**Inquiry into the convictions of Kathleen Megan Folbigg**

# FURTHER SUBMISSIONS OF COUNSEL ASSISTING

## Further information regarding CALM2 variant

1. The evidence in the Inquiry closed on 1 May 2019.[1] On 21 June 2019 Professor Vinuesa sent to the Inquiry a further statement, specifically in relation to the CALM2 variant. The statement attached a paper published in June 2019 ("the June 2019 paper"),[2] which reported a family with a variant in the CALM3 gene (p.Gly114Trp or p.G114W) affecting the same amino acid as was identified in the CALM2 gene in Ms Folbigg, Sarah and Laura Folbigg (p.Gly114Arg or p.Gly114R).

2. The statement also attached a letter dated 20 June 2019 addressed to Professor Vinuesa from one of the authors of the June 2019 paper, Professor Peter Schwartz, Director at the Centre for Cardiac Arrhythmias of Genetic Origin at the Istituto Auxologico Italiano in Milan, Italy. The circumstance in which Professor Schwartz's letter to Professor Vinuesa came about appears to be that Professor Vinuesa provided to Professor Schwartz "the Canberra report", authored by her and Professor Cook in relation to the genetic testing of the Folbigg family and tendered in the Inquiry.[3]

3. In his letter Professor Schwartz explained that the Registry of Calmodulinopathy referenced in the June 2019 paper included a family with an asymptomatic mother carrying the CALM3 variant, one child who died at age five from a cardiac arrest while playing, and another who died suddenly at age four.

4. Professor Schwartz noted that the report he had seen (the Canberra report) only linked the CALM2 variant to a long QT syndrome phenotype, ignoring the

[1] At the close of the substantive hearings, at the request of Ms Folbigg's representatives, the Judicial Officer directed that Ms Folbigg's representatives had until 7 May 2019 to seek the tender of any further documents. Further documents were tendered at this point.
[2] Lia Crotti et al, 'Calmodulin Mutations and Life-Threatening Cardiac Arrhythmias: Insights from the International Calmodulinopathy Registry' (2019) *European Heart Journal* (advance).
[3] Exhibit AF, Joint report of Canberra genetics team (29 March 2019).

possibility that the phenotype could be Catecholaminergic polymorphic ventricular tachycardia ("CPVT"). He noted that without an exercise stress test, a diagnosis of CPVT was still "fully on the table".[4]

5. It is apparent that Professor Schwartz was provided only with the Canberra Report, and none of the evidence given in the Inquiry or the historical or recent clinical presentation information in relation to Ms Folbigg, including the April 2019 stress test conducted upon her and Professor Skinner's and Dr Raju's opinions as to the results of that test.[5] Most significant of this material, in light of Professor Schwartz's view as to the potential diagnosis of CPVT, is Professor Skinner's opinion based on that stress test that Ms Folbigg does not have CPVT.[6]

## Supplementary report by the Sydney Team

6. Those assisting the Inquiry provided the Sydney team and Professor Skinner with the material received from Professor Vinuesa. Professors Skinner and Kirk and Dr Buckley provided a short report dated 5 July 2019 ("the Supplementary Sydney report").

7. In the Supplementary Sydney Report it was noted that although the June 2019 paper referred to a different gene (CALM3) than the one found in Sarah, Laura and Ms Folbigg (CALM2), the findings are relevant because the three CALM genes code an identical protein.[7] Professors Skinner and Kirk and Dr Buckley considered the information is relevant to interpretation of the potential clinical significance of the p.Gly114Arg variant, "increasing the likelihood that this variant is pathogenic and that it might be relevant to the deaths of Sarah and Laura".[8] They therefore considered afresh the classification of this variant in light of the new information available in the June 2019 paper.

8. The Supplementary Sydney Report considered that in light of the new information, the ACMG Standards criteria PP2 (missense variant in a gene that has a low rate of benign missense variation), and PM5 (novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been

[4] Letter from Professor Peter Schwartz to Professor Carola Vinuesa (20 June 2019) p 2.
[5] Exhibit BH, Further cardiac testing of Kathleen Folbigg (18 April 2019); Report of Associate Professor Hariharan Raju (18 April 2019).
[6] Exhibit BK, Letter from Professor Jonathan Skinner to the Inquiry (30 April 2019) p 1; Exhibit BJ, Further report of Professor Jonathan Skinner (24 April 2019) pp 3-4.
[7] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 1.
[8] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 4.

seen before), should be applied.[9] As a result, if the clinical information was not taken into account, the addition of PM5 would mean that the variant would now be classified as likely pathogenic.[10]

9. However, the Supplementary Sydney Report considered that the clinical information is essential to the interpretation of the significance of the variant.[11] The Supplementary Sydney Report observed, by reference to the clinical tests reviewed by two specialists in inherited cardiac conditions, that the clinical information was in conflict with the genetic evidence. The Supplementary Sydney Report concluded that the fact Ms Folbigg is alive (at age 52), has never had a cardiac arrest, and produced exercise test results within normal limits are strongly against a hypothesis of concealed CPVT.[12]

10. The Supplementary Sydney Report recognised it would be "theoretically possible" to have mosaicism in one tissue which is not reflected in another, and that this could explain the absence or greatly attenuated cardiac phenotype in Ms Folbigg.[13] However, the Supplementary Sydney Report concluded that based on the available genetic data, this was very unlikely and that testing of tissue was unlikely to be of value.[14] The Supplementary Sydney Report also said that there are no functional studies for this particular protein validated to clinical standards.[15]

11. The Supplementary Sydney Report identified four possible interpretations of the information regarding the variant:

    a. the variant could be pathogenic and the sole cause of the deaths of Sarah and Laura;

    b. the variant could be pathogenic and related to, but not the sole cause, of the deaths of Sarah and Laura (such as if the children had experienced an asphyxial event which may or may not normally have been sufficient to cause their deaths, but which, through adrenergic stimulation induced a cardiac arrhythmia that would not otherwise have happened and led to their deaths);

[9] Exhibit AC, Genetics tender bundle, ACMG Standards; Supplementary Sydney Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 1.
[10] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 3.
[11] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 4.
[12] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 3.
[13] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 3.
[14] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 3.
[15] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 3.

c. the variant could be pathogenic but unrelated to the deaths of Sarah and Laura; or

d. the variant could be benign.[16]

12. The Supplementary Sydney Report concluded that following application of the ACMG Standards, the CALM2 variant in Ms Folbigg, Sarah and Laura remains classified as a variant of uncertain significance, due to the conflict between the clinical and genetic evidence.[17]

13. The Supplementary Sydney Report noted uncertainty as to which of the possibilities identified above was most likely. The Supplementary Sydney Report did observe, however, that:

a. either of the first two possibilities would require at least two different causes of death of the Folbigg children, given the absence of the CALM2 variant in Caleb and Patrick; and

b. the first possibility would require "an exceptional clinical scenario" which is "outside the range that has previously been reported in association with variants in this group of genes".[18]

## Submissions on further information regarding CALM2 variant

14. In our submission, the further information provided by the June 2019 paper regarding the CALM2 variant has not changed the results of the genetic testing conducted by the Inquiry. In particular, the information provided in the June 2019 paper has not changed the conclusions reached by the Sydney team and Professor Skinner in their evidence in the Inquiry.

15. While the further information has changed the criteria applied in the classification process in the Supplementary Sydney Report, when the relevant clinical information is taken into account, it remains the case that CALM2 is a variant of uncertain significance.

16. Professor Schwartz expressed the opinion that CPVT was still "fully on the table", because, to his knowledge, there had been no stress testing. There was stress

[16] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 4.
[17] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 4.
[18] Supplementary Report of Professors Skinner, Kirk and Dr Buckley (5 July 2019) p 4.

testing of Ms Folbigg of which Professor Schwartz was unaware and therefore his opinion in this respect and more generally is to be disregarded.

17. We submit that the Judicial Officer will accept the opinions of Professors Skinner and Kirk and Dr Buckley. It would not only be an entirely artificial exercise to classify a variant without considering the relevant clinical information, but contrary to scientific method. This is particularly so in circumstances where the genetic information is in conflict with comprehensive relevant clinical information, as is the case with Ms Folbigg's cardiac presentation. Similarly, the Judicial Officer should be satisfied that there is no further testing available that would be of value.

18. Further, in our submission the phenotype of the family referenced in the June 2019 paper with the deaths of children at the ages of four and five years is similar to the cases already drawn to the Inquiry's attention by the experts in the Sydney and Canberra Reports and during the course of the hearings.

19. The differences between those cases, and the Folbigg children's deaths, are significant:

    a. the Folbigg children were notably younger in age;

    b. the Folbigg children all died during a sleep period, not during a period of physical exertion or stress; and

    c. the CALM2 variant was present only in Sarah and Laura despite the deaths of Caleb and Patrick, and Patrick's ALTE, occurring in very similar circumstances.

20. It remains the case that no genetic variant has been identified as being pathogenic or likely pathogenic in the Folbigg children. In our submission, it follows that it remains the case there is no reasonable possibility that the death of any of the Folbigg children or Patrick's ALTE was caused by a recognised genetic variant.

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