Inquiry into Convictions of Kathleen Folbigg

Submissions on behalf of Kathleen Folbigg

PART B

Genetics

1. In these submissions, any reference to trial transcript will be reference to Exhibit F. All other references to transcript will relate to the evidence given at the Inquiry.

Trial

2. At the trial, the Crown was cognisant of genetic defects being a possible cause of death.[1]

3. Looking at the trial transcript, as discussed earlier, the issue of genetics played its role. It was a recognised issue to be determined at the trial because it gave rise to a potential innocent explanation for one or more deaths within the Folbigg children that needed to be excluded by the Crown.

4. The Crown opened to the jury on the following basis:[2]

> *The cause of SIDS and the mechanism of death of SIDS is unknown. All that the doctors know is that there is some illness or illnesses which causes otherwise healthy babies to suddenly die from lack of oxygen during sleep.*
>
> *It is, thankfully, a rare condition, but SIDS is basically what is known as a diagnosis of exclusion. That is, where you have a baby that suddenly and unexpectedly dies that otherwise has been well and where the pathologist can find no cause of death, and where that baby is within the appropriate age range, in the absence of any other suspicions, such as child abuse or smothering or some other cause of death like a genetic defect, in the absence of any other cause of death, a pathologist will often certify SIDS as the cause of death. So SIDS equals undetermined cause of death. That is what it means.*
>
> *The incidence of SIDS is thankfully rare. The incidence of two SIDS deaths in the one family is extremely rare.*

[1] See Exh F T 30.26, T 31.15, T 31.42.
[2] Exh F T 30.10-.30.

Although the cause or causes of SIDS have still not been discovered, there has been extensive medical research over decades to try and find out what is the cause of SIDS. To date it has been unsuccessful, but it has shown a number of things. Firstly, it is not a congenital disease that finds clusters in families.

Now, there has been a lot of testing for genetic diseases to see if they can be linked with SIDS over the years. Thus far it has not been shown to be a genetic disease.[3]

5. The Crown Prosecutor went on at Exh F T 31.42:

Because SIDS is not a genetic or inherited condition, the risk of SIDS in a family that has already had one SIDS death is pretty close to the incidence in a family that has not had any deaths. In other words, a family that has had one SIDS death, a subsequent child is not much more likely to develop or to die from SIDS as a child in any other family that has not had a SIDS death.

That is, of course, subject to this: where you have a first SIDS death in a family that has those factors that I have mentioned that raise the incidence of SIDS, those same factors are going to be present for subsequent children. So a family that has raised factors for one child may have raised factors and a raised incidence for subsequent children.

6. Importantly, at Exh F T 66 was the following statements:

Firstly, in December of 1999, further extensive genetic testing was done on blood samples of all four babies and the results were entirely normal. These doctors or these specialists who are going to give expert evidence of course had the opportunity of looking at the post-mortem reports of the pathologist who had done the autopsies on the four children. These experts will give evidence about a number of things. Firstly, they will tell you how rare SIDS is. How even rarer multiple SIDS in the same family is. How extremely rare it is to have multiple deaths in the one family from natural causes of any kind in the absence of some identifiable genetic abnormality and these specialists will enable you to conclude that these deaths were consistent with induced asphyxiation, that is, suffocation caused by something being placed to obstruct the inlet of oxygen to these babies' lungs.

7. Defence counsel referred to the issue of genetics at Exh F T 87.30-.41.

8. With respect to the evidence of Dr Singh-Khaira, with respect to Patrick Folbigg he gave this evidence at Exh F T 559:

Q. And as a result of the findings of Dr Kan, did you come to any view about the possible cause of death of Patrick Folbigg?

A. We had excluded--

[3] Exh F T 31:.06-.16.

Q . Could you just answer that yes or no, or does it require an explanation?

A. I think I better explain. We had excluded infective disorders, we had excluded all metabolic disorders that we could think of, any genetic disorders we had excluded, and in view of those -none of them being a positive indicator as to the cause of death, I mean, the changes in the brain appeared to have been caused by some event which was kind of an hypoxic event in the past.

Q. Now, you say "in the past"?

A. Yep.

9. Dr Cooper gave evidence at Exh F T 608.06-.10:

Q. *Ultimately what can you now say about the question of familial or genetic links?*

A. Oh, we can say that the likelihood of a second SIDS in a family whose had had one is probably no higher than in the general population.

10. What this evidence demonstrates is that, at the trial, under the descriptor "genetic links" there was confusion between a familial disorder covering the four children, and an individual disorder which may have triggered the death in one of the individuals.

11. This dichotomy is further mentioned at Exh F T 612.40-.47 and Exh F T 614. Perhaps the most important statement is at Exh F T 614.40-.47 which reads as follows:

Q. The success of the back to sleep campaign in reducing the incidence of SIDS and the successes of antismoking campaigns to reduce the incidence of SIDS, <u>what does that say to you about whether or not there is any genetic or familial link in relation to SIDS</u>?

A. It says that if you can reduce something by more than 50%, by doing a simple social intervention <u>it can't be anything to do with breeding</u>.

(Emphasis added)

12. As a matter of logic, this statement is not correct. It fails to distinguish between SIDS and sudden death. The issue of cause of death is multifactorial. There may be an interplay between genetics and infection. The answer in part lies with the evidence of Prof Blackwell who explained the link between the success of the back to sleep program and the identification of infection as being a cause

of death. Despite the Back to Sleep program, sudden infant deaths occur. Of those remaining deaths, there is a strong association between infection and rates of death. This has been dealt with elsewhere in these submissions. Further, at the Inquiry, Prof Vinuesa demonstrated a genetic link in one family with four consecutive infant deaths in the one family . the variants in this family related to immunology. Accordingly, there can be a link between genetics and SIDS.

13. At the trial, the question of "inheritable disorders" was dealt with in a manner generally lacking in detail by Dr Seton at Exh F T 697-698. In that regard, there was the confusion between "sudden death" and "SIDS", and the fact SIDS is an exclusionary diagnosis so that if a positive diagnosis is found to explain the death, it is no longer "unexplained" and therefore is removed from consideration with respect to further research papers. In this regard, Seton says:

> … *We excluded the risk factor that I was worried about, which was obstructive sleep apnoea, which appeared to run in the family on Mr Folbigg's side of the family. <u>We excluded that. We excluded other inheritable and non inheritable disorders.</u>* …[4]

(Emphasis added.)

14. It should be noted the ambulance officer who spoke to Kathleen Folbigg recounted a conversation in which it was demonstrated clearly that doctors had informed Kathleen Folbigg there may be a genetic abnormality in her male children. In this regard, this important evidence is to be found at T 569.14-.17):

> *Q. Did she say this to you: "They think that I have some sort of genetic abnormality in my male children, so I'm surprised that I lost a girl"?*
>
> *A. Yes, or words to that effect.*

15. In cross-examination, Folbigg's counsel managed to elucidate the complexity with Dr Wilcken at Exh F T 821.36-T 822.11:

> *COOK: Q. The results of the tests that you perform, do they indicate that they tend to exclude certain disorders?*

[4] Exh F T 695.

A. Mm. Yes, I did say that. That was the earlier deposition, yes.

Q. And that the position - when you say the earlier deposition, you mean when you first made a statement about the results of testing?

A. Yes.

Q. Then was it the position that they tended to exclude?

A. Yes.

Q. And that they weren't definite in excluding certain disorders?

A. They were not definite in excluding large numbers of - all disorders, let me put it that way.

Q. Is the effect of what you are saying that advances since you made that statement have heightened your certainty about the results?

A. It has heightened my certainty about the results, yes.

Q. There are certain genetic disorders which, as yet, have not been tested for to your knowledge, is that right, in relation to the tissues of these children?

A. There are a very, very large number of genetic disorders in all, and we have tested for those which are small molecule disorders, certain class of disorders, and I think we have probably accounted for all of certain classes of disorders, all known.

(Emphasis added.)

16. Dr Cooper gave evidence at Exh F T 606 and following on the voir dire. More importantly, he gave evidence in front of the jury to the following effect at Exh F T 612.06 and following):

ZAHRA: Q . Doctor there is, however, continuing research around the world concerning the possibility of familial or inherited links?

A. Oh, yes.

Q. And that research is carried out by some of the most eminent institutions in the world?

A. Yes. We have one of them in Australia at the sleep meeting last year, a Dr Redline.

Q . There are significant overseas studies from significant institutions?

A. Oh, yes. There's a lot of work, but in terms of finding familial links to other, what I would call other sleep disorders, but certainly obstructive sleep apnoea running

through families we can find very strong links, but very, very poor linkage between, you know, SIDS and family matters.

Q. The current state of research, however, one can't exclude the possibility of a familial or inherited risk?

A. One cannot definitely exclude it but, you know, the largely familial includes interrogation that were reported originally really have gone away. They just don't really exist in today's literature, you know Steinschneider's index case eventually became remorseful and admitted that she had actually done away with her children, and that particular family was the basis for an enormous amount of that work.

Q. But this research has certainly not been put to one side, it is currently being undertaken by significant institutions around the world?

A. Yes, but I would say we would be heading in quite different directions now to looking for a simple hopefully unigenetic, you know, a single simple pattern of inheritance which was strongly suspected, say, 20, perhaps 15 years ago, and the likelihood that people will find that is remote. The likelihood conversely that they will ultimately find some sort of gene marker which probably puts people at risk is possible.

Q. And there is significant research being done in those areas?

A. A great deal.

17. Further evidence was found at Exh F T 614.40-.47:

Q. The success of the back to sleep campaign in reducing the incidence of SIDS and the successes of antismoking campaigns to reduce the incidence of SIDS, what does that say to you about whether or not there is any genetic or familial link in relation to SIDS?

A. It says that if you can reduce something by more than 50%, by doing a simple social intervention it can't be anything to do with breeding.

18. At the trial, Bridget Wilcken was called who was a certified clinical geneticist.[5] At that stage, her major role was to try to detect genetic and metabolic diseases.[6] At Exh F T 819 she was asked about whether she was able to rule out any genetic or metabolic disorder within Patrick. Again, this knowledge was based on the knowledge as at 2003. This is further explored at Exh F T 820 and Exh F

[5] Exh F T 817.
[6] Exh F T 818.

T 821. She gave the opinion the most common genetic causes had been excluded.

19. The next question was critically important as it identified the fundamental flaw in the methodology of the Crown at trial. The question was this (Exh F T 819.08-.12):

Q. As a result of the tests that you conducted on that urine sample, were you able to detect any genetic or metabolic disorder in this child?

A. We were not, and one or two genetic or metabolic -or many, could be ruled out utterly.

20. Dr Wilcken then gave evidence that they ran tests on the Guthrie cards. Again, she gave evidence which demonstrated the fallacy in the methodology of the Crown:[7]

Q. In relation to this case, again very broadly speaking, could you just tell us the testing that you did on the four samples of blood from the four Folbigg children?

A. All four children had had routine tests which were done on fresh samples at the time which were only for a certain limited number of disorders, and subsequent to their being born we had started this new process of tandem mass spectrometry. This enables us to look at some 26 or more different anolytes, different substances in the blood simultaneously which cover a range of genetic metabolic disorders. It covers pretty well all important disorders related to amino acid metabolism and fatty protein metabolism and fat metabolism, pretty well all covered.

Q. And these are all genetic disorders?

A . Metabolic disorders which might affect families.

Q . In relation to these four babies' blood samples, what were the results?

A. <u>The results were entirely normal.</u>

Q . Did you also conduct a DNA test on these four samples?

A. We conducted a limited DNA test for one disorder.

Q. Is that also a genetic metabolic disorder?

A. Yes.

[7] Exh F T 819.51-821.26.

Q . And again, was there any abnormality found?

A. No . May I enlarge? This was a disorder which had been suspected by one of the doctors who had interviewed at least the parents, I'm not sure if she saw the child. And the DNA test we did virtually, 99%, and I mean that as a very definite percentage, virtually excludes that disorder, but not absolutely.

Q. Has there been any very recent confirmation of the reliability and accuracy of tandem mass spectrometry as a means of analysing these samples?

A. Yes. When I gave my initial deposition, we in New South Wales have been rather at the forefront in introducing this but we had only been doing that testing for under two years at that time, and around the world it wasn't commonly done. It has spread widely in the United States and also in Germany and also in some parts of the rest of Australia show that we have a huge amount more experience and in New South Wales we have tested now almost half a million children, and we are much more sure of the reliability. Some aspects are not reliable, some are extremely reliable, so that we know with a much greater certainty now the reliability.

Q. Doctor, I don't propose to get you to list all of the diseases that you tested for, let alone to explain what sort of diseases they are. But can you give us an idea of how many genetic metabolic diseases you tested these children for?

A. Using tandem mass spectrometry we tested them for at least 30 disorders. The routine newborn screening that they, in any case had, would have added another three or four, and then the urine tests which we performed on Patrick, Sarah when quite well at about three weeks, and Laura when evidently well at about two weeks, would have added another handful. We might say that probably there are 50 disorders that we have tested for.

Q. So something like a total of 50 disorders?

A. Something like a total of 50.

Q. Are they in effect all of the genetic disorders that you are capable of testing for?

A. No. There are many more very specific tests, but they are probably all of the disorders, the genetic metabolic disorders which might be associated with unexpected death. I believe that to be true.

Q. Doctor, is one of the disorders that you did test for, a disorder which is known as MCAD?

A. Yes.

Q. Or MCAD?

A. Commonly MCAD, medium chain acyl CoA dehydrogenase deficiency.

Q. That is one of the diseases that these tests in combination were able to exclude?

A. We are confident that that has been excluded utterly.

(Emphasis added.)

21. The problem became compounded with the evidence of Prof Berry at Exh F T 1066 in which the question was put:

Q . <u>Putting aside the congenital or familial or genetic tests</u> that were conducted on these children, are you aware of any case in which there have been three or more children who have died unexpectedly and suddenly from some other illness other than SIDS. I think that question is a bit unclear. (Emphasis added)

A. I think I understand it. I'm personally not aware of any kindreds where there have been sudden deaths of previously fit children due to another medical condition that has affected three or more children. That's not to say they don't exist, but I'm personally unaware of any in the literature.

Q. Does that mean that you have not had any yourself, you are unaware of any of your colleagues having come across any and reported them to you, and you are not aware of any in the medical literature?

A . That's correct. My experience, knowledge of disease, is that fatal diseases are not 100 per cent instantly fatal in every case. So, some of the genetic conditions, for example, that were excluded, have very clear presentations. They don't, in fact, present with sudden death of a previously well child.[8]

22. The issue of a familial link and the confusion with a genetic link is again compounded at Exh F T 1075.30-.36.

23. At Exh F T 825 and T 826 there was a debate that took place about the Defence looking to further examine two specific genetic disorders, the IgG deficiency and the IL-10 gene variant. This was ultimately abandoned.

24. The next witness who gave evidence was Dr Berry whose evidence is dealt with elsewhere.

[8] Given the evidence of Prof de Vinuesa as to four consecutive infant deaths in the one family with an identified genetic cause, this statement has clearly been superseded by scientific advances. Further, and more relevantly relating to the submissions on infection and sudden infant death, this statement has been overtaken by the appreciation that a mild infective process has a strong association with SIDS and the descriptor that the children was "previously well" is apt to mislead. One does not need profound or continued ill health to have an infant death triggered by infection. This will be addressed later.

25. In the Crown address, there was reference to Dr Kan excluding effective causes of death including genetic disorders.[9] This statement by the Crown was incorrect in an unqualified sense.

26. Importantly, his address to the jury by the Crown Prosecutor at Exh F T 1324 with respect to Patrick demonstrates the fallacy and lack of understanding of genetics. He gave the following statement with respect to Patrick:[10]

> *The post-mortem examination was done by Dr Singh-Khaira. He gave evidence that he found no abnormality in the respiratory cardiovascular or any other of the body systems. He sought the opinion of Dr Kan who was a neuropathologist. We presume he is a pathologist that looks at brain and nerve tissue; that Dr Kan's opinion excluded effective causes of death, metabolic causes of death, genetic disorders, and that the changes in the brain from the past episode, the ALTE, appeared to have been caused by some event which is just a hypoxic event in the past. There was only signs of old damage to the brain, consistent with having been done four or five months earlier. Dr Kan and Dr Singh-Khaira were unable to find any cause of death.* (Emphasis added.)

27. In the summing up, the trial judge summed up with respect to Caleb (Exh F page 28) in which he says:

> *You will remember the evidence of Dr Wilcken that tests were carried out on blood of Caleb which had been preserved, and a large number of possible natural causes of death had been excluded, so that many, or all, of the likely candidates as a cause of death, by way of infection or metabolic or genetic causes, were excluded.*
>
> (Emphasis added.)

28. With respect to Patrick, the Crown addressed as follows:

> *The post-mortem examination was done by Dr Singh-Khaira. He gave evidence that he found no abnormality in the respiratory cardiovascular or any other of the body systems. He sought the opinion of Dr Kan who was a neuropathologist. We presume he is a pathologist that looks at brain and nerve tissue; that Dr Kan's opinion excluded effective causes of death, metabolic causes of death, genetic disorders, and that the changes in the brain from the past episode, the ALTE, appeared to have been caused by some event which is just a hypoxic event in the past. There was only signs of old damage to the brain, consistent with having been done four or five months earlier. Dr Kan and Dr Singh-Khaira were unable to find any cause of death.*

29. No reference was made to the genetics relating to Sarah or Laura.

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[9] Exh F T 1325.10-.16.
[10] T 1325.07-20.

30. The exclusion of a genetic cause was an important part of the evidence at trial. At trial, genetic tests were performed on urine samples and blood samples to exclude the 50 most common genetic causes of sudden death. The Crown advanced this evidence on the basis a genetic cause had been excluded. This was not so. This approach is misleading as it suggests that any doubt raised by a potential genetic link can be comfortably put to one side.

31. Since then, and in this case, there were over 300 potential monogenetic anomalies which could contribute to sudden infant death.

32. This statement again demonstrates the lack of understanding of the limits of genetic science at trial and the important impact of methodology or whether it was possible to positively exclude a genetic cause of death in an unqualified manner. A finding should be made to this effect.

33. The evidence presented to this Inquiry established the existence of a number of genetic disorders each of which had the potential to cause a sudden death in each of the children.

34. The genetic science at the trial was not as sophisticated as it is now.[11]

Evidence Before Inquiry

35. The most significant advance, has been the generation of whole genome and whole exome sequencing and the publication of literature that informs the clinician or researched of likely pathogenicity.

36. This has identified anomalies that potentially explain the sudden unexpected death of an infant. This information was not available at trial.

37. In this Inquiry, it is submitted the fallacious reasoning used at trial has been deployed when assessing the genetic information obtained by the whole genome and whole exome sequencing.

[11]

38. Dr Buckley proposed to examine those known metabolic neurological, cardiac and immune system disorders which had been identified in the literature. In this regard, Dr Buckley liaised with Prof Fahey who provided a list of 204 known disorders which could give rise to sudden death.[12]

39. Buckley was asked to opine "…*regarding the presence of any likely pathogenic genes, or pathogenic genetic variance in genes <u>that are known to be associated with sudden unexpected death in infancy</u>*". (Emphasis added.)

40. The problem with this technique is that it does not address all potential genetic disorders within a family. It does not accord with the recommendation of the forensic pathologists including Dr Cala, Prof Duflou or Prof Cordner (discussed below). One cannot determine the family characteristic without knowing the family lines. Accordingly, it cannot be said that a genetic cause has been excluded.

41. As set out in the report of Prof Duflou, the SIDS definition 1(a) and 2(a) requires an assessment of close genetic relatives.[13] He further goes on to assess the genetic causes of death and states:

> *This has involved multi-disciplinary teams, often based in cardiology and genetics units, investigating the blood relatives of the deceased over multiple generations, performing a range of clinical investigations on these relatives and where appropriate progressing to various forms of genetic testing.*[14]

42. Prof Cala in his report[15] advised that what is required is a detailed family history to be obtained together with testing for a selective number of diseases.

43. Further, appended to the Cordner report[16] is the statement that "*co-segregation studies in affected relatives may help clarify the pathogenicity of VUS*" ratings. Cordner gave further evidence at T 228.36-.44 setting out the ideal methodology.

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[12] See T 569.19-.28.
[13] Duflou Exh L page 39.
[14] Exh L page 36.
[15] Exh M page 17.
[16] Exh Q, appendix 2.

44. Further, Cordner[17] indicated a study of close genetic relatives (uncles, aunts and first cousins) is required for SIDS 1 A assessment. This ties in with Prof Cala's assessment in Exh N second last paragraph.

45. Prof Clancy opined the provision of a list of known genetic disorders simply relies on a matter of luck as to whether the disorder is identified or not.

46. Prof Skinner referred to it.[18]

47. The methodology employed by Dr Buckley adopted the same broad methodology which was deployed at trial which was to interrogate the known disease-causing processes and see whether they occurred within the family, rather than to interrogate the family to identify the common genetic abnormalities within the family that would explain the disease process within that family. It is accepted the second method involves a wider search of other family members and would take more time.

48. The focus on four individuals in one family, without taking into account family history, demonstrates the problem. These children may well have a genetic disorder which is incapable of being identified until such time as a proper genetic assessment has been performed.

49. Each of Dr Cala, Prof Cordner, Prof Cook, Prof de Vinuesa, Prof Duflou and to some extent Prof Kirk, give credence to the alternative methodology that was not deployed at the Inquiry.

50. While the process was "hypothesis free", by using the American College of Medical Geneticists (ACMG) guidelines, Prof de Vinuesa did not agree with this methodology. The search became constrained and focussed upon known and recognised conditions that could cause a sudden infant death.

51. The difference in methodology reflects the difference between clinical practice and research.

[17] Exh Q.
[18] T 526.10-.29.

52. As Prof Skinner noted:[19]

MORRIS SC: And to that extent, you'd agree with me, Professor Skinner, that the fact is that the relationship between genes and genetic understanding and sudden death still has some considerable way to go. Do you agree with that?

WITNESS SKINNER: Yes, I expect so. There - we've come a long way, but we still only explain 15, 20% of, of our sudden unexplained deaths genetically. We don't know how many more are genetically, but we think we've probably - through studies that I alluded to earlier - found the main players through Whole Exome studies, but there may well be more.

53. At T 514.20, Prof Kirk explained:[20]

Yes, look and I think this highlights the difference of approach. Professor Vinuesa is a very experienced and eminent researcher and is, I guess, approaching this in the way that you might approach a research project, thinking about possibilities, expanding the different, the different areas of knowledge that we currently have. Whereas our approach is more focused on known disease associations.

54. Thus, although the four deaths in the one family is unusual, genetic anomalies peculiar to that family (or otherwise of significance but not yet discovered) may yet explain the deaths of one or more of the children if the appropriate three generation genetic assessment be performed.

55. This difference of methodology is not just a matter of semantics but strikes at the very heart of the type of evidence that has been generated, the inferences that can be drawn from it, and the impact on burden of proof.

56. Ms Folbigg submits the only way in which to have greater confidence to exclude genetic disorders is to perform a proper and detailed historical genetic assessment. This would be required on both sides of the family which involves Kathleen Folbigg's natural parents and natural siblings and extended family. It would also require an assessment of Craig Folbigg and his extended family.

57. The understanding of genetic mutations that can cause or contribute to sudden death is not yet complete, and scientific papers that link mutations with various conditions are being continually published. Further, there is limited

[19] T 516.34-.43.
[20] T 514.38-.43.

understanding of the interaction between genetic mutations and environmental circumstances, medications, physiological processes such as dehydration, electrolyte imbalance, and infections and the possible relationship with sudden unexpected death. However, these are possibilities that may prove in time to be extremely important factors. As such, whether a genetic anomaly is currently graded and "*pathogenic*", "*highly pathogenic*", or "*uncertain significance*" is not to the point as to whether a specific genetic anomaly is causative in the strict medical sense. A combination of factors probably contributes to heart function, immune response and cerebral function.

58. The genetic factors may or may not cause a disease process by themselves. There is a complex inter-reaction between genes which is not well understood and those genes interact with environmental factors and other physiological conditions (such as bacteria and viruses) in an unpredictable manner.[21]

59. Further, what can be learned about the genetics in any particular individual, or a familial group really depends upon the methodology which is employed by those performing the genetic searches and analysing the material. In this regard, there is a significant variation between the methodology of Dr Buckley and that proposed by Prof de Vinuesa.[22] This difference is not readily apparent on the face of their reports but was examined closely during the week of genetic experts giving their evidence.

60. A further constraint on a ready inference being drawn that there was no genetic cause comes from the inability of the geneticists to have access to the genetic material from the Folbigg side of the family. There was the inability to interrogate the father's extended family. Prof de Vinuesa (with whom Prof Cordner agreed – see T 228.36-.44 and Prof Duflou) indicated one would need a three-generation analysis of the father's family, with an examination of the wider family including aunts and uncles, and cousins. It is clear from the ACMG scoring guidelines that a de novo mutation may well be pathogenic,

[21] See Blackwell Exh U, page 3 and page 5, Clancy Exh X and Blackwell Exh T paragraph 13.
[22] See also Prof Cordner at T 228.36-.43.

whereas an inherited mutation may be a variation of uncertain significance. Accordingly, if a genetic anomaly is not found in a parent, it may be a germ-like mutation in either the spermatozoa or ovum.

61. While there was an identified death in one Craig Folbigg's brother's children, and there was evidence the child was born premature, this does not exclude the possibility there was some genetic abnormality that triggered the sudden death. In other words, prematurity may not have been the answer as to the cause of death.

62. This methodological constraint impacted upon the exercise undertaken by the geneticists in this case.[23]

63. The first issue was the identification of the phenotype in circumstances where each of the Folbigg children may have died of the same cause, or different cause of death. There is an assumption the children were previously normal well children who died a sudden death. This gives rise to a lacuna – if they had a genetic variation were they in fact well or normal?

64. Further, it needs to be accepted that each human has about 3,000,000 variants out of three billion genes. Most of these variants are of no relevant significance to a disease process. Even when one looks at monogenetic variations, a monogenetic cause will only be found in between 2-20 per cent of SIDS disease processes.[24] A finding should be made to this effect.

65. This evidence from the geneticists is consistent with the evidence of the neurologists who indicated a genetic cause for a neurological disease process or condition can only be found in about 20 per cent of cases. A finding should be made to this effect. This leaves 80 per cent of cases in which there is a neurological condition or disease process in which no genetic cause exists, or otherwise if there is a genetic cause, no genetic cause can be identified. A finding should be made to this effect. In other words, in 80 and 98 per cent of

[23] See Cordner at T 228.36-.43, Clancy Exh W.
[24] T 519.05-.30.

cases, a genetic cause cannot be discovered which gives rise to at least four available inferences:

(a) There is no genetic cause for the relevant disease process; or

(b) There is a genetic cause for the disease process but the genetic is yet to be discovered;

(c) The genetic cause is not monogenetic but may be digenetic or multigenetic;

(d) The genetic cause requires an exogenous trigger for the onset of the medical condition.

66. On point (b) above:[25]

MORRIS SC: And to that extent, you'd agree with me, Professor Skinner, that the fact is that the relationship between genes and genetic understanding and sudden death still has some considerable way to go. Do you agree with that?

WITNESS SKINNER: Yes, I expect so. There -we've come a long way, but we still only explain 15, 20% of, of our sudden unexplained deaths genetically. We don't know how many more are genetically, but we think we've probably - through studies that I alluded to earlier - found the main players through Whole Exome studies, but there may well be more.

67. On point (c) above, there was a discussion between the experts about the fact that in research circles at least, there was growing evidence of digenetic causes contributing to disease:[26]

WITNESS VINUESA: Look, I would like to make a comment. I think we are only contemplating the most simple scenario of the single gene causing disease. There is increasing evidence of digenic causes of disease. We've dealt with many, you probably have as well. When we have digenic causes, two genes coming together, first, the frequency of each of those doesn't need to be so ultra-rare, so we can cope with frequencies like the one we've just talked about for this ADAMTS6. Furthermore, there is good evidence that even common variants can substantially modify the incidence of disease, and if I may quote one, "Crotti et al have provided evidence that the common polymorphism KCNH2 (30% carrier amongst whites - 30% carrier frequency) may modify the clinical expression of latent LQT2 mutation."

[25] T 516.34-42.
[26] T 520.36 - T 521.30.

So we can have either different genes, two that, rare variance, one common and one rare, many common. If you look at the pedigree we have in our screens we have quite a lot of variance that could be coming together to cause part of this disease, and then in those cases the frequency changes, we just can't say that because the frequency is not that rare we have to exclude a variant. On the other hand, coming back to your point, yes, and we still have to remember they show of non-penetrants. I mean, an unaffected parent does not exclude it because, as we say, most of these cardiac conditions it is typical to find non-penetrance carriers of pathogenic mutations and we have seen them where the trees have both come to MHY6, et cetera.

MORRIS SC: Does anybody have anything to say about Professor Vinuesa's statement about the combination of genes or is that a matter that's generally accepted?

WITNESS KIRK: Well, I would say that one of the problems with that is that we could conduct this exercise with any family with four children and come up with a very similar looking list of genes, and so the problem really comes down to interpretation and we have no way to interpret that kind of information that is meaningful.

MORRIS SC: Given the current state of knowledge--

WITNESS KIRK: Yes.

MORRIS SC: --of the interaction between genes?

WITNESS KIRK: Yes, well, yeah, that, that's true. We're a long way from being able to interpret that kind of information usefully.

MORRIS SC: And that is a matter which is the subject of research, isn't it?

WITNESS KIRK: Yes.

68. Further, careful consideration needs to be given to the fact the geneticists were only having regard to a monogenetic cause.

69. Further constraints were introduced in the application of the ACMG guidelines in the assumptions that were used. This related to the classification of pathogenicity. The ACMG guidelines are generated for use in a clinical setting which gives a grading of satisfaction regarding pathogenicity so it can guide the clinician in the treatment of patients.[27]

70. The second constraint was that the deaths may have been caused by cardiac arrest, respiratory arrest, neurological impairment or some immunological difficulty. This contrasts with the assumption of a previously well and normal

[27] T 515.23 - T 516.13.

child. The Sydney Pipeline were prepared to assume the children were otherwise healthy which was an important consideration in determining the pathogenicity of any particular genetic anomaly. This characterisation made a significant difference to a determination of "variation of uncertain significance ("VUS") as opposed to "likely pathogenic".

71. It is significant to note the ADAM T 6 gene was identified in all of the children by Prof de Vinuesa but not by the Sydney team or Prof Fahey. It was thought to be paternally inherited, yet this genetic anomaly was only the subject of a medical report and identification in April 2019. Prof Skinner acknowledged the importance of ADAM T 6 as indicating the progression of genetic studies by researchers at T 516.33. The report that suggests a link between this variation to the phenotype was published in 2019. Had the testing and report been performed in 2018, it would not have been identified. A finding should be made to this effect. This demonstrates the massive amount of information which is being discovered the constant publication of new information and reflects the practical limitation of today's knowledge.

72. Further, Prof de Vinuesa identified the ADAM T 6 gene in each of the children and postulated it may have been inherited from the father. This postulate is important. If it was inherited from the father, it may have been a variation of uncertain significance. If it was not inherited from the father, then it demonstrated a gonadal mosaicism may have taken place and in the face of the ACMG guidelines, there would be a high degree of suspicion this genetic anomaly was disease-causing and would likely be pathogenic. This would be more likely to explain the deaths of each child.

73. This leaves open the possibility of inter-reaction between two genes which is diagenetic. An example of the diagenetic cause of sudden death was clearly demonstrated by the evidence of Professor de Vinuesa in which she was asked to perform a study in relation to four boys in the one family who had each died of sudden death.[28] This was demonstrated to be X-linked genetic abnormality.

[28] T 517.01.

This is still the subject of a research paper. Her evidence was that her laboratory was able to identify the inter-reaction of these two genetic anomalies where laboratories in the United States of America were unable to do so.[29]

74. Prof de Vinuesa's remarks in relation to the American example demonstrates that combinations of two or more genes are having a profound effect on the understanding of disease process and pathogenicity of genes. She said at [30]

WITNESS VINUESA: No, but I -if, if I may say that, I mean, this is exactly what we do in our day to day activity, we take cases where we have a suspicion of -that a VUS may be pathogenic and we test it functionally. If I can just tell you a very brief example of one of our recent families that I think is relevant to this case. We recently were referred a family where there had been four recurrent deaths in four consecutive children between the ages of 4 weeks and two months. This family had initially been referred to the most prominent laboratory in the United States, they had failed to reach a diagnosis. When we received the DNA from the family, we reached a diagnosis within three months. We found two variants in the same gene that initially were thought to be a VUS. We established a collaboration with a, a specialist laboratory in the Netherlands that specialises in that gene. They were able to prove complete loss of function of this gene. Therefore, this variant was immediately reclassified as pathogenic, within three months. And the interesting thing about this case is that there were other children and other cases in the world that had been described with variance in this gene, but all of the deaths had occurred after ten years of age. This was the first case with four deaths where they all occurred in children below four months of age. We were a little bit intrigued, thinking that there could be a second variant that could enhance pathogenicity and, since we have found another variant in the same gene that is X linked, we are testing it and another specialist is testing it. In the last year there's been a report that this gene causes pathogenicity in the same pathway. We are submitting this manuscript for publication. So, here we have a case where we have three variants in four children, the same variants. The probability that this occurs is 1 in 64,000. But, you know, we were surprised, but in a planet of 7 billion people, these extreme cases do occur. So, again, this I think poses the question, are we trying to find something that is routine, ordinary, a common diagnosis, or are we also contemplating the probability that we might be dealing with something quite rare, unusual, with unusual type of genetics, that presents differently, earlier onset, than other variants in similar genes? And this is where, in our experience, we are seeing this all the time. We are reclassifying variants from VUS to pathogenic after validation in the laboratory and this is the beauty of genetics and why we are now going to probably increase, quite exponentially, the spectrum of variants that contribute to disease. Not just us, but the whole world is working at it.

[29] T 517.04.
[30] T 516.46 - T 517.34.

75. Prof Skinner made the same observation:[31]

> *MORRIS SC: It's fair to say Professor Skinner that there is a, if I can use a lay expression, that -well really tying in with something Professor Carola stated was that it's thought that the interplay between two separate genes may increase the potency of any genetic anomaly. That's a theory that's about but not well understood. Do you agree with that general postulate?*
>
> *WITNESS SKINNER: I do, and I think Professor Vinuesa has a good point and she quoted a particular example of a common genetic change which modifies the severity of disease, and we certainly know there are several examples where common variants can modify the severity of disease, and we will learn more about that with time for sure.*

76. The current examination by either the Canberra[32] or Sydney pipelines does not address the multi-genetic cause and it is highly likely that two or more genetic anomalies could give rise to sudden death. They limited their inquiry to monogenetic causes which only explains 2-20 per cent of sudden infant death. No criticism is made of this in the circumstances but there should be a finding that the current investigation reflects the current limits of scientific understanding.

77. A further constraint on any inference there was no genetic cause is that there was no information advanced of genetic anomalies and environmental factors which could trigger sudden infant death. It is quite clear from the evidence of Prof Blackwell and Dr Clancy that infection can trigger a cardiac arrhythmia. It is entirely possible that the inter-relationship between infection or pollution and an underlying genetic anomaly could give rise to sudden death.

78. Further, while Dr Raju had performed cardiac testing on Kathleen Folbigg, there was no drug provocation test that was capable of being performed in the time available. In 30 per cent of cardiac arrhythmia cases, no detectable arrhythmia can be found.

79. Further, Prof de Vinuesa identified a number of alternative tests that could, and should, be performed in order to come to a clearer opinion regarding any association between genetic abnormality or variation and pathogenicity. She

[31] T 526.31-.41.
[32] See T 508.33-.38.

recommended testing in vitro and functional studies. On behalf of Ms Folbigg, it was acknowledged this work cannot be performed within the current timetable for the provision of expert reports during this Inquiry.

80. In relation to determining pathogenicity, there is a great importance placed in literature relating to the incidence of genetic anomalies and disease processes.[33] Some laboratories do not publish results[34] and the geneticists have to work with the information they have. This introduces a qualification to the geneticists' opinions. A finding should be made to this effect.

81. Certain opinions may have been given by the experts but these opinions need to be seen in context in the current state of science. There will no doubt be further developments in the genetic understanding of disease, and as Dr Skinner said, they expect an "avalanche" in knowledge in coming years.

82. This being the case, the genetic evidence before this Inquiry is of limited utility in excluding a reasonable doubt when this Inquiry comes to exercise its discretion.

83. Further, that information addresses disease processes in specific families with specific genetic profiles[35] which introduces a qualifier that one is comparing the genetic profile of one family with that of another.[36] A finding should e made to this effect.

84. The ACMG guidelines recognise the need to follow up as more information is revealed by the case reports.[37] This is important for the reclassification of pathogenicity. A finding should be made to this effect.

85. With respect to Rett Syndrome, only about 90 per cent of sufferers exhibit the MECP2 gene.[38] In the last five years or so there have been studies that established Rett Syndrome can also be caused by the FOXG1 gene and the

[33] T 566.10.
[34] T 566.20
[35] T 566.47.
[36] T 567.01-.27.
[37] T 567.29-.43.
[38] T 555.34-.43. Cf T 575.01-.09.

CDKL5 gene and an association between CDKL5 and the STK9 gene.[39] The evidence of Dr Colley at T 575 needs to be assessed in that context. The certainty of the expression of opinion by her is not available.

86. With respect to Hunter Syndrome, the opinion of Prof Kirk was that it was unlikely but further tests would clarify that situation. Patrick had Hunter Syndrome genetic variants which were capable to triggering both the ALTE and the death. In this regard, Kathleen Folbigg relies on the reports of Prof Ryan and Prof Emery, and Prof de Vinuesa.

87. Additionally, it has become apparent from the report of Michael Fahey dated 30 March 2019, the deficiency has become more obvious. In his opening paragraph on page 4, he states:

> *I have discussed the whole genome sequencing results with Prof Buckley and viewed the working data document that he prepared with Prof Kirk. They undertook a thorough genomic evaluation and subsequently enriched this to examine for genetic changes associated with sudden infant death from various causes. I have further supplied a list of 204 genes explicitly related to epilepsy, metabolic conditions and dystonia. These also include specifically those genes associated with abnormal creatinine metabolism, alternating hemiplegia of childhood, neurotransmitter disorders and genetic channelopathies causing infantile encephalopathies and cardia arrhythmias. No genetic variance were identified which could be considered pathogenic as is understood in 2019 using standardised interpretative methods in Patrick, his mother nor his siblings. … <u>They virtually eliminate a recognised genomic cause for Patrick's presentation</u> …*
>
> (Emphasis added)

88. This conclusion is technically correct summation that, of the genes for which they searched, one could not be found (subject to Hunter Syndrome)[40] and without such testing would be a highly unlikely to be found as a cause of death.[41] But it does not exclude a genetic cause. It is wrong as a matter of science and logic. It was clear from the evidence of Prof de Vinuesa and from the AMCG guidelines that further information is being published on genetics and disease-causing processes regularly, and reclassification is continuing and requires reconsideration of pathogenicity and would require review and follow

[39] See T 556.03-.21 and T 556.39.
[40] See Kirk T 547.10-.27, T 551.38.
[41] Kirk T 565.17.

up.[42] Further, it was evident form the evidence of Prof Ryan (with reference to Patrick) that only in about a third of cases of neurological abnormality that a genetic cause can be found.

89. This is further compounded at page 5 of the report when commenting upon Prof Ryan's comment that there may be a genetic cause and that testing was recommended. In this regard, he reports:

As stated above and from the work of Prof Buckley and Kirk, this testing has now been done directly on Patrick's DNA sample and those of his siblings. No pathogenic changes were identified.

90. This is wrong. Genetic anomalies were identified (Hunter Syndrome) but not classified as pathogenic by the Sydney Team. Pathogenicity can be influenced by environment and other disease processes including infection. In other words, the clinical history and family information may trigger reclassification. Further information from the scientific literature may require reclassification.[43] This again demonstrates the deficiency in methodology and logic. There remains an association between Hunter Syndrome and cardiac arrhythmias.[44] This demonstrates the possible interaction between two diseases.[45]

91. The statement is made again at page 7 of his report:

Genomic testing has excluded these conditions where there is a recognised genetic cause.

92. Again, this statement is accurate as far as it goes, but to suggest that in these cases a genetic cause has been excluded is wrong as a matter of science and logic.

93. He leaves open the question at page 12 of his report:

I am confident also that testing at the time of presentation, combined with the post-mortem examination and the genomic sequencing makes neurometabolic conditions very unlikely. Genomic testing has also excluded any <u>recognised</u> conditions

[42] ACMG guidelines Exh AC pages 187-188.
[43] Exh AC pages 187-188.
[44] T 575.36-T 576.34.
[45] T 576.40.

associated with genetic epilepsies, encephalopathy, cardiac arrhythmias or sudden death.

94. Again, this statement fails to address the issues of classification of pathogenicity and the influence of other matters upon that classification process. It provides no evidential basis for a submission that genetic causes have been absolutely excluded for a disease process that has caused sudden death in one or more of these children.

95. Further, with respect to the issue of an unrecognised seizures (page 13), Prof Fahey makes the observation that Di Maio in the 2008 paper made the point that:

All of those with both ALTE and epilepsy have a family history.

96. The fact is there has been no study of the Folbigg family to determine whether there was a family history of either ALTE or epilepsy, or infantile or premature death.

97. This is further compounded at page 15 in which he says:

Specific searches for the movement disorder gene on the whole genomic examination did not identify any pathological changes in these genes.

98. Again, he fails to address the classification process of pathogenicity.

99. He finalises his report at page 16:

Although speculation of alternative genetic causes is appropriate, I am now confident that "alternative diagnoses" for 18 October 1990 event (sic) are thoroughly investigated. I have discussed with Prof Buckley the hypothesis-free approach for testing and requested specific re-interrogation for genes associated with but not limited to "disorders of creatinine metabolism, alternating hemiplegia of childhood, neurotransmitter disorders, and genetic channelopathies causing infantile encephalopathies and cardiac arrhythmias". All <u>recognised</u> pathogenic changes for all of these conditions are now excluded. "Further testing for these conditions" was accomplished by "whole genome sequencing". (Emphasis added.)

100. It is submitted on behalf of Kathleen Folbigg that this demonstrates the error in over-interpreting the effect of the evidence of Prof Fahey, Dr Buckley, Prof Kirk and Dr Colley. If the unqualified submission is to be made (as it was at trial)

that genome and exome testing has excluded a genetic cause for the deaths of one or more of the Folbigg children, then that submissions is incorrect.

Submissions of Counsel Assisting

101. There is no contest that the expert geneticists procured good quality data.[46] The submissions in part 2 [63] should be qualified so as to refer to:

(a) Known literature and database searches;[47]

(b) Known gene panel analysis on genes;[48]

(c) Any known variant annotated as pathogenic.[49]

102. The clearest iteration that the opinions are expressed on the current state of knowledge is at T 531.16-.18. However, the evidence in all of the reports and oral evidence is replete with this critically important qualification. This qualification is ignored in the submissions of Counsel Assisting and it is critical to a proper understanding of the evidence. A finding should be made to this effect.

103. However it is abundantly clear the state of current understanding is very limited and is developing rapidly.[50]

MORRIS SC: If we go to the second column there, the observations made are that "There are some cases which have got no identifiable mutation in known disease-causing genes and, therefore, highlight the necessity to discover new susceptibility genes for inherited arrhythmogenic disorders."

WITNESS SKINNER: Absolutely.

MORRIS SC: That remains the case now; do you agree?

WITNESS SKINNER: Absolutely, yes, I do.

MORRIS SC: Do you agree that there are advances in next generation sequencing platforms and targeted DNA capture strategies which hopefully will allow vastly

[46] Counsel Assisting submissions Part 2 [62].
[47] Paragraph 63(b).
[48] Paragraph 63(c).
[49] Paragraph 63(d).
[50] T 525.26 - T 526.04.

greater capacity to sequence many thousands of genes at one, offering the ability to identify new genetic loci and mechanisms for cardiac electric abnormalities; do you agree with that?

WITNESS SKINNER: Yes, I do, to a degree. I think Whole Exome Sequencing is, is allowing us to study a, a large number of genes but it's going to be a long time before the human phenotype information catches up with that. We're at the stage now where we're finding more and more and more genes as we've seen in this Court, where actual, the clinical implications are just not known and the job of people like me and, and Professor Vinuesa and other clinicians in the room is to try to tie that information together. So this is going to be an avalanche of information, an avalanche of genes that hitherto have been hidden from us, you're quite right, but it's going to take a long time before we catch that up to the human phenotype.

104. Further, the submissions do not note the variance in opinion between the experts between pathogenicity and the lack of information to qualify that statement.

105. The submissions of Counsel Assisting do not address these features at all and those submissions conflate the absence of any recognised genetic cause (which leaves open doubt about future developments as further information comes available) with the proposition that genetic causes have been excluded. The terms of these submissions reflect the approach taken at trial and impart an assessment of the material that carries a presumption of guilt rather than a presumption of innocence or even a neutral assessment. All of the material cited by Counsel Assisting relates to current knowledge of disease association and monogenetic variation.

106. The submissions neglect to refer to the face that in 30 per cent of cardiac cases, no genetic cause can be found. The same applies to neurological conditions.

107. The submissions neglect the fact that each team was looking for a monogenetic cause rather than a digenetic cause or multi-gene interaction. They did not address gonadal mosaicism. They did not address the impact of environmental factors on gene function, nor infection on gene function.

108. As such, the submissions of Counsel Assisting ~~to~~ do not set out any qualifiers to the opinion.

109. It is not suggested the genome will remain unaltered.[51] The experts opined the recovery of material from samples will probably not improve. It is conceded the data recovered probably will not improve in any significant manner .[52] But the understanding of the date is and will in future develop. The evidence demonstrates it to be so:[53]

WITNESS BUCKLEY: Yes I think so, given that we have, we've got very limited material here. It's very unlikely that we're going to be able to retest all of these samples using a putative technology that comes along in another five years. I think the data we have are reliable. I think the very fact that our Canberra colleagues and ourselves analysed these data, using different approaches, similar, using different models, but very largely we came up with a very similar set of variants that we thought were plausible, that we were confident in, that we thought should be considered as part of this matter. I, I don't see that, that we're going to come up with a very substantially different view into the future unless there is some radical change in sequencing technologies in the next few years. We have what we have. These are the data that we are best able to explain. They seem to be consistent between two groups by and large and where we depart is where - it's the different weighting and interpretation that we put on those, and I think to a degree some of the analysis reflects, says more about ourselves perhaps than about the data, that it reflects our different views. I think together the data presented by Professor Vinuesa, the data presented by us, are a remarkable snapshot of the genetics of this family at this time which we are trying to understand in the light of current knowledge.

MORRIS SC: Professor Vinuesa, do you agree with that general comment by Dr Buckley?

WITNESS VINUESA: I agree that in terms of technology, we will probably not come up with a substantial number of different variants, but we are only analysing 1% of the genome, we have not even considered 99% of the non-coding mutations. We know that - we have agreed that 50% of genetic conditions cannot be diagnosed today - of monogenic genetic conditions, and the expectation is that as soon as we have better tools to explore the significance of structural variants, other missense mutations in enhancers or cryptic supplies in sites throughout the genome might give us a, a whole new list of variants to look at. Also, we are limited by current knowledge of genes and their function. We still don't understand how at least one third of the genes in the genome work or what their function is, so I expect that over the next few years there will be more genes that will have been implicated in cardiac disease, there will be more variants. So, I think the interpretation can significantly change in a few years, not the raw data. I agree with you, the technology will not change, the raw data will not change, but we will make better sense of it in a few years.

…

[51] Counsel Assisting submissions [68].
[52] See Buckley at T 529.09.
[53] T 529.06-T 529.46. See also T 530.29-.40.

MORRIS SC: May it please the Court. This is just to clarify what was being spoken about yesterday, we expect the DNA recovery is reasonably robust, but the thing that is happening at pace is the publication of new research discoveries relating to the genetic link between a particular phenotype and the genetic discovery, is that right?

WITNESS BUCKLEY: Yes, that's proceeding at a -it's, it's a -it's a golden age of genetics.

MORRIS SC: I'm sorry?

WITNESS BUCKLEY: It's a golden age of genetics, it really is.

110. Contrary to the submissions at [66] of the submissions of Counsel Assisting, Dr de Vinuesa's opinion ought not be dismissed as a "theoretical" possibility regarding her variants. She has demonstrated she has a valid difference of opinion on pathogenicity and raised a demonstrated issue of interactions between genes that can demonstrate pathogenicity. She has established that fact with her own experience of four deaths in the one family. Her opinion is supported by Prof Clancy, Prof Goldwater. The forensic pathologists recognised its validity. It is recognised in Byard's book.[54] This evidence cannot be dismissed on this basis without some cogent and rational analysis and without specialist expert opinion from experts in the same field. To do so is to breach the admonition in *Cannings'* case about experts in one field criticising those in another without demonstrating their capacity to do so.

111. It is not suggested the Inquiry be adjourned for five years because of possible developments in medicine. To advance a light hearted quip from the Bench[55] as a formal submission[56] is specious and completely misses the point. This Inquiry cannot make a finding the genetic causes have been excluded. This is a very complicated area of science which is developing rapidly. There remains a real possibility there is a single underlying genetic condition in each of these four children, that may explain four deaths in the one family. Equally, there is a real possibility that in any one of the children, there is a genetic condition that could trigger sudden infant death. Further, there could be two or more gene

[54] Exh D at page 701.
[55] T 530.26.
[56] Counsel Assisting at [68].

variations that could have triggered the death or deaths. Additionally, there could be an association between a genetic variant and an exogenous stressor, such as infection or environmental factors. In any of these cases, the doubt is reasonable and a finding should be made to that effect.

Cardiologist's Opinion

112. The pathogenicity of any genetic variations associated with cardiac conditions was largely dependent on prior family history of disease.

113. It is not submitted there was any cardiac condition that demonstrated structural changes in the heart. No such changes were identified in any of the children at autopsy.

114. This submission is confined to the genetic variants relating to short or long QT syndromes or other cardiac conditions that might trigger a sudden cardiac arrhythmia.

115. The geneticists considered single genes that had a known association with cardiac arrhythmia.[57] In this regard, Ms Folbigg repeats her submissions on the limitations of this approach.

116. To determine the pathogenicity, it was considered appropriate to have Kathleen Folbigg examined by an electrophysiologist, Dr Raju. It should be noted there was no such examination of Craig Folbigg to determine his cardiac function which might inform pathogenicity especially in the light of the ADAMTS6 gene identified by the Canberra genetic experts.[58]

117. Dr Raju performed a range of tests that demonstrated there was no cardiac condition associated with long QT syndrome on the tests he performed on Ms Folbigg. He did not undertake a drug provocation test which is part of electrophysiological practice due to time constraints. This test uses adrenaline

[57] Prof de Vinuesa T 508.43.
[58] Such an examination was recommended by Dr Raju, Exhibit BL, page 4, "*...identification of a cardiogenetic cause of sudden death in Kathleen's children warrants similar comprehensive evaluation of their father.*" and by Professor Skinner T 505.43 - T 506.3.

or ajamline in order to induce a long QT-type response. The purpose of this test is to see if one can trigger an abnormal rhythm.[59] Further, in a certain number of patients, they can have a normal ECG and still suffer from long QT syndrome[60].

118. In short, the test results of Dr Raju do not eliminate:

(a) a cardiac condition in Kathleen Folbigg;

(b) a cardiac condition in Craig Folbigg;

(c) a cardiac cause of death in one or more of the Folbigg children caused either by a monogenetic variant, a digenetic variant or a combination of variant(s) and infection or environmental trigger.

119. The balance of the cardiological opinions were predominately directed at genetic testing and the identification of single common cardiological diseases that may have contributed to or caused the deaths of the four children. The experts did not assess digenetic causes of any cause associated with a known genetic variant and infection. This has been addressed elsewhere.

120. A report of Dr Waddell-Smith[61] was tendered to the Inquiry that addressed the use of genetic testing in confirming the presence of cardiological disease:

> *In the best case scenario, when an individual definitely has unequivocal long QT syndrome, the pick-up rate of genetic testing is approximately 75-80%.(14) In other conditions, the pick-up rate is much lower, for example 30% in dilated cardiomyopathy, and is unknown and likely much lower, in other conditions.(14) Therefore, genetic tests are not used to "rule out" disease, only to confirm its presence, to assist with cascade testing as previously described, to confirm or increase precision of diagnosis and to help guide or increase precision of risk stratification and treatment."*[62]

[59] T 510.
[60] T 511.30-33.
[61] Exhibit AV.
[62] Exhibit AV, page 4.

121. Dr Waddell-Smith was not called to give evidence at the Inquiry and her warning that genetic testing ought not be used to "rule out" disease should not, and cannot, be ignored[63].

122. Prof Skinner was called to give evidence in conjunction with the geneticists. He opined that the genetic testing had not revealed a genetic cause for the deaths[64] despite his assessment being only monogenetic.[65]

123. Prof Skinner did not rule out a number of genetic explanations including de novo changes and germline mosaicism[66] as well as "*combined gene coming down from both sides*".[67] These were not explored by the Inquiry as a consequence of no sample having been supplied by Craig Folbigg.

124. When questioned about the mutation ADAMTS6, found in each of the children, Dr Skinner did not proffer an opinion and differed to his genetics colleagues.[68] This variant was not commented upon in his report. ADAMTS6 was assumed to be inherited from Craig Folbigg[69] who was not tested genetically or cardiologically.

125. Prof Skinner's ultimate conclusions were coupled with the caveat that:

> *"We've come a long way, but we still only explain 15, 20% of, of our sudden unexplained deaths genetically. We don't know how many more are genetically, but we think we've probably - through studies that I alluded to earlier - found the main players through Whole Exome studies, but there may well be more."*[70]

[63] see for instance Exhibit Z, pages 8 and 9 where the pronouncement, "*After detailed review, none of the variants identified were deemed causal for the phenotype in these children*", appears.
[64] Exhibit Y, page 11: "*Genetic testing, when combined with the available phenotypic data, has not revealed a cardiac genetic cause for the deaths*", and, T 450.16, "*...the commonest and most plausible genes which cause sudden death in infancy are not present in this family.*"
[65] Exhibit Y, page 10.
[66] T 433.48 – T 434.20.
[67] T 455.22-.23.
[68] T 514.5-.17.
[69] Exhibit AF, page 14.
[70] T 516.39-42.

126. From a clinical perspective, Prof Skinner viewed ECG and echocardiogram records for Patrick and concluded that they appeared normal.[71] His views were confirmed during the giving of his evidence at the Inquiry.[72]

127. In relation to Laura, Prof Skinner reviewed "*a rhythm strip recorded by the ambulance officers during the resuscitation attempt*".[73]

128. He gave evidence that conditions including myocarditis could trigger an arrhythmia.[74] Whilst he had earlier concluded, from analysis of the rhythm strip alone, that, "*I think my conclusion was that this rhythm makes a non-cardiac death more likely than one from a primary cardiac arrhythmia, but I don't think that's a conclusive thing*"[75] Prof Skinner conceded that the agonal rhythm, "*these final death throes*",[76] was likely extended by paramedical interference.[77] This evidence was consistent with his report:

> *An agonal heart rhythm like this can be seen after any sudden death, be it cardiologic, respiratory or neurologic. It is a sign of a very sick, dying heart.*
>
> *Clinicians see this rhythm in children most commonly during or after a failed resuscitation after a respiratory arrest, or asphyxia, or from a neurological cause. However it can also occur following a primary cardiac arrest most typically in people with an already sick heart from a heart muscle disorder (cardiomyopathy)*[78].

129. Laura had an already sick heart, suffering myocarditis, regardless of whether the condition itself was fatal.

130. Further, in relation to Laura, Professor Skinner opined that "*[t]he ECGs available are not of a quality whereby a cardiac ion channelopathy can either be diagnosed or excluded.*"[79]

131. Whilst Prof Skinner commented on the historical presentation of Ms Folbigg, his evidence was ultimately overtaken by Dr Raju's report who had the

[71] Exhibit Y, page 5.
[72] T 386-387.
[73] T 387.24-25.
[74] T 511.35-50.
[75] Exhibit Y, page 6 and T 388.3-.23.
[76] T 388.20.
[77] T 509.21-26 and T 509.48 - T 510.03.
[78] Exhibit Y, page 6.
[79] Exhibit Y, page 7.

opportunity to examine Ms Folbigg. Prof Skinner did, however, address the issue of a drug provocation test that has yet to be undertaken.[80]

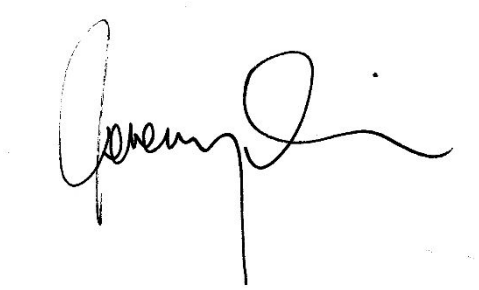
132. On the issue of a pro-inflammatory cytokine IL-6 which can introduce a level of toxicity which can trigger an arrhythmia Prof Skinner advised that he did not have any knowledge of that area at all.[81] He advised he would defer to an infectious disease expert or immunologist.[82]

Summary

133. In summary, a genetic or non-genetic cardiac cause of death in one or more of the children has not been excluded. There is still incomplete medical knowledge on this issue and the experts are expecting an avalanche of material that may shed new light on the association between monogenetic and digenetic variants and disease and the interaction between genes and infection and other exogenous causes. The lack of genetic material and cardiac function tests provides a further impediment to assessing the likelihood of a cardiac cause for the deaths of one or more children in the Folbigg family. Findings should be made to this effect.

[80] T 510-511.
[81] T 526.12-.15.
[82] T 526.20-.23.

Dated: 7 June 2019



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