Inquiry into the convictions of Kathleen Megan Folbigg

GENETICS HEARING

OPENING

1. This week the Inquiry will primarily hear evidence about advances in the field of genetics since Ms Folbigg's trial in 2003, and the application of those advances to the understanding of the deaths of the Folbigg children.

2. As I outlined in the first opening address, some genetic-related investigations had been undertaken in respect of the Folbigg children by the time of the 2003 trial. The results of those investigations were described as normal and did not indicate the need for further testing or investigation.

3. Significant advances have been made in the field of genetics since the trial. Those advances permit a much broader scope of investigation than was possible in 2003.

4. Genomic sequencing technologies emerged in 2009. Since 2013, two major genomics sequencing technologies have become mainstream.

5. Whole Exome Sequencing sequences the exome, which is that small part of the genome (approximately 1-2% of the whole) that is involved in coding for proteins. Proteins are the key components of cells and damage to them can cause serious, if not catastrophic,

problems. This part of the genome is the location of the majority of the variants that cause developmental or cognitive disabilities and disorders.

6. Whole Genome Sequencing sequences all of the genome that is accessible. In addition to the exome, this comprises non-coding elements in the genome and mitochondrial DNA.

7. This technology enables hypothesis-free study of DNA where a known or presumed diagnosis as a starting point is not needed. Rather DNA sequences are studied and variants are interrogated against the known healthy human genome and the phenotype or clinical features of a person.

8. In 2015, the American College of Medical Genetics and Genomics ("ACMG") published Standards and Guidelines for the interpretation of sequence variants, including assessing the pathogenicity of variants.

9. The ACMG Standards refer to variants being 'pathogenic', that is, causative of disease, 'likely pathogenic', 'of uncertain significance', 'likely benign' and 'benign'. This terminology has been employed in the reports prepared for the Inquiry.

Available samples

10. Material produced to the Inquiry by the NSW Ministry of Health in compliance with summonses included samples containing DNA from each of the four children.

11. Blood spots taken from each of the children at the time of their birth as part of the Newborn Screening Program and held at the Children's Hospital Westmead were available.

12. In respect of each of Patrick, Sarah and Laura, tissue samples taken at the time of their autopsies in 1991, 1993 and 1999 respectively and fixed in glass and wax block slides held at the Coroner's Court were also available.

13. In respect of Patrick, additionally available were kidney, liver, skin, skeletal muscle and heart tissue samples taken at the time of his autopsy in 1991 and frozen at minus 80 degrees.

14. In respect of Sarah, additionally available was one tube of extracted genomic DNA from fibroblasts, and two ampules of archived fibroblast cells stored in liquid nitrogen, held at the Children's Hospital Westmead.

15. In respect of Laura, additionally held at the Children's Hospital Westmead, was formalin-immersed brain tissue taken at the time of her autopsy in 1999.

16. In December 2018 the Inquiry was informed that Ms Folbigg had provided to her legal representatives a sample for the purpose of genetic testing. Ms Folbigg consented to the sample being made available to the Inquiry for further genetic testing.

Engagement of multi-disciplinary panel of experts

17. The interpretation of genetic data involves consideration of both the genetic pathology and the clinical presentation of a person. It is a single, but multi-faceted, interpretation process.

18. Accordingly, the Inquiry gathered together a multi-disciplinary panel of experts to interpret and provide opinions about the data produced by the genetic testing undertaken for the Inquiry, and the available clinical information in respect of each of the children and Ms Folbigg.

19. These experts were associated with two separate laboratories with genetic sequencing interpretation capabilities: in Sydney and in Canberra.

20. Dr Michael Buckley is a genetic pathologist and clinical director of the NSW Health South Eastern Area Laboratory Services at the Prince of Wales Hospital in Sydney. He holds a PhD in the field of molecular genetics, obtained in 1991.

21. Professor Edwin Kirk is a genetic pathologist and clinical geneticist at the NSW Health South Eastern Laboratory Services as well as co-head of the Centre for Clinical Genetics at the Sydney Children's Hospital. He has additionally trained in paediatrics and provides a cardiac genetics clinical service, which focuses on adults and children with cardiomyopathies and disorders of cardiac rhythm.

22. Dr Alison Colley is a clinical geneticist and the Director of Clinical Genetics Services for various local health districts in NSW. She has trained in paediatrics as well as clinical genetics. She is a conjoint

Senior Lecturer at the University of New South Wales. Dr Colley is a renowned dysmorphologist.

23. Professor Jon Skinner is a paediatric cardiologist and cardiac electrophysiologist working as a consultant at Starship Children's Hospital in Auckland, New Zealand. He is an Honorary Professor in Paediatrics, Child and Youth Health at the University of Auckland.

24. Professor Matthew Cook is a professor of medicine at the Australian National University, and a practising clinical immunologist at Canberra Hospital. He is also co-director of the Centre for Personalised Immunology at the Australian National University, and medical director of the Canberra Clinical Genomics laboratory. That laboratory is accredited to conduct bioinformatics analysis of DNA and RNA sequences, such as those produced by Whole Exome Sequencing or Whole Genome Sequencing.

25. Professor Carola Vinuesa is an Australian National Health and Medical Research Council Principal Research Fellow, and Professor of Immunology at the Australian National University. She is also the chief scientist at the Canberra Clinical Genomics laboratory of which Professor Cook is the medical director. Together with Professor Cook, she is also the co-director of the Centre for Personalised Immunology.

26. Professors Cook and Vinuesa were assisted by Dr Todor Arsov, a visiting fellow at the Centre for Personalised Immunology. He holds a PhD in biomedical sciences and a Masters of Genetic Counselling.

Testing process

27. The Inquiry held three consultation meetings at which the interpretation panel experts discussed the options for genetic testing on the produced samples.

28. On the basis of these discussions, Whole Genome Sequencing was conducted on:

    i. DNA extracted from a frozen liver tissue sample from Patrick;

    ii. DNA in the existing sample extracted from fibroblasts from Sarah;

    iii. DNA extracted from a blood spot sample from Caleb; and

    iv. DNA extracted from the sample from Ms Folbigg.

29. Whole Exome Sequencing was conducted on DNA extracted from a blood spot sample from Laura, which was unsuitable for Whole Genome Sequencing because of microbial contamination of the sample.

30. The Australian Genome Research Facility conducted the sequencing on the samples of Sarah, Patrick and Ms Folbigg. The Victorian Clinical Genetics Service conducted the sequencing on the samples of Caleb and Laura.

Analysis and reports

31. At the NSW Health Pathology Genetics Laboratory at the Prince of Wales Hospital in Sydney, variant analysis of the sequencing data was

conducted through a genomic analysis bioinformatics pipeline called the Genomic Annotation and Interpretation Application.

32. At the Canberra Clinical Genomics laboratory, variant analysis of the sequencing data was conducted through a separate bioinformatics pipeline.

33. Ultimately, each laboratory analysed the same data and the same genes. Almost 1400 unique candidate genes were identified for analysis.

34. In addition, the data was re-analysed considering:

    i. cardiac/non-cardiac genes which had been published in relation to sudden death in infancy/childhood;

    ii. genes associated with childhood neurological disorders;

    iii. genes associated with immunology;

    iv. genes associated with metabolics; and

    v. likely pathogenicity in any phenotype not restricted to sudden death in infancy/childhood.

35. It was agreed by the expert panel that the ACMG Standards and Guidelines would be used for assessing the pathogenicity of variants.

36. All experts involved in the interpretation of the sequencing data were provided with documents relevant to the phenotype or clinical presentation of the children and Ms Folbigg. The phenotype or observable clinical features of the children is of healthy, well grown,

normally developing children who are normal in appearance, each of whom suffer a catastrophic event leading to death instantly in three of them and severe neurological sequelae in the fourth child which precedes his later death.

37. The relevant medical history and results of historical and other recent cardiac-related investigations on Ms Folbigg have been considered by the experts in the interpretation process. Further information will be available from cardiac-related testing scheduled to be conducted on Ms Folbigg on 18 April 2019.

38. Dr Buckley, Dr Colley and Professor Kirk prepared a joint report interpreting the significance of genetic variants, identified through the Sydney pipeline, present in the children and in Ms Folbigg and potentially relevant to the children's causes of death ("the Sydney report").

39. Professor Cook and Professor Vinuesa, with the assistance of Dr Arsov, prepared a joint report and a supplementary report interpreting the significance of genetic variants identified through the Canberra pipeline ("the Canberra report").

40. The Canberra report concluded that no known pathogenic or likely pathogenic variants in genes that could explain unexpected death were found in all the children. The Sydney report came to the same conclusion and added that none of the variants identified were deemed causal for the phenotype in the children.

41. The key differences of opinion expressed in each of those reports is as to three variants, primarily relating to cardiac function. One variant was found only in Patrick, another only in Sarah and Laura and the third was found only in Laura and Caleb.

42. Professor Jon Skinner prepared a report specifically addressing cardiac-related variants in the children's and Ms Folbigg's genes as reported by the Sydney and Canberra pipelines, and the cardiac clinical presentation of each of them. He concluded that the available clinical phenotype data and genetic analyses in respect of the children and Ms Folbigg provide no convincing evidence for the presence of any known form of cardiac inherited disease as a potential cause for the sudden death of the four children.

Paediatric neurologists – Patrick

43. Professor Monique Ryan is a senior paediatric neurologist and Director of the Department of Neurology at the Royal Children's Hospital in Melbourne. She was engaged by those representing Ms Folbigg to report on her assessment of Patrick's neurological condition. She concluded that she was not convinced that Patrick's clinical history was consistent with him having neurologic deficits resulting from a single hypoxic-ischaemic episode on 18 October 1990. She listed a number of alternative diagnoses which were potentially causative of his neurologic condition which she said could be the subject of Whole Genome Sequencing. Her report dated 15 March 2019 was prepared without knowledge of the Whole Genome Sequencing results.

44. Associate Professor Fahey, a paediatric neurologist and clinical geneticist, is head of paediatric neurology at the Victoria Paediatric Rehabilitation Service at Monash Children's Hospital. He prepared a report at the request of the Inquiry, following the Whole Genome Sequencing performed in relation to Patrick. He was provided with Professor Ryan's report. To assist his analysis, he provided Dr Buckley with a list of 204 genes associated with childhood neurological disorders for analysis. Most of those genes had been identified and analysed, however the data was separately re-analysed.

45. After receiving those results, Associate Professor Fahey concluded that the testing at the time of Patrick's acute or apparent life threatening event and death, and the genomic testing conducted at the request of the Inquiry, have excluded any recognised conditions associated with genetic epilepsies, encephalopathy, cardiac arrhythmias or sudden death, including the alternative potential diagnoses identified by Professor Ryan. He opined that the comprehensive investigations virtually eliminated a recognised genomic cause for Patrick's presentation.

46. With the exception of Professor Cook who is not available, each of the experts will give evidence this week about the interpretation and analysis they undertook, and the opinions they formed from those exercises.