROF DUFLOU: Forensic pathologist.

PROF SKINNER: Good to hear you Johan.

MS FURNESS SC: He's not been engaged in relation to the Inquiry, as I've been told, and his role is purely as an observer, as I understand it, in today's meeting, just for your benefit, and Dr Colley, if you wanted to introduce yourself.

DR COLLEY: Alison Colley, I'm the Director of Clinical Genetic Services for South West Sydney.

MS FURNESS SC: Dr Buckley.

DR BUCKLEY: Hi Jonathon, my name's Michael Buckley, I'm a genetic pathologist based in eastern Sydney and I have a separate role as president of the Human Genetics Society of Australasia.

MS FURNESS SC: And Professor Cook?

PROF COOK: Good morning, Matthew Cook's my name, I'm the medical director of Canberra Clinical Genomics and Co-director, Centre for Personalised Immunology, with Professor Vinuesa.

MS FURNESS SC: Thank you for that, Professor. So as I say, the purpose of today's meeting is primarily for Dr Buckley to describe what has happened to date with the samples and the sequencing which has happened and then to lead a discussion with an end result being there is a process going forward in terms of interpretation, which will ultimately result in one or more reports. Can I first, just by way of introduction, emphasise the confidentiality of this discussion? This is a discussion between the participants for the purpose of the Inquiry and should not be otherwise made public and should not be discussed with anyone other than individuals that have been notified and agreed with by the Inquiry.

PROF SKINNER: Can I just say one thing before we start?

MS FURNESS SC: Yes.

PROF SKINNER: I'm listed here as a cardiac geneticist. That's not what I am. I'm a paediatric cardiologist and - so - and an electrophysiologist, so my expertise is in the area of arrhythmia, childhood heart disease, and sudden death, and I also have been involved in multidisciplinary investigation of sudden death over this last 15 years or so. So those are my qualifications, I'm not a geneticist, just so that people are clear about that.

MS FURNESS SC: Thank you for that clarification, Professor. Now, I was speaking in terms of confidentiality, which is very important in terms of the way in which the Inquiry operates, and to the extent that any of you - that is, those who will be involved in the interpretation - propose to involve any other person in that process, then it is necessary to provide the Inquiry with their details, including their CVs, and for the Inquiry to approve their involvement and particularly the terms of their involvement, including confidentiality. Now, the Inquiry has directly engaged or caused to be engaged I think a number of you with, the exception of you, I think, Professor Vinuesa, and there have been letters that have been written which set very clearly the terms of the engagement, including the expectations of any report.

Now, I think we've sought but not been provided with a letter that would meet that criteria in relation to you, Professor, and so that needs to be sent and we will organise that so that you are under the same circumstances as every other

person that's going to be engaged in this process. Finally, in relation to that issue, there will be a non-publication order issued promptly in respect of the data and any reports or documents created flowing from that data, and that order will continue until such time as the Judicial Officer makes an order to the contrary or varies it in any way, so that everyone is very clear at this stage the status of any information that is to be generated or created.

Does anyone have any questions about that? No? Well, if that's the case I'll hand over to Dr Buckley to tell us what's been happening over the last month or so.

DR BUCKLEY: Thank you very much, Gail. Since we last met in early December, November, I can't remember - early December, I think - we have undergone a process of discovery of samples and we have managed to access some samples which have been suitable for genomic analysis. You would have been provided with a spreadsheet - and apologise for the misspelling of Laura Folbigg's name, but which specifies the samples that we've been able to access, the, the external laboratories who have been contracted to analyse those samples, and what testing has been conducted on those. So we have a buccal - we have saliva and buccal swab, courtesy of the Australian National University, frozen liver tissue and fibreglass DNA which have been sent to the Australian Genome Research Facility in Melbourne, and they have undertaken whole genome sequencing and they have produced some data and entries which you can see on the document.

There is some variation in the quality of sequencing which appears to reflect the age and characteristics of the sample. A further set of testing was done, largely prompted by comments from Dr Vinuesa, Professor Vinuesa, and that Guthrie card material which was held in New South Wales was provided to the Victorian Clinical Genetics Service, initially with the intention of performing whole exome sequencing, but after extraction of DNA from those cards it was found that there was either inadequate mass or inadequate concentration, or both, of DNA available from the cards to perform whole exome sequencing on all four samples.

In fact, there was only sufficient material to perform whole genome sequencing on two of those individuals. Fortunately those two were able to complement data which had otherwise been sent to the AGRF, and therefore we will have data of various sorts from Kathleen Folbigg, Caleb, Patrick, Sarah, and Laura, not equivalent data but comparable data. At the moment we hold also SNP testing for copy number variation which was performed at the AGRF on the same samples from Kathleen, Patrick, and Sarah. We don't have the ability to perform copy number variation testing for the samples which have been sent to the VCGS as there was insufficient material and quality for that purpose.

The AGRF have provided us with three copies of the - of their data, which we have here at the commission this morning. We are waiting also for the VCGS to provide their data later in the week. The intention would be that we hold a copy of the data here at the commission, that a copy of the data is provided to the Sydney-based team, and that a further copy of the data be provided to the

Canberra-based team. I will ask a bioinformatician in my laboratory to do a checksum on those three data types to ensure that the number of lines of data and the number of bytes of data in each disc are equivalent.

MS FURNESS SC: Can I just say at this stage, in terms of the Sydney team, you might just indicate, Dr Buckley, who you encompass by that?

DR BUCKLEY: So for the interpretive process it will involve the ordinary staff of the genetics laboratory at Prince of Wales Hospital, so some of the scientists there who - the bioinformaticians who work for us. There will be Professor Edwin Kirk co-examining the data with myself. Dr Alison Colley will also be involved in assessment of those data.

MS FURNESS SC: Thank you, and by the Canberra team, we understand that, Professor Cook, you, and Professor - I'm sorry, I've not pronounced your name. I was trying to - the D in it. How do you pronounce your name, Professor?

PROF VINUESA: Vinuesa is good, Vinuesa.

MS FURNESS SC: Thank you. The two of you work in the same facility, is that right?

PROF COOK: Correct.

MS FURNESS SC: And so we take it then that the process that you will engage in is a process that you will engage in jointly, is that right?

PROF COOK: Yes.

MS FURNESS SC: So we will provide you with one copy of the data for that purpose?

PROF COOK: Yes, that will be fine.

MS FURNESS SC: Thank you. Sorry, Dr Buckley.

DR BUCKLEY: That's fine. Are there any questions up to this point? Just dealing with the mechanics of sample selection and data production.

PROF COOK: I just had a question. I think at the last meeting we discussed not only looking at these five family members but potentially the father as well. I was wondering what the status of that sample was?

MS FURNESS SC: As I understand it we haven't been provided with any answer from the father as to whether he will be involved. It was made clear, I think, at the last directions hearing that there was an approach made to him which he reacted very badly to, and accordingly he to date has certainly been reluctant to engage, and we have had no final answer. So at the moment we're proceeding on the basis that we don't have it.

DR BUCKLEY: So this meeting is really to my mind mainly about process, not about content.

MS FURNESS SC: Yes.

DR BUCKLEY: It's about once we have the data, then what do we do with it? I thought it sensible that the data will go through two different genomic pipelines, one at New South Wales Health Pathology, Randwick, and the other at the Australian National University. Those pipelines will have different settings and will almost certainly generate a different set of variants for further filtering, and they will differ between the two laboratories. Welcome back, Jonathon.

PROF SKINNER: Thank you, sorry, technical glitch.

DR BUCKLEY: We've just talked about the samples which have been made available to us, the types of testing which have been performed on those, and some of the timelines. We expect that the VCGS will - sorry, the Victorian Clinical Genetics Services will generate whole genome sequencing data on two Guthrie card derived DNA samples by the end of this week and that they will be made available. There will be, in addition, some copy number variant data via SNP microarray produced on the three samples that were provided to the Australian Genome Research Facility.

So there will be essentially genome data on every individual plus copy number variant data from Kathleen, Patrick, and Sarah from the AGRF as well.

PROF SKINNER: I have some questions, if I may.

DR BUCKLEY: You certainly may.

PROF SKINNER: Yes, so is Craig completely out of the loop?

MS FURNESS SC: Well, we haven't got an answer yet, so we're working on the basis that he's not involved. It's a matter for him.

PROF SKINNER: Right, and the - it strikes me that, certainly looking at it from a cardiac perspective, that there's really no - I've got no phenotype to go on here other than that the children are dead. I don't know anything about the mum, I don't know anything about the father in terms of their clinical history, and the ECGs that are - presumably there are some ECGs available, or other cardiac tests available on the children, but I haven't seen any of those and I don't know what the quality of them is, I don't know what the quality of the expert review is. I can see looking through the report by Professor Peter Berry that he said that no electrocardiograph abnormality was noted in any of these children in life, but I don't know on what evidence that was based, except that he does say that at some point there was an electroencephalogram being done and a single ECG was being recorded at that time and somebody looked at that.

So I think, just from my impression, if we are considering any form of cardiac pathology then we have to try harder to get some cardiac evidence, and I wonder what we know about this so far.

MS FURNESS SC: The fact that the children died such a long time ago and their health records are similarly dated, we have obtained all the information that we have been told is available in respect of them, and so the material either you have, Professor, or will shortly have, covers all the material that is available in respect of the children.

PROF SKINNER: So I have not seen any ECGs at all, and I have not seen any reports of any ECGs either, and I've not heard anybody discuss even any ECGs on the children, other than that one (indistinct) in Professor Peter Berry's report, so I think, you know, one of the - if we're looking at, for example (indistinct) issue in the mother, she needs to be properly investigated from the heart point of view, and we need to get as much as we can from the children, so that's going to be really important.

DR BUCKLEY: So that was one of the outcomes of the meeting we had in December, that the cardiac - that there was a recommendation that the mother be asked if she would provide an ECG.

MS FURNESS SC: Has that happened?

MS REED: That's in the process at the moment. She's been - and you can imagine she's with Corrective Services so the wheels move fairly slowly, but she has seen a GP and has been referred and she did hear the other day - I mean, they don't give inmates times or dates for when they're to be referred or who they're to be referred to, but she has been told that she is being referred, so I imagine it will be sooner rather than later for further testing to be done, but I understand that an ECG - it would have just been a basic ECG - has been performed with Justice Health, but we're requesting it at the moment.

MS FURNESS SC: Can you send us correspondence you've had with the prison about this? Cause it's possible that we could expedite any of this material.

MS LYONS: I can (indistinct) records from Justice Health if I have the details.

MS REGO: I sent through a request this morning to obtain various records, so I'm happy to send you the correspondence, if you would--

MS FURNESS SC: I think you need to copy us into that correspondence, both Health and the Inquiry, because we have powers of persuasion that you may not have.

MS REGO: Yes, I understand that.

MS FURNESS SC: And timing is everything in relation to that.

PROF SKINNER: Sorry, so I had a phone call from counsel for Kathleen Folbigg and they asked me whether I knew anybody who might be appropriate to investigate Kathleen, so I've made a couple of recommendations for cardiac electrophysiologists to see them, so they may or (indistinct) be actioning that, I don't know.

MS FURNESS SC: Can I just stop you there?

PROF SKINNER: There are some very good cardiac electrophysiologists in Sydney. Yes.

MS FURNESS SC: If I can stop you there for a moment, I'm not aware of the discussions you've had.

MS REED: A couple of recommendations have been made for Kathleen for experts for her to be referred to, but I wasn't aware of the experts that Professor Skinner was referring to, but I think really in her situation she just gets sent to whoever they ordinarily use at--

MS FURNESS SC: Experts in what area?

MS REED: Cardiac--

MS FURNESS SC: This is in addition to the ECG?

MS REED: So she had - with Justice Health, when she saw the GP at the gaol, she had just a basic ECG, and from that they've now referred her to a specialist, a cardiac specialist.

MS FURNESS SC: For what purpose?

MS REED: Further testing.

MS FURNESS SC: For what?

MS REED: I'm assuming a stress test or - well, because there's the query about whether she's got long QT syndrome.

MS FURNESS SC: So who has been recommending this testing process? Has it come from advice from any particular person who is advising you? I understood what Professor Skinner said in terms of him being asked to provide some recommendations, and I didn't quite catch as to what area.

MS REED: That I'm not aware of, but I do know that the referral that has been made for her now is a referral to a cardiac specialist at Westmead.

MS FURNESS SC: Do we know who that is? Just looking meaningfully at Health.

PROF SKINNER: I think it's likely to be Saurabh Kumar.

MS FURNESS SC: I beg your pardon?

PROF SKINNER: It's likely to be Saurabh Kumar. I mean, I think that this - we're throwing a lot of money and effort into looking at the genes here, and a couple of things have already cropped up, genetic, you know, variants of uncertain significance. Now, if we're going to make any sense of this we have to make an equal effort to look at the phenotype, not just the genotype, in those who may be affected. I think if you're looking at - potentially what we're looking at, if it's anything, it must be something that's exceptionally rare and exceptionally severe, and either there should be some sign of it in Kathleen and/or Craig or both, so if we were doing this as a medical investigation, never mind the legal side of things, and we were genuinely interested in finding out what the cause of death was, you know, taking away all the other stuff, then we would be throwing a lot of time and effort at the cardiac side.

MS FURNESS SC: Well, we had no idea what--

PROF SKINNER: Not just an ECG, exercise tests, echocardiogram (indistinct)

MS FURNESS SC: Thank you, Professor. We had no idea of the discussions, the arrangements, or the fact that Ms Folbigg was being tested for anything, and so this is all very new to us, and it's unfortunate, I must say, that it's new to us because, as I've said, between Health and the Inquiry, there are various things that could be done more quickly. Now, Professor, I still didn't quite catch who you were recommending and for what purpose, and perhaps if you could spell who you're referring to and for what purpose that would be of assistance.

PROF SKINNER: Okay, so, I mean, I think it's good that you've got me on this Inquiry, so - you know, that's the whole purpose that I'm here for, I think, it's the translation of the genetics into a sudden death scenario. That's what I do all day. So the, the particular doctor, his name is Saurabh Kumar, that's S-A-U-R-A-B-H K-U-M-A-R. Now, I just recommended him because he's a cardiac rhythm specialist with a particular interest in inherited heart conditions who happens to be based at Westmead. There are other people who would be suitable but he sprung to mind when that counsel phoned me up.

Bear in mind I'm a paediatric cardiologist, not an adult electrophysiologist, so we should be looking hard for evidence of electrical and - primary electrical disease is what we're looking for, and you don't do that just with an ECG, you might also look for long QT interval on a resting ECG but you also require exercise tests, an echocardiogram, even magnetic resonance imaging, that sort of thing.

MS FURNESS SC: You're talking about Kathleen?

PROF SKINNER: Yes, and also (indistinct) particularly interested in seeing any evidence that's been obtained (indistinct) the children because, I mean,

the - what's striking is that they had several - at least some of them had several interactions with the health service, particularly Patrick, who became resuscitated - sudden death, by the sound of things, in the night, then went (indistinct) had a seizure (indistinct) I would assume that they would have done ECGs on him, they should be - at least these days there would be several.

MS FURNESS SC: Professor, to the extent we haven't we will provide you with all the material we have and all the material we have is all the material that is in existence, and we all might wish more for various purposes, but we don't have any more, so we'll give you what we have and we'll engage in a separate discussion with you. In terms of Kathleen, her representatives need to tell us what they're doing, frankly, because otherwise time is going to be running out.

Ms REED: Yes.

MS FURNESS SC: So I can't say anything more about that because we know nothing other than what's being told to us today. So, do you have any other questions or comments you wanted to make at this stage, Professor, given what Dr Buckley has told us to date?

PROF SKINNER: No, I'd be interested just to hear how the discussion develops.

MS FURNESS SC: Thank you, Professor.

DR BUCKLEY: The very next thing I was going to say, Jonathon, was a quote from (indistinct) saying that the assertion of pathogenicity for a variant is not equivalent to diagnosing the patient with the associated disorder, and that we need to bear that in mind, but I think you've made that point adequately in the previous discussion. Alison, sorry.

DR COLLEY: So I was just going to say, I mean, as a clinical geneticist, Professor Skinner, obviously I agree absolutely with everything you have said about phenotype. The only point I wanted to make was that we elected here inasmuch as we could to do whole genome sequencing, cause we didn't want to just limit our thoughts to cardiac death, and so I think we're talking today about - we have just been talking about going down the path of long QT, which obviously is really important, but doing whole genome sequencing, we wanted to really make sure that we didn't overlook genes related to brain stem function, sort of neuronal problems, central breathing regulation, and any other genes that we can think of that might lead to early death.

So I think we just have to make sure that we are thinking broadly and that when we're looking at the whole genome we're thinking of anything that could be variants that could be related to early death.

DR BUCKLEY: So one of the process issues that's important--

PROF SKINNER: Absolutely, I get that completely.

DR BUCKLEY: One of the process issues (indistinct)

PROF SKINNER: Sorry, just for the sake of it (indistinct)

DR BUCKLEY: I'm just going to continue, I'm sorry.

MS FURNESS SC: Hang on, sorry, Dr Buckley is continuing for the moment.

DR BUCKLEY: Is that because the two pipelines have been set up separately in Canberra and in Randwick they will have different settings and they will almost certainly generate different lists of variants for examination. I think we should - the very first thing we should do is decide whether we pursue parallel analyses of the primary data through the dual pipelines and then amalgamate the results into a single record for discovery - for - not for discovery, for furthering filtering and curation, or whether we continue to operate independently of one another.

I strongly believe that it would be in the Inquiry's best interest if we used both pipelines, they would act as quality controls for each other, they will have slightly different settings, they will focus on different things, but an amalgamated set of variants which is then made available to all people who are going to be looking at the data should be made available. Matthew, do you have an opinion on that? Would you like to express an opinion on that?

MS FURNESS SC: Are you there, Professor Cook?

DR BUCKLEY: Professor Vinuesa, do you have an opinion on that?

PROF VINUESA: I agree that it's important to both do it separately and then generate a single amalgamated list so that the two (indistinct) can also interrogate each other's variants.

DR BUCKLEY: Yes, absolutely, great, thank you so much, so I think that's our first decision, an action point, thank you.

MS FURNESS SC: Professor Cook, are you back by any chance? No. We'll continue.

DR BUCKLEY: Once we get to the process of assigning data filtering and pathogenicity assignment I think the logical thing to do is to use the ACMG, the (indistinct) medical genetics and genomics criteria for assessing pathogenicity of variants. That's a well-accepted international standard. We know from international comparisons that when those are used that there is instantaneous agreement on 70% of (indistinct) and that a further 20% can be then workshopped (indistinct) form of agreement, so I think that's a sensible process. Is that acceptable, Professor Vinuesa? I see you nodding, so I assume it is, but--

PROF VINUESA: Yes, absolutely.

DR BUCKLEY: Great, thank you. So we will need to use not only the process for deciding the pathogenicity of variants but also the process which Stand published for the strength of the phenotype genotype association, so whether a particular gene has got an association with a particular disorder, independent of whether a particular variant is known to be pathogenic or not. Those criteria I again believe as part of the ClinGen consortium are well recommended, and that's what I would be advocating for, to establish whether a particular gene has got an association with any particular disorder. Is there any disagreement about that?

PROF VINUESA: Will you take into account publications in the last few years? That's my (indistinct) to ClinVar.

DR BUCKLEY: I'm not talking about ClinVar, I'm talking about the ClinGen consortium and about the Stand publication. I'll give you the PubMed ID if you've not read it already, Dr Vinuesa. So it's PubMed ID 28552198, 28552198, which sets out a process for establishing phenotype/genotype associations.

PROF VINUESA: Yeah.

DR BUCKLEY: Thank you, good, and the sorts of evidence that that publication cites for inclusion is the inclusion of both genetic evidence at case level and at cohort level, but also population data, also experimental evidence, including biochemical function, protein interactions, and so on. I think it's able to be used with any evidence which is out there in the peer-reviewed medical literature. I would hesitate using anecdotal reports which have not been through peer review as a general process. I think un-peer-reviewed data is of less quality and of less standard, so single reports in ClinVar, depending on how much evidence was provided, can be included, but we can go through a process of discussion. Do we have agreement on that? Alison, is that--

DR COLLEY: Yeah, definitely.

DR BUCKLEY: Matthew, are you back at all?

PROF COOK: Yes, sorry, there were a few technical glitches there but I've heard the most recent discussion, I agree with that.

DR BUCKLEY: Okay, so that should then give us a framework to work from, that we'll have genes that we agree are associated with disorders and then a process for establishing pathogenicity of variants within genes, all under the overarching assumption that we will - that the assertion of pathogenicity is not the same as diagnosing a particular patient, that requires clinical evidence as well. So I think that's where - that's the process I would like to adopt. The main issue in the timeframe is for us to be - is to receive the data from the testing laboratories and then to distribute that.

Time is of the essence, however, and once the data are available we will need

to go through the process of data filtering I think independently for each of the four children, and the mother, and then to produce an amalgamated list of variants from each of the four children and the mother separately, as soon as possible, preferably within a week of receipt of the data, of the entire data set. Is that technically going to be possible? That puts it no more than about ten days away when we will need to be having a - shall we call it a genetics jamboree, where we try and look at which variants are available for discussion and further filtering and interpretation? Is that practical?

PROF VINUESA: I think ten days might be pushing it a little bit for our pipeline, because of the workload at the moment. Matthew, what do you think?

PROF COOK: When do we expect to actually have the data?

DR BUCKLEY: I expect to have the data from VCGS later in the week. I've not been given a particular day, but presumably they are going through the process of data generation at the moment, that will be their primary alignment and things to produce the FASTQ, the BCF files, and the BAM and the biofiles for us to look at. That will take a number of days.

PROF COOK: Are you talking about ten days from now or ten days from receipt of the datasets?

DR BUCKLEY: I would like - I'm actually going to be away in Hong Kong for the week of - starting the 18th until the 22nd, so I'm not going--

MS FURNESS SC: February.

DR BUCKLEY: February, so I'm not available in that week, so if it's not going to happen next week, the week starting the 12th, is it? Something like that.

MS FURNESS SC: 11th.

DR BUCKLEY: 11th, then it will have to default to the week starting the 23rd. 21st, sorry.

PROF VINUESA: One thing that might make this analysis slightly longer is that I think it is important for those variants that we consider that are most or best candidates, we need to report the exome coverage in the other - in all the affected, because the fact that it might not be found in a particular child might simply mean that that exome wasn't sequenced properly. Now, that takes quite a bit of extra manual work to do the individual determination, and I think that is essential because, as you know, this is an important supported criteria to declassify a variant from uncertain significance to likely pathogenic, which in legal terms means that we could have an indication that it's more probable than not to be positive.

So if we want to do every (indistinct) analysis I think we have to determine whether - do we first come up with lists of variants that even in one or two

children are going to be best candidates, and then we look at those more carefully in all of the affected and determine whether we have sequencing data for all the affected. It is very likely that the quality of the sequencing is not going to be good enough and the coverage is not going to be even, because we already have a little bit of insight and some type of description of what the broad data looked like for the (indistinct) so I think it - we should say that we know that we are not going to get all parts of the genome sequence for all four of the deceased children. So, Michael, what do you suggest we do so that (indistinct) prioritise--

DR BUCKLEY: I suggest that we look at the data when the data are available and make decisions based on the data.

MS FURNESS SC: Can I ask that we set a date for a discussion, jamboree, that you've described, and then there will have been at least a first look, and hopefully more than that, of the data, and any discussions such as we have just had can be finalised on that occasion?

DR BUCKLEY: The date the commission requires a report from us is the end of the month, the 28th, is that correct, thereabouts?

MS FURNESS SC: Yes.

PROF VINUESA: Michael, I still think that we did come up with a couple of variants that looked particularly important and interesting because they--

DR BUCKLEY: I think from my reading and investigation of those, those are variants of uncertain significance.

PROF VINUESA: Actually the MYH6 could already be classified as likely pathogenic. It--

DR BUCKLEY: No, I disagree, actually. I disagree. I think these are variants of uncertain significance and we would need to go through a process of discussion.

PROF VINUESA: We can discuss it, but just segregation would take them to the likely pathogenic. They already meet sufficient criteria. You need one more supportive criteria, particularly the (indistinct) so segregation we know will be the additional criteria. It's so simple to do a PCR on Sanger resequencing, saves time, why not do it now? Inexpensive and fast.

MS FURNESS SC: Professor Cook, can I ask you your view of what's being discussed?

PROF COOK: Well, I think there's the specific question about the - proceeding with the segregation analysis of these particular genes and then the broader question about whether we should be doing that, which follows on from this discussion that we might not have data from all of the whole genomes, and broadly speaking I think that this is a information gathering exercise and I

would be in favour of pursuing the segregation analysis.

MS FURNESS SC: Dr Buckley?

DR BUCKLEY: I'm undecided at the moment. I have looked at those two variants and I don't see that these are other than variants of uncertain significance and I'm not convinced that segregation, given that it's a very - that it's going to be very low level segregation, with quite a high priority risk that a variant that's totally unrelated to disease will segregate anyway - I don't think that segregation is going to make a big difference.

PROF COOK: And I think it--

DR BUCKLEY: Dr Colley would like to speak, would you mind? Sorry, Alison?

DR COLLEY: I was just going to say that, going back to what Professor Skinner said before, however you look at those variants, they were actually found in a live adult and - who can be seen by a specialist electrophysiologist, cardiac electrophysiologist, and I think a determination can be made as to whether that person actually has long QT syndrome or sick sinus syndrome, and I think that's going to be very important because if the clinical phenotype doesn't add up, if that lady doesn't have those conditions, then it doesn't - to a clinical geneticist they just become a variant.

PROF VINUESA: Having said that, we already know she has had several syncope episodes, and I think there are quite a few. The pathologies could also be quite significant, given that we cannot always diagnose long QT syndrome even under stress.

MS FURNESS SC: Professor Vinuesa, you speak of what has occurred with Ms Folbigg, however we have not received any evidence of that at all. I think in your report you said something to that effect, and I'm sure we asked for more information, and I'm not sure whether - and we've never received it, so I understand the comments that you made in your report, but we've never received any evidence to support them, and - notwithstanding that we have requested them, which means no one in this room is in a position to understand the basis for what you have just said in respect of Ms Folbigg.

PROF VINUESA: Yes, our basis was a simple clinical history taken at the time of ethical consent to have her exome sequenced. We enquired about routine conditions and on interrogation she (indistinct) quite a number of fainting episodes, under exercise, under stress, that fit very well initially with some types of cardiac--

DR BUCKLEY: I would like to guillotine this discussion, if you don't mind, because I don't want to get into - in what is a process meeting, into discussion of particular - whether a patient has a particular disorder or not, which is best left up to Professor Jonathon Skinner to decide, or other colleagues.

PROF VINUESA: I would make one--

DR BUCKLEY: I would like to decide on the process issue about whether we should at this point set up the PCRs to examine these variants, really only because of the tight timeframe, not because of the - it's in any way a presumption that those variants contribute to the disease in any way, shape, or form, that the only reason for doing this is the timeframe and because you would like it done, Professor Vinuesa, and we would like to be collaborative.

PROF VINUESA: Thank you. I appreciate that.

DR BUCKLEY: Is this a reasonable way to proceed? Matthew, do you disagree or agree?

PROF COOK: No, I agree, but I think that - and I agree with - of course, with the discussion about maximising the phenotypic information that we can possibly get. It's fairly artificial at the moment, but we don't have this basic phenotypic information, but then of course with regard to the children it seems like we're going to be largely flying blind with regard to most of the phenotypic information that we would like, and so I think we need to bear that in mind when thinking about what approach we're going to take to the - any segregation analysis that we do, and I think we'll have to consider doing that under more than one model.

But I would - one further comment I would make, though, is whether - and we sort of went down this path a little bit in our December meeting, and apologies if it's an inappropriate comment now, but it comes to this question of whether we're seeking to establish evidence of pathogenicity or whether we're seeking to find evidence that makes pathogenicity extremely unlikely, and they're quite important differences.

MS FURNESS SC: Dr Buckley, do you have anything to say about that? Or maybe Dr Colley?

DR COLLEY: I would have thought the process that Professor Buckley has outlined would take it - would look at the data from a more neutral stand rather than saying we're looking for pathogenicity or we're looking to make sure there's no pathogenicity. I would have thought that the process that Professor Buckley has outlined goes from a neutral position and just takes the data at value, the way it is, and uses the pipelines that are available to assign whether it's likely or not likely.

DR BUCKLEY: And the ultimate - my experience with exome sequencing is that they should have got a lot of clinical information when being able to confidently ascribe a disease process to a pathogenic variant. It's very difficult. In the absence of clinical information I think that's an extreme ask. I'm pretty sure that Jonathon and Alison would agree on that.

PROF COOK: That's really my point there Michael, that I think that in the face of this uncertainty the gap between proving pathogenicity and excluding pathogenicity is quite substantial, and so I think we really need to set out what

our objective is.

PROF VINUESA: And to extend your point, Matt, just for our legal colleagues, when we talk about a variant being likely pathogenic it means that there is a 90% chance that it is the cause of disease, but a variant of no significance doesn't mean it is not pathogenic. It means that to date we don't have sufficient functional evidence or additional evidence that it can be pathogenic, so we have to--

DR BUCKLEY: That evidence will never exist, in fact. Indeed, there will never be evidence that it is pathogenic. That in fact may be totally benign. It means all of those things.

PROF VINUESA: Yes.

DR BUCKLEY: It encompasses all of those possibilities.

PROF VINUESA: Exactly.

DR BUCKLEY: Emphatically so, yes.

MS FURNESS SC: And from the Inquiry's point of view, what Dr Colley said about a neutral position is precisely that, we have no end game at all. Whatever comes out of the data and the interpretation of it comes out of it and ultimately the Judge will form a view whether he has reasonable doubt as to her guilt based on all the information, including the reports you provide, so in the event there is not certainty, there is not certainty. We're not seeking certainty. We're seeking the data and a fair expert interpretation of it, if that helps.

DR BUCKLEY: I think that helps completely, thank you, because I think what we're trying to do is to describe the data in each of these individuals as advice to the commissioner. Commissioner? To the Judge.

MS FURNESS SC: Yes, to the Inquiry. What remains outstanding, subject to any other comments, is a date for the meeting where there can be some discussion as to where we're up to and further discussion, if necessary, as to whether anything else has to be done. Now, my suggestion is that we do that on 5 February, which is before Dr Buckley goes away, and--

DR BUCKLEY: That's tomorrow.

MS FURNESS SC: 15th. Sorry, what's today?

DR BUCKLEY: Today is the fourth.

MS FURNESS SC: Fourth, so the 15th is ten days' time.

PROF VINUESA: I will be travelling from the US to Ghana on the 15th. Is it not possible to have it a day later?

MS FURNESS SC: Well, not unless you want to sit on Saturday, but some may. We just need to decide a date. I understand what you're saying, Dr Vinuesa. Professor Cook?

PROF COOK: Well, I would be available on the morning of the 14th.

DR BUCKLEY: The 14th would work for me. The 15th is almost impossible, I'm afraid, for me, but the 14th could be (indistinct)

MS FURNESS SC: Dr Colley, yes?

DR COLLEY: 14th is much better.

MS FURNESS SC: Thank you. Professor Vinuesa? 14th?

PROF VINUESA: Yes, I will make it, yes.

MS FURNESS SC: So 9.30 on the morning of the 14th?

DR BUCKLEY: Yes.

MS FURNESS SC: And we will then have a further discussion. One thing I'm not clear on, when will we be in a position to provide the data to the Canberra people?

DR BUCKLEY: As soon as the VCGS provide the data to us, then we'll be able to courier it overnight, but--

MS FURNESS SC: And that's likely to be the end of this week?

DR BUCKLEY: By the end of this week.

MS FURNESS SC: By the end of this week.

DR BUCKLEY: That's the undertaking I have. Amber, you--

MS RICHARDS: Yes.

MS FURNESS SC: All right, now, I think from my inexpert point of view you've come to decisions about the various matters that you need to for the moment. It's clear, I think, to everyone the timeframe, and the commission is under a significant timeframe, and that is of little flexibility, it has to be said. The hearing is set for 18 March and that hearing is fixed and it's based on a whole range of technical and - logistics, and it is fixed for that week, so there will be a hearing on that week and the hearing will be preceded by reports and there will not be evidence given by any person who hasn't participated in or provided a report to the Inquiry.

That's all been made clear before, I'm just restating it because, one, I can't

help myself, and two, I think it's important that everybody is on the same page. Now, is there anything more we need to talk about today? Professor Skinner?

PROF SKINNER: Just a process thing, really. Obviously you're going to chase up regarding the cardiac tests that are happening with Kathleen. Will I be able to get access to those as well, and will I be able to liaise with Dr Kumar?

MS FURNESS SC: Well, I think we have to have a separate discussion about that in terms of what's involved, who does what and when and for what purpose, so can I suggest, Professor Skinner, we have a separate discussion about that process? Because I'm not at all clear from those representing Ms Folbigg what they're doing and where they're up to, and I think I need to understand that in order to go forward, so if that's all right with you we'll talk about that separately.

PROF SKINNER: Sure.

MS FURNESS SC: Professor Vinuesa, is there anything further you wanted to say?

PROF VINUESA: No, thank you.

MS FURNESS SC: Professor Cook?

PROF COOK: No thanks.

MS FURNESS SC: Dr Colley?

DR COLLEY: Only to make comment for the Ministry of Health, is that I do believe that one of the children did attend Westmead Children's Hospital, and I can imagine there would obviously be ECGs. What's kept and what's not kept I don't know, but Professor Skinner's counterparts at Westmead Children's Hospital, excellent paediatric electrophysiologists, might be able to have access to find any records. I agree it would be worthwhile trying if at all possible.

MS FURNESS SC: We have obtained, we are told confidently, all the records in relation to all of the children, and so we will look further, but as I understand it we have gone through all of those records and identified the ones that fit the general category we are speaking of.

PROF DUFLOU: At least some of those are ECGs.

MS FURNESS SC: But we have ECGs.

PROF DUFLOU: Yes, those have been provided.

MS FURNESS SC: We've got ECGs. We've got ECGs from Patrick and Laura. We will provide all of the material we have, and I have been told

confidently that we have got everything, and so we have what we have, there's nothing more we can do, and we will put together a bundle for each team and - of the material we have selected from the thousands of documents which we understand to be relevant to this exercise, and we will provide that to you this week, and it will be, obviously, duplicating some of the material you have already got, but we all need to have the same bundle in the same order, so that will happen this week.

Just coming back to the reports, we would expect that any references you add to the report will be provided to us, so we expect the report to contain copies of all documents referenced. It's been impossible for us to obtain some of this material, so it's essential that that's provided, and I can't imagine that that would pose a problem, because that's what you do for a living, all of you. Dr Buckley?

DR BUCKLEY: I would just say that there is going to be plenty of scope for different opinions in this, even with the ACMG criteria, defining, you know, thresholds for absence from controls and what's a functional domain and what functional assays are deemed to be well established, gives plenty of room for disagreement on these things, so I would like to try and minimise unnecessary disagreement as much as possible, and that we focus on the main issue of providing high quality information to the Inquiry.

MS FURNESS SC: Well, I agree with that. All right, well, if that's the case then we might adjourn until next Thursday at 9.30am and, Professor Skinner, you will obviously be on the phone, on the video, if we can organise it, and same with you, Professor Vinuesa, and, Professor Cook, if we can get you on AVL we will, other than that we'll have you on the telephone. Is that right?

PROF COOK: Yes, yes.

MS FURNESS SC: Lovely, and we'll have the Sydney team in person, and perhaps with Dr Kirk, or not. All right, thank you very much for your time and it's been a very useful discussion and we have a plan going forward, which is very good, so thank you.

ADJOURNED