EXHIBIT CB

Inquiry into the convictions of Kathleen Megan Folbigg

Meeting of geneticists

Date: Monday 10 December 2018 at 10:30am

Location: Level 2, 50 Phillip Street, Sydney

Attendees:

- Gail Furness SC (Senior Counsel assisting Inquiry and Chair of meeting)
- Sian McGee (junior counsel assisting Inquiry)
- Amber Richards (senior solicitor assisting Inquiry on behalf of Crown Solicitor)
- Jeremy Morris SC (Senior Counsel for Ms Folbigg)
- Dr Robert Cavanagh (junior counsel for Ms Folbigg)
- Rod Blume (attending on behalf of Stuart Gray, solicitor for Ms Folbigg)
- Dr Alison Colley (Director of Clinical Genetics, Liverpool Hospital)
- Dr Michael Buckley (Clinical Director SEALS Genetics Laboratory, NSW Pathology)
- Professor Matthew Cook (Director of Immunology, Canberra Hospital)
- Professor Carola Garcia de Vinuesa (Head of the Department of Pathogens and Immunity, ANU)
- Professor Jo Duflou (Senior Forensic Pathologist)
- Blaise Lyons (solicitor for NSW Health)

Technological issues meant the teleconference call with Professor Bridget Wilcken AM (Metabolic Physician, Sydney Children's Hospital) and Professor Jon Skinner (paediatric cardiologist at Starship Hospital, Auckland) could not take place.

Recording started approximately three minutes after the meeting commenced, after each of the attendees introduced themselves. During the course of the introductions, Professor Vinuesa specified that she is a researcher and is not a clinician in Australia, however was previously a clinician in the United Kingdom.

GAIL FURNESS SC: Ms Folbigg was found guilty of the murder of three of her children and the manslaughter of, and something equivalent to grievous bodily harm, in respect of the other. The children died between 1989 and 1999 and were varying ages from 19 days, Caleb

the first, to about 19 months, Laura, the last child. There was a petition presented to the Attorney General and it was ultimately accepted this year. An inquiry was called by the Attorney General, effected by the Governor, and Judge Blanch, formerly the Chief Judge of the District Court and DPP of New South Wales, has been appointed to run the Inquiry.

The purpose of the Inquiry is, according to its direction, inquiring into part of the evidence to see whether it raises a question or doubt as to the convictions. That's his Honour's job: is there a doubt or question as to the convictions? The scope of the Inquiry hasn't been finally determined. I made submissions a few weeks ago to say that it should be related to medical advances and to determine what medical advances there have been that may assist in looking again at the causes of death of these children. The Judge hasn't ruled on that, largely because Ms Folbigg's lawyers have not yet made submissions about it, but it is fair to assume it will concern medical advances, whether it concerns anything else is another matter.

The purposes of today's meeting is really to obtain from you your understandings of the changes in genetics and also to assist the Inquiry in determining what testing it now does in relation to these four children. I think it is fair to say that we would all agree that the area of advance relevant to what we are doing is in sequencing. Does anyone disagree with that?

DR MICHAEL BUCKLEY: Not only sequencing, but also in variations.

GAIL FURNESS SC: So there are a number of issues that I'm interested in that I wanted to raise with each of you, and then perhaps at the end of that there will no doubt be issues each of you wish to discuss, but can I start with each of you, Dr Buckley, you provided an email to us that I think has been sent to everybody? Does everyone have a copy of that email? Yes? It was sent on Friday. So let me – do you have a copy of that with you? Now firstly, Dr, you refer to a proposal for whole genome sequencing and there is clearly a distinction between that and whole exome sequencing. Perhaps if you could start by telling us the difference between them?

DR MICHAEL BUCKLEY: Whole genome sequencing sequences the whole genome, it doesn't focus on particular regions of the genome that code for protein genes. It is viewed as being superior form of exome testing in that the coverage is more uniform and distributed... It is in essence a superior form of exome sequencing.

GAIL FURNESS SC: And you recommend that this be used in respect of these four children?

DR MICHAEL BUCKLEY: I think that given there is NATA accredited whole genome sequencing in Australia we should avail ourselves of that.

GAIL FURNESS SC: Now you've talked about NATA-accredited testing, tell us what that is?

DR MICHAEL BUCKLEY: So NATA is an organisation that assesses whether clinical laboratories are providing to an accepted standard.

GAIL FURNESS SC: And the one that you referred to [in your email] the Australian Genome Research Facility in Melbourne does that have accreditation?

DR MICHAEL BUCKLEY: It does.

GAIL FURNESS SC: What other facilities have it around Australia?

DR MICHAEL BUCKLEY: To my knowledge, only Genome.One, which has been recently acquired by Australian Clinical Laboratories and for the period December-January will not be accepting additional samples.

GAIL FURNESS SC: And you would say that the testing should be at a NATA-accredited one because that forms a standard that is accepted in Australia?

DR MICHAEL BUCKLEY: Yes, that provides the necessary standard for testing.

GAIL FURNESS SC: Now you've had a look at the information, I think we all have, as to what's available as to specimens from the four children, and I think you've formed a view about the DNA in respect of particularly Sarah?

DR MICHAEL BUCKLEY: From Sarah there is available some DNA from 2003. Without knowing about the concentration or suitability of that sample it would seem to me to be a logical tissue sample to start with. I would also submit that it would be better to do the testing using information available from the whole family.

GAIL FURNESS SC: Sorry, when you say the family, do you mean the children?

DR MICHAEL BUCKLEY: I mean the parents and Sarah. The best way to do the testing is the familial tree structure, so mother, father and Sarah and to do whole genome sequencing as well as looking for variations.

GAIL FURNESS SC: Sorry, I'm having difficulty hearing you.

DR MICHAEL BUCKLEY: Sorry, so in addition to whole genome sequencing we would also perform testing for copy number variant detections (CNV detection) which can be done on exactly the same sample assuming the sample is of sufficient quality and size.

GAIL FURNESS SC: So you don't know from the material you've got whether we have sufficient in respect of each of the four children and that it is in a condition that can still be used?

DR MICHAEL BUCKLEY: So just focussing on that sample of Sarah, we don't know that that DNA sample is fit for purpose, but I note that it is a fibroblast cell which is stored in liquid nitrogen and could be revived and DNA freshly prepared from that sample in order to provide a high-quality DNA sample if that was needed.

GAIL FURNESS SC: What is it about the samples available in respect of the other three children that make them at first blush not as useful?

DR MICHAEL BUCKLEY: They have been fixed in formalin or paraffin and this procedure causes significant degradation of the DNA.

GAIL FURNESS SC: Is it able to be used at all?

DR MICHAEL BUCKLEY: It can be used, I would propose that the best use of that is to explore possible causes using Sarah's sample as an index case and then if we find something determine if the other three children in the family have the same single variant. I'm using variant and mutation almost interchangeably.

GAIL FURNESS SC: If it was to occur in the way you suggest, that would take significantly longer I imagine because the six or so weeks that you have indicated [in the email] in

relation to Sarah, putting aside the parents for the moment, and then you have another six or so weeks in relation to the other three?

DR MICHAEL BUCKLEY: I believe so, yes.

GAIL FURNESS SC: It would certainly be preferable from the Inquiry's perspective to do them all at the same time in order to save the period of then doing the other three.

DR MICHAEL BUCKLEY: You could certainly aggregate the three individuals who have paraffin imbedded samples and do those together in the same analysis with appropriate controls.

GAIL FURNESS SC: Could you do the four of them without the father?

DR MICHAEL BUCKLEY: Yes. But you get so much additional power from the familial structure that if the father were to be available, that would be to everyone's advantage I think.

GAIL FURNESS SC: If for whatever reason the father was not available, it could still be done?

DR MICHAEL BUCKLEY: Yes. The amount of extraneous information you would generate would be significant and it would take longer to work through and you may not fully be able to understand the consequences of some variants without the father's information. But yes, you could do that.

GAIL FURNESS SC: Now the testing could be done by someone, presumably appropriate, at the facility. And then what would they provide?

DR MICHAEL BUCKLEY: They would provide a final DNA report that could then be analysed by any interested party around the table.

GAIL FURNESS SC: You've suggested in your email a team of geneticists that would be in your view appropriate to do the testing?

DR MICHAEL BUCKLEY: Yeah, I think whole genome sequencing is best understood as a second test which starts as a strong phenotyping component, a laboratory component and then a post-analytical component of the results. The natural response to a complicated situation is to put together an experienced team to do the best testing.

GAIL FURNESS SC: In relation to the team you have suggested, Professor Kirk, who can't be with us today, he has a particular cardiac interest?

DR MICHAEL BUCKLEY: Yes, he is a clinical geneticist. He has a PhD in cardiac genomics and is a clinical geneticist and genetic pathologist (he is dual-trained) who advises the cardiac genetics team and has been doing that over a period of at least 15 years to my certain knowledge. He would be well-placed to add extra value to that interpretation.

GAIL FURNESS SC: Now, you'd obviously need some sort of authority to have access to the samples?

DR MICHAEL BUCKLEY: True.

GAIL FURNESS SC: Assuming you have the samples, how long would it take to perform the testing as you decide, including the interpretation, leaving aside the availability of any of the interpreters at the moment?

DR MICHAEL BUCKLEY: So I have here an email from Matthew Turner of … who says that if we provide the sample by Friday 4 January 2019 he can provide the data by Friday 1 February.

GAIL FURNESS SC: Oh, that's good. I'm pleased we've got that in writing.

DR MICHAEL BUCKLEY: It is expensive, depending on how many samples are available. If it just the test case, Sarah, then maybe as low as $1,000, if the other three samples are available, it may be as high as $10,000.

GAIL FURNESS SC: Is that for the facility to test it, or does that include to your understanding the work of the interpreters as well?

DR MICHAEL BUCKLEY: No, just the cost to the facility of providing the information in a form to be interpreted.

GAIL FURNESS SC: Can I just turn to you, Dr Colley, do you have anything to add to what Dr Buckley has said?

DR ALISON COLLEY: No, I agree with what Dr Buckley has said, I think there is a great advantage to having both parents' DNA, particularly in this case where we know the likelihood of having good quality DNA is really from Sarah, because of how it has been stored, whereas the DNA from the other three children as we have heard will not be as plentiful. We do of course have from the other three children, the newborn screening cards and if we were to do a trio with Mum, Dad and Sarah and come up with a limited number of variants which we believe might cause early infantile demise, then we could use the limited DNA from the bloodspots to test just for those interesting variants, likely variants, and then that way we wouldn't have to go to the extremes of trying to get the DNA out of the paraffin blocks, which could be done. But an easier and quicker way, and timeliness as you say has some role, would be doing the trio and then looking at the other three children's blood spots for a limited number of variants would be my probably preferred option.

GAIL FURNESS SC: So would it take six weeks for the other three?

DR MICHAEL BUCKLEY: I'm afraid it's not a process I'm familiar with. It could be quite a short period of time depending on the expertise of the laboratory.

GAIL FURNESS SC: So the laboratory could tell us?

DR MICHAEL BUCKLEY: The laboratory could tell us. I think the thing is, and it's not included in my email and I apologise for not doing that, there another form of testing and that is micro-array testing. This covers different types of mutations, larger scale mutations which would also be useful in a setting like this.

GAIL FURNESS SC: Just explain that to me?

DR MICHAEL BUCKLEY: It's testing which looks for differences in DNA sequences – rather than the letters which make up the instructions for how to put a human together it looks at whole paragraphs, whole pages, whole chapters, whatever the analogy is. It looks at large

changes or things that might be absent, or things that might be duplicated, e.g. three copies of something.

GAIL FURNESS SC: So would that be done alongside the other testing?

DR MICHAEL BUCKLEY: That could be done in parallel but would have to be done in a different laboratory, I think. No, actually AGRF could actually do it

GAIL FURNESS SC: With the same specimen?

DR MICHAEL BUCKLEY: Yes.

GAIL FURNESS SC: So it could then be done, as you say, in parallel?

DR MICHAEL BUCKLEY: Yes.

GAIL FURNESS SC: Ok well we'll come back to that. I don't understand very much about that at all. We'll come back to that. Did you have anything else you wished to say, Dr Colley?

DR ALISON COLLEY: I think my role presently as a geneticist is that I would work with genetic pathologists along with other clinical specialists which would include a metabolic specialist, a cardiac genetic specialist and probably other genetic specialists with all of us looking for variance and saying for this particular gene what would be due to the DNA sequence, what would be due to the amino acid sequence and therefore how would it change the protein and structure and function and what would we seek that altered protein to do on a cellular and organ basis on a child and would it lead to their demise. As you know there are thousands of variants to sift through but the question is: are those variants relevant to the phenotype we are looking at here which is early demise in children who well nourished, did not have malformations. So I think a team of geneticists and genomicists is the way to go.

DR MICHAEL BUCKLEY: Also I'm inclined to say that the family structure will show whether mother or father have a disorder which could possibly arise from a channelopathy.

DR ALISON COLLEY: I met the parents a long time ago. In the nineties we did not have this understanding of gene testing and I have not seen them again, so I can't give you anything further on that.

DR MICHAEL BUCKLEY: The four children have died and so the parents –

GAIL FURNESS SC: Well, Professor Vinuesa has seen them more recently.

PROF CAROLA VINUESA: I haven't seen Kathleen, but a member of her team went to see her at the facility to consent her and get a detailed personal history and family history. She has had at least three episodes: she fainted while swimming when she was young, she has fainted on several occasions during pregnancy when her blood pressure drops, so she does have some conditions which could have different causes, including cardiac arrhythmias.

GAIL FURNESS SC: The information you've described was provided to you, I take it, in writing?

PROF CAROLA VINUESA: Yes, I can circulate it.

GAIL FURNESS SC: Yes, thank you, let's just hold that, we'll come back to you in more detail for the work you've done, so thank you for that. Can I just turn to you Professor Cook, you've heard what's been said?

PROF MATTHEW COOK: Yes.

GAIL FURNESS SC: I don't understand the laboratory that you have access to, and particularly that Professor Vinuesa used, in relation to what Dr Buckley said about being accredited. Can you help me there?

PROF MATTHEW COOK: About explaining our laboratory? Well we have two genomics pipelines if you like. One is for our discovery programme, and the other is a diagnostic pipeline, both for whole exome sequencing, although our bioinformatics pipeline is capable of handling whole genome and whole exome data, and we have considerable experience in handling both data sets.

GAIL FURNESS SC: Forgive my ignorance, the facility that Dr Buckley spoke of, is that the same sort of facility that you operate, or not?

PROF MATTHEW COOK: Well I think Dr Buckley is referring to the AGRF facility, which is as I understand it NATA accredited for medical testing, is it NATA accredited for whole genome?

DR MICHAEL BUCKLEY: Yes.

PROF CAROLA VINUESA: It's not on their website.

PROF MATTHEW COOK: Right and then I don't think they provide a clinical report? So they provide the sequence. Now whether they are accredited for sequencing the sort of material we are discussing here is another question. So we have a clinical sequencing facility which is not formally accredited, we have just been through the formal accreditation process and we have been recommended for accreditation and that recommendation has gone to the board of NATA and we are waiting for the formal documentation that we have satisfied all of the criteria for accreditation. So we would be surprised if that doesn't flow in the next week or two, but we were not in a position to perform the sequence under our NATA accreditation for a DNA sample recovered from a blood spot or a paraffin tissue. Now that doesn't mean we couldn't bring to bear our resources, but that's an important distinction.

GAIL FURNESS SC: You've heard what Dr Buckley says about who he believes would be involved in the next step, which is to interpret it and that is something that you would obviously be familiar with.

PROF MATTHEW COOK: Yes, so, I don't disagree with Dr Buckley has said, I think that our task here is to minimise chances of uncertainty. Although there has been enormous progress, relative to genetics, one of the consequences is a substantial increased risk in uncertainty because of the enormous amount of data that is obtained, so we need to do what we can to minimise that, and that can be done at the technical level, so thinking about what sought of laboratory should actually run the sequencing and generate the sequenced files is one way to reduce that uncertainty and going back to the step to think about whether we should run an exome or a genome is another way of mitigating that risk of uncertainty. I would say that there is empirical evidence that if you do a head to head comparison between an exome and a genome on the same sample, there will be some variants that will be

missed either way. I think this has been demonstrated. Now there are more that are missed on the exome than on the genome, but there are false positives and false negatives either way.

So I think that there is possibly a case to be made that depending on the material available, another way of mitigating this risk of uncertainty at the technical level is even to sequence more than once. There are stochastic factors at play no matter what techniques are used or where it is performed, even if it is in a NATA-accredited facility. So that would be something to consider. Even if we agree that the sequencing might run at one facility, certainly the analysis of that sequence could be run through more than one pipeline to annotate variants, even before it gets to the desk of whoever is going to interpret those variants.

I think the other thing to consider though is that NATA accreditation provides a summary assurance within the clinical setting that proper quality control measures are in place and the complete process from sample collection through to reporting has been evaluated on a regular basis according to those procedures. That's the basis of that assessment, to engender confidence in the laboratory. There are clear parameters that we can use to assess the quality of sequencing, the technical quality of sequencing, we can look at depth of coverage which is an important determinant of the quality of sequencing, how many times we look at the same stretch of DNA over and over again, and the proportion of genome or indeed the exome which has met a predetermined criteria for sequencing.

GAIL FURNESS SC: So what you're suggesting is that there is a whole range of work that could be done which would be the equivalent of accrediting.

PROF MATTHEW COOK: No, sorry, so I'm suggesting that we're dealing here with a single kindred, it is possible that the material we are dealing with is in some way exceptional and it may be that we need to determine what parameters are acceptable when we make the quality assessment of the sequencing that is performed.

GAIL FURNESS SC: I understand that, I thought that you were seeking to make a distinction between NATA accredited and those that may not be, but could nevertheless do a variety of things which could provide one with the same level of satisfaction that one would have with NATA accreditation.

PROF MATTHEW COOK: No, I'm suggesting that irrespective of where we did it, we would apply these parameters of quality to determine how reliable the results might be.

GAIL FURNESS SC: In terms of the two parents and the four children, would it be your view that that would be –

PROF MATTHEW COOK: Right, so this moves us on to the next way of mitigating uncertainty, which is to consider the possibility of the analysis of the kindred rather than of individuals and here we have the potential for considerable power by sequencing all four children as well as both parents and I think that again, just as we are spending a lot of time considering the technical limitations, I would be strongly in favour of sequencing the entire family to ensure that we maximise the power that flows from that.

GAIL FURNESS SC: But you would agree with Dr Buckley that in the event for whatever reason the father wasn't available, it would still be a worthwhile exercise?

PROF MATTHEW COOK: Well, again by analogy we might say it still might be a worthwhile exercise if we started with DNA which is not of optimal quality as long as the sequencing results meet an optimal standard, similarly we might say if the father is not available, there still might be value in sequencing the family members that are available, but we would have to recognise that that is going to increase our uncertainty.

GAIL FURNESS SC: Did you want to say anything else Professor?

PROF MATTHEW COOK: Not at this stage, no.

GAIL FURNESS SC: Can I turn to you then, Professor Vinuesa, in terms of your report, that was done at the laboratory that you and Professor Cook work at, is that right?

PROF CAROLA VINUESA: Yes.

GAIL FURNESS SC: And who did it?

PROF CAROLA VINUESA: So we have a standard procedure, sample arrives and it goes through standard sequencing pipeline and this has been formally recommended for approval. This gives us a list of the variants and using some generally accepted algorithms… Here we only have a single family member who could be a carrier, particularly in view of her personal history, we run a list of candidate genes which have previously been reported as causing sudden unexpected death syndrome or sudden unexpected cardiac death and see if there are any variants which would be likely to cause these diseases. Here there is one candidate which is novel and has never been reported, it is in a gene which has now been shown to cause infant death syndrome and a cause of long QT syndrome. In every single case that it has been reported it is heterozygous: a single copy of the gene can cause sudden infant death syndrome. To date, there is not a single variant of this gene that has not been shown to be pathogenic.

GAIL FURNESS SC: Do you mind if I just stop you there, does everyone have a copy of this report? Dr Colley, you don't, Dr Buckley you do [Blaise passes on a copy to Dr Colley].

PROF CAROLA VINUESA: So of course this doesn't mean that the four children have this mutation, but if they did, it would be a very strong candidate for causation. Of course in this case, it might cause arrhythmia known to cause sudden infant death or long QT syndrome, there are people who have these mutations and are undiagnosed until adulthood and might have a mild form of this disease. It is recommended that Kathleen Folbigg has a cardiac investigation because she reported fainting during exercise, it might be that she needs an ECG during exercise. This doesn't mean the kids would have this, but I would strongly recommend that they are tested for these mutations, there is a second one which has also been shown to be involved in cardiac death, and is rare. If I may comment, I agree with Michael Buckley's approach but I still think it is essential to seek testing from four affected children because there is enormous power in being able to interpret in an unbiased way the entire genome, not only the candidate genes. Even though we might have information about potentially pathogenic mutations, we will not have the power to detect any potential genes in the genome that we at the moment might not know at this stage causes cardiac death but could with further investigation...

GAIL FURNESS SC: Do you mind if I just ask you to slow down one bit?

PROF CAROLA VINUESA: Yeah, really sorry. Just to cite an example we have recently had a family referred to us from Macedonia. There have been four infant deaths in the family similar to this. In this case they had symptoms and it was only because we could sequence the four affected that we could find the gene that back then had not been shown to cause this particular syndrome. This is about to be published that this is a known cause of death. We would have never found it if we had only sequenced one because it was only when we asked what do these four dead neonates share that is rare and damaging anywhere in the genome? Starting looking at genes with completely unknown functions. So I think if we really want to err on the side of caution, and use every tool to potentially find the damaging mutations, we should sequence the four children if possible.

GAIL FURNESS SC: Thank you. Can I just ask you one thing about your report, you said the analysis of the exome for genes previously shown to cause sudden unexpected death – I wasn't aware that there were genes that have been proven to cause it?

PROF CAROLA VINUESA: Yes. There is now a long list of genes that can be proven to cause unexpected infant death in infants, in children and in adults, and that list is growing.

GAIL FURNESS SC: Is there a publication we could look at?

PROF CAROLA VINUESA: Yes there is.

GAIL FURNESS SC: Maybe we can get it from you later. I saw those two in your references.

PROF CAROLA VINUESA: These are now considered to be pathogenic. They are all de novo and have all show function mutation and degradation.

DR MICHAEL BUCKLEY: The problem in every instance is they have been shown to be de novo and causing disease and yet we have people walking around with –

PROF CAROLA VINUESA: So she also has these mutations so there could be –

GAIL FURNESS SC: Sorry, who are we talking about now? Are we back to Macedonia or are we talking about Ms Folbigg?

PROF CAROLA VINUESA: Ms Folbigg.

GAIL FURNESS SC: Thank you, go on.

DR MICHAEL BUCKLEY: I read the literature too and I noted that in all instances the people who had died had de novo mutations.

GAIL FURNESS SC: Can you tell me about that?

DR ALISON COLLEY: De novo means it is a new mutation just in that person. If something is always de novo one would think that it always causes a condition and the person doesn't live long enough to pass it on, otherwise it would be inherited.

GAIL FURNESS SC: Thank you.

PROF CAROLA VINUESA: Can I say that one of the people was diagnosed due to cardiac issues, heart racing, she was 29 years old. For all we know there could be something in Kathleen and she might have long QT syndrome, but having said that I've reported that

there is another eight mutations, there could be another one… this provides support for the fact that it could be genetic.

GAIL FURNESS SC: Can I ask from you Jeremy if we could have whatever it was that Professor Vinuesa relied on in her testing? I think we have the instructions, but –

JEREMY MORRIS SC: I'll make some inquiries.

GAIL FURNESS SC: And equally if we could have the articles she has been referring to that would be very useful. Now, is there anything else you wanted to say Professor? No? Just going back to you Dr Buckley, Dr Buckley, you obviously want to say something first? Go on.

DR MICHAEL BUCKLEY: I think that we can only offer an opinion to this Inquiry based on evidence if we know that the only variants that we come across have been reported as de novo then I would be tending not to speculate beyond that. That would be my general approach that I will base my submissions to the Inquiry based on published evidence rather than speculation.

GAIL FURNESS SC: Just leaving that to one side, I am not concerned about that for the moment. Is anyone wanting to persuade the Inquiry to do anything other than go down Dr Buckley's path?

JEREMY MORRIS SC: I have got some queries for Dr Buckley if that's ok? Dr, I am Senior Counsel representing Ms Folbigg. There are really two issues, I will get to the second one because it relates to your last comment. The first one is the likelihood of DNA recovery from degraded samples only using NATA accredited recovery kits and so forth? I understand that there are a number (two or three) kits that have been demonstrated to recover seriously degraded DNA and bearing in mind we are not in a clinical environment in this Inquiry, we are in a forensic environment and I am told that these kits have a better strike rate and that those results can then be sequenced in a NATA accredited facility – I would like your observations on that?

DR MICHAEL BUCKLEY: So I think we are talking about the difference in sequencing between the generic approaches vs whole genome sequencing and that if you have the robustness of using DNA extracted from, if it be, the samples for whole genome or exome sequencing, to my knowledge the only danger that I have seen from sequencing is if the samples show more uniform coverage than standard procedure – I think that the most robust way is to use the technology which is best suited to the materials that are available and then to explore whether the other people in that family carry that same variants – to my mind that is the most robust way to approach it given the degraded nature of the DNA samples.

JEREMY MORRIS SC: So what DNA extraction methods or kits were you proposing to be utilised in the DNA extraction of the degraded material?

DR MICHAEL BUCKLEY: So I would refer to the laboratories that are NATA accredited to extract DNA from the samples and mostly in Australia that is done on tumour cells of cancer and there are a large number of laboratories which are accredited to do that procedure, looking for simple or for two or three or a small number of DNA variants.

PROF CAROLA VINUESA: [inaudible]

GAIL FURNESS SC: Look, I'm sorry because I'm having trouble both hearing and understanding you.

PROF CAROLA VINUESA: When Dr Buckley proposes that whole genome sequencing is only performed on Sarah and the other three children are only tested for variants…

GAIL FURNESS SC: Can I just stop you there, it is unlikely that we will go down that path, with respect to Dr Buckley, so if you want to argue against it you don't need to.

PROF CAROLA VINUESA: If we are testing the four from scratch at the moment it is very unlikely that there will be a NATA accredited protocols for extracting DNA from a highly degraded 13 year old sample, so I think you have to be flexible in assuming that this part of the work will not be under a NATA accreditation, it will be research-type exercise and any relevant results identified will then need to be confirmed by a NATA accredited lab.

GAIL FURNESS SC: Dr Buckley can you explain your take on that?

DR MICHAEL BUCKLEY: Can I have a think about that?

GAIL FURNESS SC: Yes certainly. Yes, Professor?

PROF JO DUFLOU: On the forensic note it refers to extracting DNA on very poorly graded samples including form-fixed paraffin tissue. I don't know specifically if the DNA lab FASS in Lidcombe is accredited for that but they certainly have a forensic NATA accreditation and that would include for extraction – I don't know what the scope for the extraction would be.

GAIL FURNESS SC: No, but the preference for the Inquiry is related to time and this is not an Inquiry which is going on for years and so the extent to which properly we can have relevant testing done at the same time and using the same facility the better, that is fairly obvious. I have no doubt that there are a whole range of laboratories and other facilities that one could use, I am interested in whether or not we can have one provide whatever it is that ultimately is accepted to be the tests so I appreciate what you are saying Professor that you are saying that there are others are available but I am particularly interested in whether we have one, preferably accredited for obvious reasons, that can do whatever you tell me is necessary. That's my starting point. So is there anything you want to say about that?

DR MICHAEL BUCKLEY: So in response NATA accreditation provides a uniquely high standard of guarantee that samples are handled well and that results are not at risk. I think the search base is to explore hypotheses that may or may not be proved to be correct. Otherwise there is little if any control over what is done to samples. My preference for an Inquiry which has got quite significant outcomes it would be safer to use a NATA accredited laboratory.

GAIL FURNESS SC: And that can do everything that you think is needed to be done in order to have a report generated?

DR MICHAEL BUCKLEY: Well yes I am not sure there is NATA accredited laboratory to do whole exome sequencing on the old samples, I haven't heard of one.

PROF CAROLA VINUESA: So I enquired with VCGS and they have accreditation to perform Guthrie card testing but they have only trialled it for two year [old samples] and they

themselves said they are good at doing it but do not have NATA accreditation to do it from probably highly degraded 13 years old DNA.

GAIL FURNESS SC: Does anyone?

PROF CAROLA VINUESA: So that is what we think that there is none.

GAIL FURNESS SC: So we do not have a choice, no one does it.

PROF CAROLA VINUESA: That's correct.

GAIL FURNESS SC: Thank you for that, is that your understanding that no one does it?

DR MICHAEL BUCKLEY: That is my understanding – I know that there are some research laboratories which have published on the area but as far as I'm aware, they are not NATA accredited.

GAIL FURNESS SC: Thank you.

PROF MATTHEW COOK: I just wanted to reiterate this point, that NATA accreditation provides confidence that over the course of a defined period, a year or two, laboratory results are being performed up to a particular standard. Here we have the opportunity to determine what standard is required for these specific samples and it's going to be done on exceptional samples, I think, irrespective of where it is run we can assess the quality of the results based on the parameters that we determine from the sequencing.

GAIL FURNESS SC: I understand that, I understand that, I understand your point – did you want to ask anything more of Dr Buckley?

JEREMY MORRIS SC: Dr Buckley, the remaining concern I have is probably a more broad philosophical one and you no doubt understand that Ms Folbigg was convicted and has served 15 years of her sentence and one of the problems at the trial is that there were a limited number of genetic inquires that could be made at the time and it seems that the knowledge of genetics with respect to cardiac conditions at that time was extremely limited, there was one test that was performed and that was only done generally which is problematic and one of the other problems is when I assume that the sample used for the Guthrie testing is used we end up with the destruction of the genetic material which means you can't – it might not be available for further testing, and in circumstances where we have this one opportunity to test more broadly rather than just testing for specific known genomes there is something of a difficulty from my client's perspective by confining that on what we know today rather than what might otherwise become apparent, and in other words we are introducing at the very beginning of the Inquiry a filter on the range of examination rather than making that determination once the results are in – is that a real concern or would the approach be proposed or?

DR MICHAEL BUCKLEY: I'm sorry, you'll have to put the question more clearly, I don't quite understand where you are going.

DR ALISON COLLEY: I think what the real issue is about whole genome sequencing is that it is hypothesis free – you start off without knowing what the condition is or what the problem is or whether there is a problem. The old way of just doing genetic sequencing is

that if a clinician like myself will go "I think there might be a cardiac problem" we will look at all the cardiac genetics. Or "oh gee we were wrong" and we will look at the brain stem function genes in case breathing stops and see if we can find something and then on and on we go until perhaps we get on the right gene or perhaps we can't get on the right gene because that gene has not really been revealed before. Whole genome sequencing is the new technology when you start without a hypothesis – you look at every gene – exome, coding, non-coding and you look for variations against what is considered normal and what is considered normal for that family. So that is why whole genome sequencing I think is the test of choice in this situation because we don't know if there is a genetic condition or not and if there is a genetic condition is it immune, is it immune gene, cardiac, genetic, brain stem function, metabolic – so we are not limiting we are opening up and saying let's just look at everything, is anything possible.

Now because there are so many variations in the human genome, the more people in the family you get obviously the testing is better as the experts said because if you look at the statistics if there is something that is dominant, one faulty gene that has affected all four children the risk of that happening is 1 in 16. If it is a recessive condition the risk of it happening is 1 in 256, so you are less likely to have mistakes and more likely to find out an answer by having the whole family and starting off with a whole genome, it means you are looking at everything not just cardiac genes. You might find something you don't even know about, something you never thought of, there might be nothing when we look at everything. But I think to do fairness to the job, to be hypothesis free from the beginning and keep an open mind and interrogate all the data we can get, a whole genome sequence is an advantage. Our problem with the other three children is not that we don't want to do it, it's what sample that we've got to do it.

GAIL FURNESS SC: And we don't know, and we won't know precisely until someone looks at the samples to see if they are sufficient – that's the bottom line – we all understand that and we don't know that answer.

JEREMY MORRIS SC: So, can I just apologise, my knowledge of genetics is pretty barnyard ok, so that makes it very clear and I think here is the concern I have –

DR MICHAEL BUCKLEY: I do have a concern that arises out of that though, if we find a variant in a gene which is shared by all four children and it is not a gene that's got a normal function, and no-one has had much experience with that gene, then if we report that as being a likely cause, then I think that's not appropriate, you have to base any reporting on this, not on proposition, supposition or hypothesis, but the evidence.

GAIL FURNESS SC: And that is what we are relying, hang on Jeremy, for you for to provide us with a report that you clearly state what the evidence is that supports your conclusion and what your reasoning process is, so in the event you were of the view that there was no evidence, however if one supposed to presume x, y and z you might get there, that's what you tell us, and if other people have a different view then that is what you tell us, it is then up to us to consider how that report fits into the role of the Judicial Officer in deciding what he has to decide. So it is not your job to worry about whether it causes a doubt in terms of the conviction, that is our job – your job is to reason logically and on the basis of your expertise from whatever it is you have got to a conclusion and if you reason differently and come to a different conclusion that's fine, that's what you do. We would not seek to constrain anybody in any way and the outcome is not something that we seek to impose at all, we want you to tell us what the outcome is ultimately, testing and

interpretation, and then the Judicial Officer will take that on board in determining what he has to determine, so we ask nothing more of you than you apply your expertise and the evidence to a report. So I just want you to be put at rest about that.

It is actually a matter for the Judicial Officer what that means, you just have to apply your expertise to whatever it is you come up with and then he will consider whether that gives rise to a doubt or a question as to the conviction, which is his job so you are providing evidence based on your expertise to assist. So, clear line, which is quite handy for both of us.

PROF JO DUFLOU: there seems to be an assumption specifically that there are no frozen tissues – I don't have the documentation associated with that but at that time at least it would have been part of the protocol to take frozen tissue.

GAIL FURNESS SC: Can I just ask whether you have seen the four pages or more than four pages about the material that we have got – so is there anything on these few pages that –

PROF JO DUFLOU: I have only seen Cordner's report

GAIL FURNESS SC: Don't worry about that, we have what we have in fact so we don't have to speculate.

PROF JO DUFLOU: That's not what I'm referring to. That is only the histology slides, frozen tissue would be kept in –80C. [Reads sheet].

GAIL FURNESS SC: Does that answer your question?

PROF JO DUFLOU: In theory yes assuming proper documentation, in practice, not necessarily.

GAIL FURNESS SC: I'm sorry I don't understand that.

PROF JO DUFLOU: The reason why I say that is that I know what normal procedure was at that time and it should've included frozen tissue.

GAIL FURNESS SC: So you're saying that you think that there should be something more than is on this list?

PROF JO DUFLOU: There should have been, yes.

GAIL FURNESS SC: Ok, Blaise, do you want to take that on board?

PROF JO DUFLOU: Now there's an urgency in relation to movement of the facility –

BLAISE LYONS: I can assure you that relevant inquiries have been made and I doubt there is anything else.

GAIL FURNESS SC: I think you can assume, Professor, that all stops will be taken out of the equation when we're looking at these. So thank you for your contribution but we'll –

PROF JO DUFLOU: No, fair enough.

GAIL FURNESS SC: We're confident through the Department of Health that they're doing all they can and now that you've raised that I'm sure that Blaise will take that on board and see specifically whether that's available.

Now, is there anything anyone else wanted to say? Can I then just say what we need as a result of this. Firstly, in relation to Professor Vinuesa, we need the material that she has relied upon, but in addition, the DNA from Ms Folbigg is where?

JEREMY MORRIS SC: I'm not –

GAIL FURNESS SC: No, I'm not looking at you, Jeremy.

JEREMY MORRIS SC: You've got it?

GAIL FURNESS SC: You had it?

PROF CAROLA VINUESA: Yes, at Canberra Clinical Genomics.

GAIL FURNESS SC: Beg your pardon?

PROF CAROLA VINUESA: Yes, it is at Canberra Clinical Genomics in our facility.

GAIL FURNESS SC: Right, thank you. Is there any objection to the Inquiry having access to it?

JEREMY MORRIS SC: Ah, I would say no, but I would just like to confirm instructions.

GAIL FURNESS SC: Alright if you can do that, that would be very helpful.

JEREMY MORRIS SC: I can't give the concession now –

GAIL FURNESS SC: No, no, I perfectly understand, I perfectly understand. Now, as you've described it in your report, is that sufficient for your purposes, to test whatever it is you need to test, the DNA?

DR MICHAEL BUCKLEY: If it has already been sequenced it should be perfectly adequate.

PROF CAROLA VINUESA: I'm happy to share the findings with everyone. I think that it would be more useful with the rest of the family –

GAIL FURNESS SC: Well let's leave that to, leave us to worry about that and the rest of the family. But yes, if you can tell us whether or not we can have access to that, that would be good. Now, having listened to the various discussions, what I need to understand is whether there's any objection, as opposed to "we could discuss other ways of doing it", to Dr Buckley doing what he has suggested he'll do, both here and in his report? Professor? With the group of interpreters, which includes you.

PROF MATTHEW COOK: No objection, no objection, but –

GAIL FURNESS SC: Sorry, let me just add, with all four children.

PROF MATTHEW COOK: And both parents?

GAIL FURNESS SC: Well I don't know about that, I can't speak in terms of –

DR MICHAEL BUCKLEY: They'll need to understand the protocol that's been proposed –

GAIL FURNESS SC: I beg your pardon?

DR MICHAEL BUCKLEY: They'll need to understand, the proposal I had made was again preferably trio sequencing the mother, father and Sarah with any indication of variants in Sarah's sample then be examined on the three other paraffins, the three other children, using paraffin samples.

GAIL FURNESS SC: Can I suggest a variation to this, that it's done at the same time?

DR MICHAEL BUCKLEY: So the three children will get done as a group, but you can't do the second group of testing before you've done the first or at the same time, you have to get your results first then you go on to do the –

GAIL FURNESS SC: And what's the time consequence of that? We don't really know, do we?

DR MICHAEL BUCKLEY: I don't know, sorry.

GAIL FURNESS SC: Ok. So understanding that that is what you propose, and leaving aside the question of the father for the moment because I certainly can't speak on his behalf, do you have an objection to that process?

PROF MATTHEW COOK: Well I would favour doing all samples at once –

PROF CAROLA VINUESA: As long as –

GAIL FURNESS SC: Sorry, can we just take it one at a time because it's important.

PROF MATTHEW COOK: And because, you know, it might end up taking us much longer because we might have to reanalyse the family trio in light of the additional children anyway, if we got those it would be preferable to do everything all at once. And look, if it turns out that the quality of the sequencing in one or more of the individuals is not up to scratch then we'll have to modify our approach, but that's what I would aim for. But the other thing I –

JEREMY MORRIS SC: Modify your approach how?

PROF MATTHEW COOK: Well to our analysis, so we might have to do the analysis by omitting one or more of the individuals' samples if it's not of sufficient quality, but I think that that would be, that would be my preferred approach. And then, you know, in terms of thinking about the protocol, well we could still consider whether sequencing is going to be done at a single place or more than once place, in parallel, again it wouldn't take, wouldn't increase the time, it would increase the expense and it might not be feasible depending on

how much DNA we have available, but that would also reduce the risk of errors by doing that.

GAIL FURNESS SC: Why would that reduce the risk of errors?

PROF MATTHEW COOK: Because there's always some, if two laboratories perform the same, because it's such a complicated test, if two laboratories –

GAIL FURNESS SC: Well how realistic is that?

PROF MATTHEW COOK: Hmm?

GAIL FURNESS SC: That there will be an error that would be made at the one laboratory and in two things it might be picked up if two of them do it. That doesn't make sense.

PROF MATTHEW COOK: Oh, well, the extent of–

GAIL FURNESS SC: I understand that errors can happen.

PROF MATTHEW COOK: The signals that you need to, it's based on the number of signals that are obtained when you sequence an exome or a genome –

GAIL FURNESS SC: But you're not suggesting the same thing be run in two laboratories, you're suggesting that part be run in one and the other part be run, for example the three other children be run in one –

PROF MATTHEW COOK: Oh no, no, I would suggest that everything be run in the same, all samples be run in the same laboratory and I would question whether it should be duplicated in the second laboratory.

GAIL FURNESS SC: I understand.

PROF MATTHEW COOK: And –

GAIL FURNESS SC: Is that usual practice?

PROF MATTHEW COOK: No it's not usual practice, but this seems to me to be an exceptional situation.

DR MICHAEL BUCKLEY: There is a research tool where we looked at a whole group of samples by exome sequencing and by genome sequencing… and what we found was, there is a very small increase in the number of identifiable variants between exome sequencing and genome sequencing –

GAIL FURNESS SC: I understand that but I thought the point was quite different, that you should duplicate the test in two different laboratories, is that what it is?

PROF MATTHEW COOK: That's what I'm suggesting.

GAIL FURNESS SC: Which is quite different from –

DR MICHAEL BUCKLEY: No I don't think it's quite different it's just a different way of getting the same data but I think the issue is really that you don't see a lot of difference between the two technologies but I don't see that it affects –

GAIL FURNESS SC: I'm sorry, I didn't understand you to be speaking in terms of one doing the whole genome and the other doing the exome, is that the distinction you're seeking to make?

PROF MATTHEW COOK: Not necessarily but it's a fair enough inference to draw because we might only have one opportunity to, one lab might only be able to, we might only have one lab to do a whole genome, the other lab might only be able to do the exome.

GAIL FURNESS SC: Which one is better, whole genome, why wouldn't you just do the whole genome?

PROF MATTHEW COOK: For the same reason that, as Michael has just explained, there is empirical data to suggest that if you do this, if you run the same sample by two different approaches there is not complete congruence of results.

GAIL FURNESS SC: I must say, what I don't understand is what you're suggesting. Are you suggesting that one lab do the whole genome and another lab do the exome, is that what you're suggesting?

PROF MATTHEW COOK: Yes.

GAIL FURNESS SC: By the same standards with the same result. Okay. I don't understand why that's beneficial.

PROF MATTHEW COOK: Because there will still, it's highly likely there will still be variants which are detected, it's just to improve the pick-up rate of variants.

DR MICHAEL BUCKLEY: So you could just change the depth of sequencing on the genome in the sequence –

PROF MATTHEW COOK: It's possible but there are still going to be factors that are probably going to come into play. I mean there are parts of the, look it's probably a small yield. So I'm just raising it as a possibility. But then the second point is then what we do with the sequencing files, and there I would certainly be in favour of those sequencing files being run independently through different pipelines –

DR MICHAEL BUCKLEY: Absolutely.

PROF MATTHEW COOK: If there are going to be different individuals involved, then we should—

DR MICHAEL BUCKLEY: If using slightly different parameters, there will be inherent biases…

GAIL FURNESS SC: Right, just to be clear then, your area of concern is that you do it twice and that you do the exome somewhere and the genome somewhere else?

PROF MATTHEW COOK: That would be my preferred.

PROF CAROLA VINUESA: I just want to clarify exactly, if I understood correctly, Michael proposes to only do whole genome sequencing on Sarah and only then only to look at candidate genes in the other three children.

GAIL FURNESS SC: Ok let's just stop there for a moment. As I've indicated, we would only be interested in doing it on all four, and the question of whether, I've accepted the DNA available in a different form perhaps degrades in relation to the other three –

DR MICHAEL BUCKLEY: I don't think it's feasible for the AGRF to provide whole genome sequencing on the paraffin samples.

GAIL FURNESS SC: But can somebody do that for us?

DR MICHAEL BUCKLEY: I know of somewhere.

GAIL FURNESS SC: So we need to find out if it can be done and it's going to depend upon the nature of the sample and we don't know about that either.

DR MICHAEL BUCKLEY: Certainly a research laboratory could do it, and the Garvan Institute would be one such place. I don't know if their genome researchers – they would certainly do so under quite stringent restrictions.

GAIL FURNESS SC: So as I understand it from our previous discussion, no one is accredited to do that work but there are laboratories that could do that work. And the basis upon which we would choose one laboratory over the other is not accreditation, it must be some other criterion. Can you suggest what that might be?

DR MICHAEL BUCKLEY: Well there's really only two games in town, there's the Genome.One facility at the Garvan Facility.

GAIL FURNESS SC: Yeah but I think they're not –

DR MICHAEL BUCKLEY: They are not accepting new samples.

GAIL FURNESS SC: They're in a different state at the moment.

DR MICHAEL BUCKLEY: For whole genome sequencing, we have an issue –

PROF CAROLA VINUESA: I think they said yes. They have experience in this so I think it's more important that they get as best quality DNA as they can from these samples and by those that are most experienced. VCGS has experience in whole exome sequencing from –

GAIL FURNESS SC: Sorry, who? You've got to not use acronyms or we will go mad.

DR MICHAEL BUCKLEY: Victorian Clinical Genetic Service.

GAIL FURNESS SC: So you're saying they could do it?

PROF CAROLA VINUESA: They're very experienced… they're used to handling Guthrie cards.

DR MICHAEL BUCKLEY: I have the feeling that they actually use AGRF.

PROF CAROLA VINUESA: I've contacted them and I've got two names and it's important that it's done by those with experience –

GAIL FURNESS SC: Can I suggest that someone, and we'll just leave to one side who that person is, contact the facility that you've been referring to in terms of Sarah to see whether or not they could use the paraffin blocks that are available in respect of the other three children and do a test for us. Is that a reasonable place to start?

DR MICHAEL BUCKLEY: We'd have to get DNA extracted by someone then once we've got DNA of a sufficient mass for sequencing then we'll –

GAIL FURNESS SC: Who should extract it?

DR MICHAEL BUCKLEY: There are numerous places around here. You have –

GAIL FURNESS SC: What we need, to be brutally frank, is a package because of the time we have, and the package is, who can do each stage of the process, the more stages that can be done by the one facility is so obviously better, but I perfectly understand if that can't be the case, I'm not trying to stretch it to fit that, but we need to understand who can do what stage with the view, ideally, to have the four children done at the same time, understandably different purposes, perhaps different facility, but nevertheless from a timeline point of view to the extent we can do it that way. I understand what you're saying that if you do Sarah first then it's easier in respect of what you look for in the other three, my concern is time for that.

DR MICHAEL BUCKLEY: So the material, the paraffin-embedded tissue, it's nanograms of quantity, maybe 50, 100 nanograms –

GAIL FURNESS SC: Well if whoever undertakes that task tells us, because of the nature of the material and the extent to which it degraded, that it can't be used then that's fine. Again, as I say we're not pushing an outcome, all we want to know is the answer to that and if that's the answer then there's nothing more we can do in respect of those three. But we do actually need to know that answer quite quickly.

DR MICHAEL BUCKLEY: So there is a secondary technique we've been talking about, the difference between whole genome versus whole exome sequencing, there is also a split in exome sequencing, you can either use a capture approach or you can use a different form of identifying the DNA and go behind the Ion Torrent procedures which are quite robust on genetic samples, and certainly it's low input masses, so that's another possibility you might want to consider. If we wish to do the examination on the same platform at the same time, then we can certainly do a VCR-based approach using an Ion Torrent platform rather than a capture approach.

GAIL FURNESS SC: And who could do that?

DR MICHAEL BUCKLEY: We could do it in my laboratory.

GAIL FURNESS SC: So you could arrange for whatever DNA is able to be extracted?

DR MICHAEL BUCKLEY: We could arrange for the DNA to be extracted for the three and we could do the Ion Torrent-based approach.

GAIL FURNESS SC: And then at the same time as you're extracting it, the facility you've mentioned could begin work on Sarah, is that how it works?

DR MICHAEL BUCKLEY: You could do exactly the same test for Sarah. We couldn't do genome sequencing on the other children –

GAIL FURNESS SC: No, no, I understand that. If you did the same testing you're referring to on all four, and then, this is my ideal world, simultaneously you do the whole genome testing on Sarah, that sounds achievable. Or am I simplifying it?

DR MICHAEL BUCKLEY: It's possible. So the genome would be outsourced again to AGRF because we could not do that at ours. One of the problems then are the data paths that come off the torrent system are probably not –

PROF CAROLA VINUESA: [inaudible]

GAIL FURNESS SC: What's preferable about that over what Dr Buckley has suggested?

PROF CAROLA VINUESA: Because there are two forms of standard sequencing technology platforms, not just Ion Torrent and they sequence with machines that analyse genes and they have serious… in regards to paraffin tissue.

DR MICHAEL BUCKLEY: I think before we committed limited material to these issues, I'd like to have a much better idea of their experience: how many samples they've done, what their success rate is before I'd be prepared to send it.

GAIL FURNESS SC: But how do we get to that stage of your satisfaction?

DR MICHAEL BUCKLEY: We have to write to VCGS, ask for them to provide the information.

GAIL FURNESS SC: Yes look well we will, we need to resolve this very quickly from the Inquiry's point of view. So again from the Inquiry's point of view we want everything to be tested in such a way that as many people as possible can be satisfied as to it, but equally we need to do it. And so if you, Dr Buckley, could talk to that Victorian facility which you keep using the acronym for, I don't know the name of it – can you tell me the name of it?

DR ALISON COLLEY: Victorian Clinical Genetics Service.

GAIL FURNESS SC: Thank you. So you can contact them, Dr Buckley and –

DR MICHAEL BUCKLEY: Should I do that now?

GAIL FURNESS SC: No. Well just because I want to complete this discussion first, sorry you can contact them and then that can be determined in terms of the other three children?

We're all dependent upon the DNA, whether it's sufficient or not, it'll just be answered. If it's not sufficient, we can't do anything with it, that's the end of that story. If we can do something, we'll do whatever we can do with it. And in terms of Sarah, we've spoken about going down the Sarah path. Now is there anything else that we –

BLAISE LYONS: Can I just ask a question, you talk about the paraffin samples, are the Guthrie samples any different or are they useless?

DR MICHAEL BUCKLEY: They degrade in a way, they're not fixed so they don't get clinically cross-linked by the formalin agent which is used to preserve tissue samples coming out of surgery so yes, they do degrade, but it's a different form of degradation.

GAIL FURNESS SC: What, Blaise, I am expecting is that whatever is available to be tested, will be tested, and whether it's of a condition or not, there you go. We're not seeking to limit the testing to any particular bit.

BLAISE LYONS: No, but we've been talking about the extraction process for the blocks and slides and I am wondering whether there is a different process Guthrie sample.

DR MICHAEL BUCKLEY: Every technology has its issues. The issue we haven't really addressed is whether we need to pursue copy number variants.

GAIL FURNESS SC: Sorry, pursue what?

DR MICHAEL BUCKLEY: Micro-array testing for copy number variants. Another very large percentage of mutation genes which frequently have mutations.

PROF MATTHEW COOK: But if we run a whole genome then –

DR MICHAEL BUCKLEY: They're not going to detect –

DR ALISON COLLEY: That's something that I would seek that we do with Sarah's sample. We would be looking large chunks of DNA that are deleted or missing, not a spelling mistake but the actual physical amount of DNA, whether there's anything missing but that's something we can do on Sarah's sample, then I don't think necessarily we'd need to do it on all, in the first instance, on all children.

GAIL FURNESS SC: I'm just concerned about the "first instance" bit. We really have to do this in the most efficient time possible and I understand that there are –

DR ALISON COLLEY: But doing that last one we were talking about is a quick test, we can have that done in a week.

GAIL FURNESS SC: Can I suggest that we need to move forward in terms of a plan and why don't we have a break and Dr Buckley can you ring whoever you want to ring? And then we'll come back in ten minutes.

DR ALISON COLLEY: Can I just ask – obviously you've heard from us that having a sample from the father would be very beneficial for the robustness of the interpretation of the data, is that, is someone able to approach –

GAIL FURNESS SC: Dr Colley don't you worry about that. You'll be told whether it's available or not. I understand the reasoning that it'd be preferable, I completely understand that, so it's a question – so you don't need to worry about that.

PROF MATTHEW COOK: If I may, though, it's more than preferable, it will influence our approach.

GAIL FURNESS SC: No I understand that, I can't answer the question as to whether we will or not, which is the fundamental question. The value of it is unmistakable, that's not the answer, it's not in any of our control. Um, so does anyone want to just walk around, or happy to sit here? Or do you want to think about a how we're going to have move forward, because we're going to need a plan of action.

[BREAK]

GAIL FURNESS SC: Are we missing anybody? So, shall we resume? There was no one sitting next to you, was there?

PROF MATTHEW COOK: No

JEREMY MORRIS SC: Professor Duflou has just gone to use the facilities so he will be back shortly.

GAIL FURNESS SC: I don't know that he's absolutely critical to this meeting.

DR MICHAEL BUCKLEY: Can I just close that window?

GAIL FURNESS SC: Yes it's very hot and noisy out there.

DR MICHAEL BUCKLEY: So I spoke with the director of the Victorian Clinical Genetics Service, her name is Kathryn she said, she confirmed that their facility does do whole exome sequencing on blood swabs and that she would be prepared to cooperate. What I really need, as we discussed, is an indication from the company, what is their success rate, what were the quality parameters, because we have limited tissue and if you use a blood spot and its unnecessary then you lose options for the future and we don't want to do it unless we are convinced that there is a reasonably likelihood that we will get something out the other end.

GAIL FURNESS SC: So, in terms of that information about that facility, how do we go about it?

DR MICHAEL BUCKLEY: So I, what I said was I'd write to Kathryn and copy in yourself or whoever else wishes to be in it and will ask the specific questions –

GAIL FURNESS SC: Thank you for doing that. Alright so if we do that, let's assume for the moment you're satisfied, then we will, could you organise that through her or do you need us to do it?

DR MICHAEL BUCKLEY: It would be better I think, the initial exchange is simply to confirm it's appropriate and after we've got that, I think a formal letter from the Inquiry –

GAIL FURNESS SC: Right well if you could perhaps contact us when you have had that, sent off that letter—

DR MICHAEL BUCKLEY: Yes I will send through a draft of the letter—

GAIL FURNESS SC: Well no I don't want everyone to be settling a letter, if you draft the letter and send it to us then we will take it from there. So, once she agrees to do it we need to get the material to her, and you [Blaise] have that material, and you require from us an order of some sort to direct you to give it to her? Is there any form for that? Alright well Sian will talk to you about that afterwards to organise what it is we need so we will provide that, then when she's done what she's done, what will she provide?

DR MICHAEL BUCKLEY: So it will be data files, they won't do any in-house interpretation, the interpretation will be as we discussed.

GAIL FURNESS SC: So that's for the three children? Is that for all four?

DR MICHAEL BUCKLEY: That will be for all four children and in addition we propose that we do whole genome sequencing on Sarah.

GAIL FURNESS SC: On Sarah?

DR MICHAEL BUCKLEY: On Sarah. And if possible a familial trio –

GAIL FURNESS SC: Am I right to assume that the mother will be engaged in this?

JEREMY MORRIS SC: [inaudible]

GAIL FURNESS SC: Yes, so that means that the, at what stage do you need the mother's DNA?

DR MICHAEL BUCKLEY: At the point that we are having, providing DNA to AGRF, so before January 5th.

GAIL FURNESS SC: Alright so how are we going to do that?

JEREMY MORRIS SC: We can make arrangements for that.

GAIL FURNESS SC: Alright. So you can do that. I mean, if we give it to you, you can then give it to them? Or do you want us to give it to them directly?

DR MICHAEL BUCKLEY: The fewer that handle the samples the better, it can go direct to AGRF –

GAIL FURNESS SC: You can send it directly and you can do that now?

CV/DR MICHAEL BUCKLEY: Yes.

GAIL FURNESS SC: Ok. Alright so then the interpretive team gets together in respect of the four children, what the Victorian facility is doing, and then ultimately in relation to Sarah and what you're doing, what the facility in NSW are doing. Is that right?

DR MICHAEL BUCKLEY: Yes. [inaudible]

GAIL FURNESS SC: Yes, you can't do the whole genome testing on the other three?

DR MICHAEL BUCKLEY: I don't think it's feasible.

JEREMY MORRIS SC: [inaudible]

GAIL FURNESS SC: Well we'll see what the results are when it comes back.

PROF MATTHEW COOK: Whole genome on the DNA of the blood spots. Unlikely.

DR MICHAEL BUCKLEY: Is it possible Carola?

PROF CAROLA VINUESA: VCGS mainly do whole exome from Guthrie cards but once you've obtained DNA you could potentially do both whole exome and whole genome.

DR MICHAEL BUCKLEY: [inaudible]

GAIL FURNESS SC: If it can be done it'll be done. If it can't, it won't. Everything seems to suggest it can't be done but we'll just find out. Ok now.

DR MICHAEL BUCKLEY: On the same sample, well no on Sarah's sample we could ask VCGS to do a micro-array test to do the copy number variants.

GAIL FURNESS SC: Right and that's what you mentioned earlier on? Ok that's good.

DR MICHAEL BUCKLEY: I think it's another important addition which is not being accurately addressed.

GAIL FURNESS SC: No, no, that sounds very sensible. Ah, now we need to write up what we're doing and the process of it and I suggest that Sian here will write up what she understands, and we've recorded this so that you can tell us whether it's right and so we know where we are going forward and, because we will, that is the Inquiry will have relationships with various places too.

DR MICHAEL BUCKLEY: I have alluded to my surgery tomorrow.

GAIL FURNESS SC: Tomorrow? Ah. Good luck.

DR MICHAEL BUCKLEY: To get my shoulder put back in, um so I won't be able to write or type or anything so –

GAIL FURNESS SC: No, that's alright.

DR MICHAEL BUCKLEY: So do you want me to –

GAIL FURNESS SC: Sian will talk to you about all that. We will do what we can to help you. Now, what else do we have to do going forward other than "do what the plan says"?

PROF MATTHEW COOK: Could I just clarify, if, you know I hope it all runs smoothly from beginning to end, but it's possible that there may be some decisions that have to be made halfway through, depending on which samples are obtained and everything. What's going to be that process for making decisions halfway through?

GAIL FURNESS SC: Well, we're not going to all get together every time there needs to be a decision because that's not workable. So I will take advice from Dr Buckley, unless Dr Buckley says that he needs other people to participate in that decision.

DR MICHAEL BUCKLEY: We probably do need to set a limit on how much of the Guthrie cards we should actually use for this purpose because we don't want a situation where we get to the end of this process and we've used everything and then suddenly there's a revolution in gene sequencing in the next couple of years and we don't have enough so my strong recommendation is that we keep some in reserve.

GAIL FURNESS SC: I accept that, it makes sense. If we can, it's a limited amount we have, we need to use as little as we can, but we also need to use enough to result in a result. But no one would disagree that you'd use as little as you needed to. And we just have to rely upon your and the others' judgment as to how much they need.

JEREMY MORRIS SC: Any critical decisions that you are talking about –

GAIL FURNESS SC: If I think it's critical and if I think it's not going to delay things, I will be happy to talk to you about it, but I'm not going to –

JEREMY MORRIS SC: No I'm not suggesting a panel but –

GAIL FURNESS SC: Yeah, no, certainly if Dr Buckley tells me it's a critical decision and it makes a, has some serious consequences, we'll have a talk about it. But not run of the mill stuff, not anything less than that. Because otherwise we'll get bogged down. Now, anything, yes?

DR MICHAEL BUCKLEY: The Victorian Clinical Genetics Service, it's not known for being inexpensive.

GAIL FURNESS SC: No, I understand that. There's no point talking money here, we'll talk money elsewhere. There's limits on money and there's limits on the samples and we have to work within what we reasonably have. And I know nothing about the budget so I can't say anything.

JEREMY MORRIS SC: We want the raw data –

GAIL FURNESS SC: Yeah, so let's just talk, rather than at the same time, individually. Dr Colley?

DR ALISON COLLEY: My apologies.

GAIL FURNESS SC: You had a question, Jeremy?

JEREMY MORRIS SC: Doctor, when the VCGS get to the point of having the raw data available, would you be able to at least let us know so that we can, through counsel

assisting, so that we can then make an application for a copy of that raw data and we can have that data looked at ourselves. It just helps us facilitate people going on holidays or work commitments or whatever it happens to be, we have a sense of the timeline.

GAIL FURNESS SC: Yes, but you communicate with us.

DR MICHAEL BUCKLEY: So I communicate with Gail?

GAIL FURNESS SC: Yeah, or Amber or Sian. Probably Amber.

DR MICHAEL BUCKLEY: I will make sure there are multiple copies of the data available and tissue to check.

GAIL FURNESS SC: We will surround all of this with confidentiality in whatever form is available to us, legislative or otherwise, and we will expect it to be kept, including by yourself, that material that's being sent, it's for sensitive purposes only. We've got to be very clear in the letter that's being sent. Alright so I think the next thing is that we get together with you, Dr Buckley, and perhaps you, Dr Colley, in your absence, we'll put together what we understand is the plan going forward and then we need to put in place the various engagements that we, the Inquiry, will need to have and some timelines. Does that make sense? Does anyone want to say anything else? No? No?

We'll deal with Professor Skinner and Professor Wilcken, I mean I know Blaise you might talk to her as well, but we'll talk to them and explain where we're at. I mean from Professor Wilcken's point of view she's provided a report and I think that, from what she has said in the report, the way we're heading is something that is consistent with it and Professor Skinner, I'm not sure about, but we'll need to talk to him.

BLAISE LYONS: Professor Wilcken has said she wouldn't be needed today anyway.

GAIL FURNESS SC: Oh good, oh thank you. Well, we'll talk to Professor Skinner who is in New Zealand and I'm not sure what's available, sorry to say this, Amber, because Amber's from New Zealand, uh what they do differently. But I'd be surprised if it changed our course. But nevertheless I'll talk to him.

Alright, well thank you very much for coming, we appreciate it.

PROF CAROLA VINUESA: One more thing, would it be possible to get a cardiac genetic expert, not just in Australia but overseas, to assist and run the analysis? Because unless we know—

GAIL FURNESS SC: We do have one.

PROF CAROLA VINUESA: Because most of the academics, who are most published, they are overseas and the things that are not that published –

DR MICHAEL BUCKLEY: If they're not published then they're not evidence so –

PROF CAROLA VINUESA: Unless they are not yet published so we have to err on the side of caution.

DR MICHAEL BUCKLEY: No, we have to err on the side of accuracy.

PROF CAROLA VINUESA: Okay.

GAIL FURNESS SC: In the event that you wish to have any material of that type put before us, then by all means do so. And then it'll ultimately be a matter for Dr Buckley's judgment and Dr Kirk's judgment, as to whether or not the people, based on the articles that you provided, have the skills that perhaps they don't have. So it'd be a question of judgment as to whether or not the skills and the qualifications and the publications of those people are sufficient to warrant us going there. So you need to make a submission to us about that and it will be considered. That's the best way to do it, with copies of any articles that are published.

Alright, is there anything else? Alright, thank you very much for coming and we'll be in touch.