EXHIBIT AT

Additional Report for the Inquiry into the Convictions of Kathleen Megan Folbigg

I have now read the report of Professor Rosemary Horne dated 10 February 2019 and the transcript of Inquiry proceedings from 18 March 2019. I was asked to submit any further material after my consideration of this material.

In response to those reports I make the following commentary.

Conclusion

1. Those children suffering ALTE's with a pre-existing mild airways infection share a pathogenic pathway of immune disturbance with SIDS. In my area of expertise, based on verifiable data, [redacted], there is a sound scientific basis to consider that SIDS and ALTE's are two sides of the same coin in many instances. Evidence for this includes the careful prospective study undertaken in the Hunter region (as annexed to my first report dated 13 March 2019). These studies also connected for the very first time smoking exposure to SIDS/ALTE's via a common mechanism, adding significantly to support the link between ALTE's and SIDS (at least in Australia).

2. Data is provided showing significant clustering of SIDS and ALTE's within a family.

3. Data from earlier studies relating to control of breathing in SIDS and ALTE's does not establish the primary causative factor. The control of breathing is a secondary to the

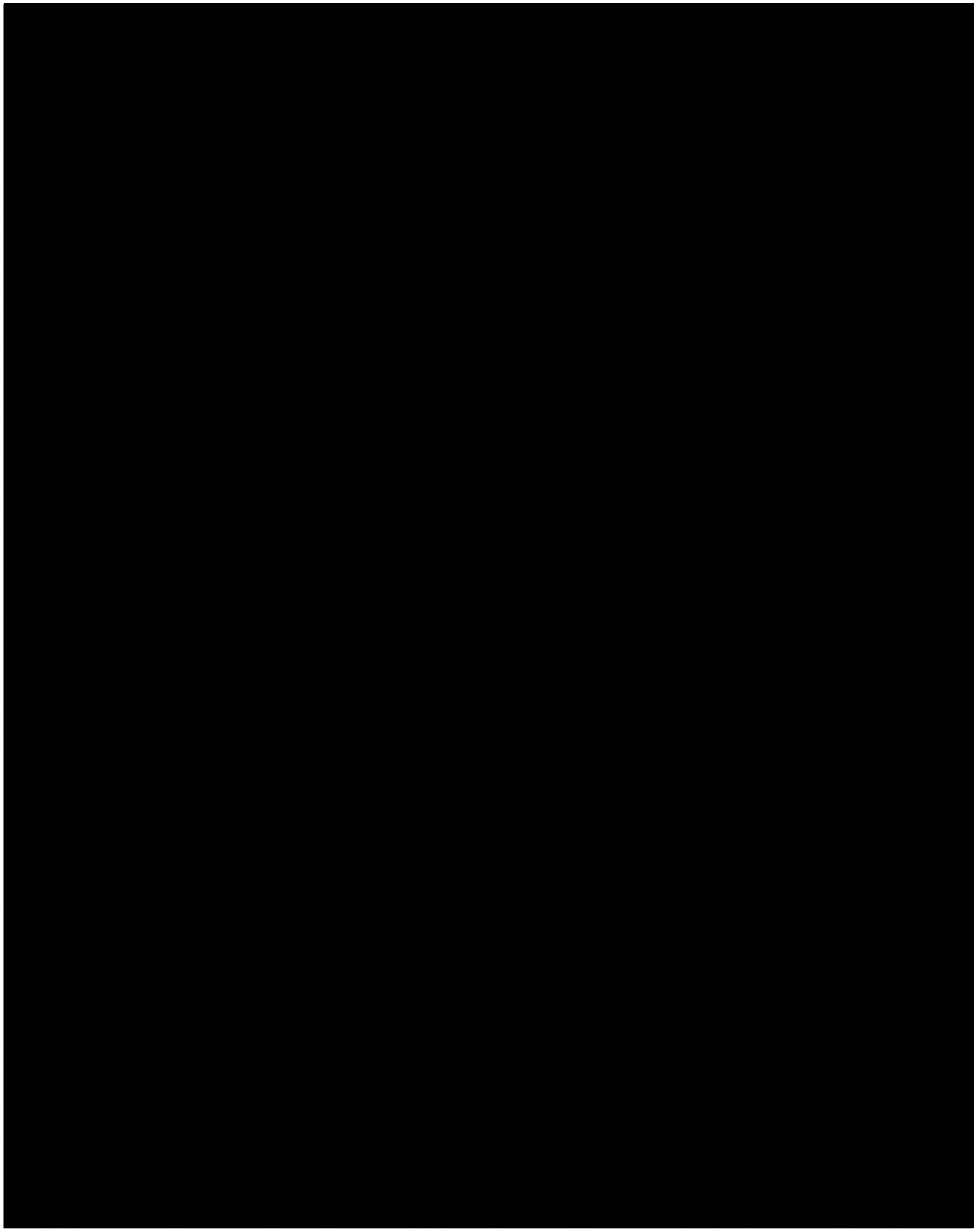
causative factor in both SIDS and ALTE. The control of breathing is a consequence to the causative factor.

4. Professor Horne makes no reference in her report to the data identifying disturbed host-microbe relationships in driving SIDS. The Professor's approach focuses on earlier ideas regarding breathing control, apnoeas, breast feeding, use of dummies, use of formula, sleeping arrangements and other matters relevant to her specialty in respiratory physiology. There is no doubt that these studies are important, and the work of respiratory researchers has provided valuable insight as to how to maximse respiratory function, but it does not assist in establishing the cause of respiratory difficulties that compromise respiration.

5. Professor Horne acknowledges on page 4 of her report the role of infection and immune response in half of all sudden infant deaths without developing or discussing that statistical feature with respect to the likely causal potency of infection.

6. The causal connection between mild infection and sudden death in the infant is clearly set out in Chapter 30 of Duncan and Byard's 2018 text, "Sudden Infant and Early Childhood Death, The Past Present and Future". I agree with the information contained in that chapter and it reflect the latest scientific endeavor arising from the studies of microbiologists and immunologists. [redacted]

7. Professor Horne properly accepts that immunology and microbiology are areas outside of her expertise in her oral evidence (T49.10).



12. Advances in SIDS since 2003:

(i) Cardio-respiratory control dysfunction/immaturity:

This is discussed above and is a continuing area of study. The data is of marginal scientific validity as a "cause" when examined, with considerable overlap with control and suffers an absence of a 'denominator' to enable relevance or specificity. There are internal inconsistencies with the data which the author properly identifies. However this inherent respiratory instabilityespecially as it related to 'arousal', could be a key component to converting an apnoeic episode caused by other mechanisms, to be fatal (see also below with respect to ALTE's). But it is clear that some infants have an additional vulnerability, that triggers death.

(ii) Genetics:

The more one looks, the more polymorphisms will be found - some of which will be relevant to SIDS, as coding for "contributing causes". Currently, it is not possible to make dogmatic statements, because no current genetic findings

clearly related to causative events. Genome searches will only increase these findings and uncertainties. Brain pathology has its own complexisties that are not yet fully understood. Brain physiology may be relevant to unrecognised pre-death hypoxic episodes (as may have occurred in Patrick). In reality, the extraordinary range of difficult to understand neural abnormalities, is reflected in the number of research grants given to study this complex disease.

Note in a very carefully identified and studied ALTE group of 26, 50% had infection (⅔ of which were RSV infection).

(iv) I refer the Inquiry to the following academic papers and studies in this area since 2003 (many of which have been referred to in Professor Blackwell's report and my own):

1. Aoyagi, M, Shimojo N, Sekine, K, Nishimuta T and KKohmo, Y. (2003) Respiratory syncytial virus infection suppresses IFN-gamma production of gamma delt T cells. Clin. Exp. Immunol. 131, 312-317.
2. Bettelheim KA, Luke RKJ, Johnston N, Pearce JL, Goldwater PN. A possible murine model for investigation of pathogenesis of sudden infant death syndrome. Curr Microbiol (2012) 64:276–82. doi:10.1007/s00284-011-0065-4.

3. Blackwell, C.C., Moscovis, S.M., Gordon, A.E., Al Madani, O.M., Gleeson, M., Scott, R.J., Roberts-Thomson, J., Hall, S.T., Weir, D.M., Busuttil, A. (2004) Ethnicity, infection and Sudden Infant Death Syndrome. FEMS Immunol. Med. Microbiol. 42, 53-65.
4. Blackwell, C.C., Moscovis, S.M., Gordon, A.E., Al Madani, A.M., Hall, S.T., Gleeson, M., Scott, R.J., Roberts-Thomson, J., Weir, D.M., and Busuttil, A. (2005) Cytokine responses and sudden infant death syndrome: genetic, developmental, and environmental risk factors J. Leukocyte Biol. 78: 1242-1254.
5. Blackwell C, Moscovis S, Hall S, Burns C, Scott R. 2015. Exploring the risk factors for sudden infant deaths and their role in inflammatory responses to infection. Frontiers in Immunol. https://doi.org/10.3389/fimmu.2015.00044/.
6. Blood-Siegfried, J. 2015. Animal models for assessment of infection and inflammation: contributions to elucidating the pathophysiology of sudden infant death syndrome. Frontiers in Immunol https:// doi.org./10.3389/fimmu.2015.00137.
7. Brownstein CA, Poduri A, Goldstein RD, Holm IA. The genetics of sudden infant death syndrome. In Duncan J R and Byard R W. SIDS Sudden infant and early child hood death: The past, the present and the future. University of Adelaide Press, 2018; pp 711-730.
8. Ferrante, L., Opdal, S.H., Vege, A., Rognum, T.O. (2008) TNF-alpha promoter polymorphisms in sudden infant death. Hum. Immunol. 69: 368-373.
9. Garcia AJ, Koschnitzky JE, Ramirez J-M. The physiological determinants of sudden infant death syndrome. Respiratrory Physiology and Neurobiology. 2013;189(2):doi:10.1016/j.resp.2013.05.032.
10. Gentile, DA, Doyle, WJ, Zeevi A, Howe-Adams, J, Kapadia S, Recki J and Skoner DP (2003) Cytokine gene polymorphisms moderate illness severity in infants with respiratory syncytial virus infection. Human Immunol 64, 338-344.
11. Gleeson, M, Clancy, R L, Cox, Amanda J C, Gulliver, S A, Hall, S T and Cooper D M. (2004) Mucosal immune responses to infants with acute life threatening events

classified as 'near-miss' sudden infant death syndrome. FEMS Immunol. Med. Microbiol. 24, 105-118.

12. Gleeson, M and Cripps A W. (2004) Development of mucosal immunity in the first year of life and relationship to sudden infant death syndrome. FEMS Immunol. Med. Microbiol.
13. Goldwater, P. (2004) SIDS pathogenesis: pathological findings indicate infection and inflammatory responses are involved. FEMS Immunol. Med. Microbiol. 42, 11-20.
14. Goldwater, P.N. (2009) Sterile site infection at autopsy in sudden unexpected deaths in infancy. Arch. Dis. Child. 94: 303-307.
15. Goldwater, PN, Bettelheim, K.A. (2013) SIDS Risk Factors. Time for new interpretations. The role of bacteria. Pediatrics Res Intern. J. Article ID 867520 http://www.ibimapublishing.com/journals/PRI/prij.html.
16. Goldwater PN. Infection: the neglected paradigm in SIDS research. Arch Dis Child (2017) 2017:312327. doi:10.1136/archdischild-2016-312327.
17. Halvorsen, M, Petrovski S, Shellhaas R, Tang Y, Crandall L Goldstein D, et al. Mosaid mutations in early-onset genetic diseases. Genet Med. 2016; 18: 746-9.
18. Highet AR, Berry AM, Bettelheim KA, Goldwater PN. Gut microbiome in sudden infant death syndrome (SIDS) differs from that in healthy comparison babies and offers an explanation for the risk factor of prone position. Int J Med Microbiol (2014) 304(5–6):735–41. doi:10.1016/j.ijmm.2014.05.007.
19. Hill, R. 2005. Reflections on the cot death cases. Significance. 13-15.
20. Hoebee, B, Rietveld E, Bont L, Oosten, M, Hodemaekers, HM, Nagelkerke, Neijens HJ, Kimpen JL and Kimman TG. (2003) Association of severe respiratory syncytial irus bronchitis with interleukin-4 and interleukin-4 receptor alpha polymorphisms. J Infect Dis. 187, 2-11.
21. Hu D, Barajas-Martinez,H, Medeiros-Domingo A, Crotti L, Veltmann C, Schimpf R et al. A novel rare variant in SCN1Bb linked to Brugada syndrome and SIDS by

combined modulation of na(v)1.5 and K(v)4.3 channel currents. Heart Rhythm. 2012; 9: 760-9.

22. Jehi L, Najm IM. Sudden unexpected death in epilepsy: Impact, mechanisms and prevention. Cleveland Clin. J. Med. 2008; 75 suppl 2: s66-70.
23. Klassen TL, Momben VC, Patel A, Drabek J, Chen TT, Gu W et al. High resolution molecular genomic autopsy reveals complex sudden unexpected death in epilepsy risk profile Epilepsia. 2014; 55: e6-12.
24. Korachi, M., Pravica, V., Barson, A.J., Hutchinson, I.V., Drucker, D.B. (2004) Interleukin 10 genotype as a risk factor for sudden infant death syndrome: determination of IL-10 genotype from wax-embedded post-mortem samples. FEMS Immunol. Med. Microbiol. 42, 125-129.
25. Kruger, M.M., Martin, L.J., Maistry, S., Heathfield, L.J. 2018. A systemic review exploring the relationship between infection and sudden unexpected death between 2000 and 2016: A forensic perspective. Forensic Sci. Int.. 289: 108-119.
26. Law, BJ, Caronell-Estrany, K and Simoes EA (2002). An update on respiratory syncytial virus epidemiology: a developed country perspective. Resp. Med. 96 (Suppl. B) S1-S7.
27. Legg, JP, Hussain IR, Warner JA, Johnston SL and Warner JO. (2003) Type 1 and type 2 cytokine imbalance in acute respiratory syncytial virus bronchiolitis. Am. J. Resp. Crit. Care. Med. 168, 625-627.
28. Mage DT, Latorre ML, Jenik AG, Donner M. The Role of Respiratory Infection in Sudden Infant Death Syndrome (SIDS). Scand J Forensic Sci 2016;22(1);15-20 - doi: 10.1515/sjfs-2016-0004.
29. Morris JA. Common bacterial toxins and physiological vulnerability to sudden infant death: the role of deleterious genetic mutations. FEMS immunology and medical microbiology. 2004 9/1/;42(1):42-7.
30. Morris, J.A., Harrison, L.M., Partridge, S.M. (2006) Post mortem bacteriology: a re-evaluation. J. Clin. Pathol. 59:1-9.

31. Morris, J.A., Harrison, L.A., Telford, D.R. (2012) Postmortem cerebrospinal fluid pleocytosis: a marker of inflammation or post mortem artefact? Int. J. Pediatr. doi: 10.1155/2012/964074

32. Moscovis, S.M., Gordon, A.E., Al Madani O.M., Gleeson , M., Scott , J., Hall, S.T., Burns, C.J. , Blackwell, C.C. Genetic and environmental factors affecting TNF-α responses in relation to Sudden Infant Death Syndrome. Frontiers in Immunology.

33. Moscovis, S.M., Gordon, A.E., Al Madani, O.M., Gleeson, M., Scott, R.J., Hall, S.T., Weir, D.M., Busuttil, A., Blackwell, C.C. (2004) Interluekin-10 and Sudden Infant Death Syndrome. FEMS Immunol. Med. Microbiol. 42, 139-145.

34. Moscovis, S.M., Gordon, A.E., Al Madani, O.M., Gleeson, M., Scott, R.J., Roberts-Thompson, J., Hall, S.T., Weir, D.M., Busuttil, A., Blackwell, C.C. (2004). Interleukin 1-β responses to bacterial toxins and sudden infant death syndrome. FEMS Immunol. Med. Microbiol. 42, 130-138.

35. Moscovis, S.M., Gordon, A.E., Al Madani O.M., Gleeson , M., Scott , R.J., Roberts-Thomson , J., Hall, S.T., Weir, D.M., , Busuttil, A., Blackwell, C.C. 2006. IL6 G-174C associated with sudden infant death syndrome in Caucasian Australian infants. Hum. Immunol. 67: 819-825.

36. Moscovis S, Gordon A, Al Madani O, Gleeson M, Scott R, Hall S, Burns C, Blackwell C. 2015. Virus infections and sudden death in infancy: the role of interferon-γ. Frontiers in Immunology. 2015-March-11;6.

37. Moscovis S, Gordon A, Al Madani O, Gleeson M, Scott R, Hall S, Burns C, Blackwell C. 2015. Genetic and environmental factors affecting TNF-αresponses in relation to Sudden Infant Death Syndrome. Frontiers in Immunology. 2015-July-27;6.

38. Nascimento FA, Borlot F, Cossette P, Minassian BA, Andrade DM. Two definite cases of sudden unexpected death in epilepsy in a family with a DEPDC5 mutation. Neurol Genet. 2015; 1:e28.

39. Opdal, S.H., Opstad, A., Vege, A., Rognum, T.O. (2003) Il-10 gene polymorphisms are associated with infectious cause of sudden infant death. Hum. Immunol. 64, 1183-1189.

40. Opdal, S.H. (2004) IL-10 gene polymorphisms in infectious disease and SIDS. FEMS Immunol. Med. Microbiol. 42, 48-52.

41. Poduri A. The expanding SCN8A-related epilepsy phenotype. Epilepsy Curr. 2015; 15: 333-4.

42. Pearce JL, Bettelheim KA, Luke RK, Goldwater PN. Serotypes of Escherichia coli in sudden infant death syndrome. J Appl Microbiol (2010) 108(2):731–5. doi:10.1111/j.1365-2672.2009.04473.x.

43. Prtak L, Al-Adnani M, Fenton P, Kudesia G, Cohen MC. Contribution of bacteriology and virology in sudden unexpected death in infancy. Arch Dis Child (2010) 95(5):371–6. doi:10.1136/adc.2009.162792.

44. Prtak L, Cohen M, Fenton P, Adnani M, Kudesia G. Bacterial toxins and sudden unexpected death in infancy. Lancet (2008) 372(9640):714–5. doi:10.1016/ S0140-6736(08)61297-0.

45. Ravindran K, Powell KL, Todaro M, O'Brien TJ. The pathophysiology of cardiac dysfunction in epilepsy. Epilepsy Res. 2016; 127: 19-29.

46. Tan BH, Pundi KN, van Norstrand DW, Valdivia CR, Tester DJ, Medeiros-Domingo A et al. Sudden infant death syndrome-associated mutations in the sodium channel beta subunits. Heart Rhythm. 2010; 7: 771-8.

47. Vege, A. and Rognum, T.O. (2004) Sudden infant death syndrome, infection and inflammatory response. FEMS Immunol Med. Microbiol. 42, 3-10.

48. Weber, M., Klein, N., Hartley, J., Lock, P., Malone, M., Sebire, N. (2008) Infection and sudden unexpected death in infancy: a systematic retrospective case review. Lancet 371: 1848-1853.

49. Weber, M.A., Hartley, J.C., Brooke, I., Lock, P.E., Klein, N.J., Malone, M., Sebire, N.J. (2010) Postmortem interval and bacteriological culture yield in sudden unexpected death in infancy (SUDI). Forensic Sci. Int. 198: 121-5.

13. Relationship between ALTE & SIDS:

Professor Horne's report, with its focus on sleep disorders, does not address what, in my area of expertise, is the putative relationship between ALTE and SIDS. Here the relevant papers have been reviewed and an Australian study in the Hunter Region (Gleeson *et al* 2004; attached to my first reported dated 13 March 2019) discussed in detail. The conclusion cannot be avoided is that ALTE's contain a range of diagnoses requiring sleep studies, barium swallows etc. which are not done/identified in the retrospective study discussed by Professor Horne (her reference 64) i.e ALTE's do not occur earlier than SIDS at least in Australia. A careful prospective study of 26 (Gleeson *et al*) involving in hospital assessment of all patients, full investigations, questionnaires to parents and attending doctors in two Australian centres contemporary with the Folbigg deaths, reveal a very different picture:

(i) The median age was 39 weeks - considerably later than that for SIDS - and much later than the 8 weeks quoted in the reference 64 (Horne).

(ii) Contrary to Professor Horne's comment, in the study the recognised "SIDS - risk factors" were present (exposure to passive smoking 62% (control 16%); male sex predominant (77% compared to 52%); immunisation status 42% (control 80%); low socioeconomic status 36% (control 8%).

(iii) A major observation is that compared to the control population in the study, there was a family history of SIDS in 15% of ALTE cases (P = 0.03).

(iv) The critical laboratory finding of relevance to the question of SIDS/ALTE relationship is the significant hyperimmune mucosal response common only to SIDS and ALTE and the increased mucosal permeability (i.e. leaky mucosa). ALTE cases contain several entities (as shown in this study) and which Horne discusses. However, when those that most resemble SIDS (i.e. infection – initiated) are compared with controls, the saliva IgA (i.e. the unique mucosal surrogate immunoglobulin) was 15 times higher (as found in the SIDS study, but not in any other situation) (Table 5). That is very impressive – it is rare in complex biological systems to have that clarity.

(v) For the first time the important risk factor of exposure to smoke has been given a mechanism (i.e. significantly higher IgA levels in those exposed to smoke – a powerful support for the linkage between ALTE's and SIDS).

Specific comment on Prof Horne's review re ALTE

(a) Evidence that SIDS and ALTE are not related:

The quoted studies point to the heterogeneity of ALTE and the remarkable thing is the extraordinary variation in subject selection. Most are vague and reviews are of retrospective analyses with limited patient information. The difficulty has been that there has not before been a diagnostic test that allows identification of a more homogeneous group. That is now available and detailed in the Hunter Region study (Gleeson *et al* 2004). The central

importance of this latter study is that it is a prospective study, using all investigational tools - and reflects exactly what is seen in the Hunter Region at the time of Patrick's episode of ALTE (range of age of ALTE's: 18-235 days; Patrick's ALTE (approx) 120 days). Thus, the age of Patrick's ALTE is in the middle of documented Hunter Region ALTE's at around the same time as his death.

[redacted] A reasonable explanation could include a shift towards ALTE's as sleeping posture/removal from smoke etc reduces SIDS, so that less fatal (i.e. milder) ALTE's occur, i.e. the preventative methods such as sleep posture, prevent a terminal outcome, but does NOT prevent the essential trigger i.e. a mild infection at the time of great mucosal/immune instability (genetically influenced). [redacted] However, given that the SIDS subjects as a group tend to have some impairment of arousal (where ALTE's may not - and that was the case in the Gleeson study as sleep studies were done) then a logical explanation is that the outcome of an apnoeic episode is influenced by how well (via arousal) the subject responds, and that immaturity of breathing control can contribute to whether an infant dies or arouses. There is no magical explanation for most ALTE's occurring in the daytime - that is when they would be observed and resuscitated. A self-limited ALTE would be missed at night (as many seem to be, as they are missed at night). The mortality of those suffering

from an ALTE is about 1% (from Horne's quotations) with most of those having "a medical problem." That was the case with Patrick (who had multiple cerebral infarcts). It is again hardly surprising that ALTE's uncommonly go onto SIDS, as after an ALTE has been recognised and identified by treating medical practitioners, the infant would be obsessively monitored and managed (e.g. sleep posture) and of course are moving out of the age - danger zone for infection-initiated apnoea. This would provide a statistical distortion in the studies.

I should add, none of the ALTE's were found prone, reflecting 'best practice' maternal management. As indicated this may well have been a factor in preventing the infant from being SIDS, rather than an ALTE.

(b) Multiple SIDS:

Professor Horne covers data related to this, including a paper by Hill (2004) where 9 families have 3 infant deaths. Overall, about 1% of families with SIDS will have a second case. It is likely that genetic factors are involved and isolated reports suggest some genetic influences are powerful indeed (Diamond 1986). The problem in identifying genetic factors at the moment is that all that can be done is to scan genomes and look for variations in genes that influence factors that may or may not have a pathogenic role (e.g. cytokines). Any such data has little more value than 'interesting'. Valuable genetic markers will only become available when specific components of a pathogenic pathway are clearly identified (e.g. delayed regulation of mucosal IgA response) through further research. The significant family history data in the Hunter Valley study not only connects SIDS and ALTE's, but adds considerably to our understanding of intra-family genetics.

Comments Re Transcript Provided from 18/3/19

16. Page 26. I agree that a 'Triple Risk Model" (developed in the 1990's) is helpful, but needs to be updated to include current data. In my opinion, current evidence would have as a primary cause in half of the population of sudden death infants a mild intercurrent airways infection at a critical time of immaturity of the local mucosal immune response leading to an inappropriate excessive immune response - leaving the airways paresed and unable to clear bacteria that descend all the time from the upper airways. Apnoea results from this inflammatory response and/or toxins produced by the colonising bacteria. As the breathing control is also at a stage of immaturity (as Professor Horne's sets out in her report) outcome is influenced by how effective 'arousal' is. This in part explains differences between SIDS and ALTE's, i.e. in ALTE, 'arousal' is more effective. This model 'fits' all the risk factors discussed (see also my earlier comments) and all the facts found by research study, and is well accommodated by an updated 'Triple Risk Model'. Chapter 30 of Duncan and Byard's book demonstrates the revised Triple Risk Model based on scientific advances in the

understanding of the role of infection.

Page 27. Professor Elder's comment in relation to regional differences in SIDS and ALTE's is very interesting - I have not understood the very clear differences between the early age of ALTE's in a large retrospective study (The Utah Study) and the Hunter Region study which was prospective and very detailed, showing ALTE's occurred in significantly older children. It may be that in Utah, they were looking at a different group of infants with less defined breathing disorders. I have pointed out above that the Hunter Region study has particular relevance to Patrick, whose ALTE fitted neatly into that study group (where his ALTE was at 4 months).

Page 32. One has to be careful not to use recent epidemiological data to assess conditions in the 1990's - note for example that 15% of ALTE cases (early 2000's) had a close relative that died from SIDS, and was statistically significant (p=0.03) when compared with normal controls.

The data regarding three or more SIDS in a family is well known e.g. a paper quoted by Prof Horne includes 9 such families. The Professor refers to this a 'non-scientific paper' in downplaying the paper's significance. I simply do not agree. A case report of an unusual medical issue is very important. Whether such a paper would or "would not be accepted today" for publication does not detract from the value of this case report. Such a paper written today would easily be accepted in quality journals for publication as a clinical scientific contribution to the literature.

[redacted]

[redacted]

Page 37. Sarah: a sleep study showed "a small handful of apnoeas" - in retrospect, as a clinician I wonder if these would be accepted as "normal for age" by present day experts, given the fact that she subsequently died of SIDS. This outside my area of expertise, but I note that it is not commented by any appropriate expert of which I am aware.

Page 38. Sarah: her pre-SIDS infection - though mild - was treated with antibiotics so was significant. Prof Horne is correct in that it would not be severe enough to directly cause her death, but it would be exactly the kind of infection that the Hunter Region group has shown causes the profound and abnormal immune reactions of SIDS and ALTE's.

Page 40. Laura: Professor Elder states that SIDS-like death in her experience can occur in children with recent viral infection. [redacted] deaths have in fact been documented at post mortem to be clinically unrecognised myocarditis (e.g. JAMA 203 (1968) 1-8). I note that Laura had an airways infection at the time and the post mortem showed a lymphocytic myocarditis (the pathology of a viral myocarditis). Almost certainly, in my opinion, she had a coxsackie, adenovirus or similar viral infection. In my opinion as a clinical immunologist it is most likely she died from a complicating arrhythmia.

Page 45. Professor Elder is correct about smoking and its effect in utero, but as seen in the Hunter Region study, exposure to smoking post birth has been linked to an impact on an

immature mucosal immune system.

Page 48. Current ideas re infection and immunity are not a "theory." A theory is an idea that is untested. In the case of mild infection leading to disturbed immunity in a genetically-influenced immature mucosa, this moved from being a theory to a probable reality with the accumulation of data that has been summarized elsewhere in my report. There is now a clear pathway that operates in SIDS/ALTE's from the Hunter Region studies and those of many other studies, many of which are referenced above that substantially supports mild infections triggering a pathogenic dysregulated immune response that leads to SIDS in some cases. It remains to be determined how many of each are caused by this mechanism, though current evidence suggests that such a trigger operates in at least half of the cases.

Page 51. Professor Horne expresses more confidence than would I, that genome-wide testing would identify a "subtle abnormality". Without a target phenotype, you would need to be very lucky to establish a single genotype with a link to sudden infant death in my opinion.

Page 52.

The scientific hypothesis linking infection to ALTE's and SIDS is just that, a scientific hypothesis. However, that hypothesis becomes substantiated when it is tested and supported by data, which it is. The developments in the last decade have established a significant link, which is matched by the clinical history of half (at least) of the sudden death fatalities.

[redacted]

Page 54. I have commented on the Utah study elsewhere.

Review of Chapter 30 of Byard and Duncan 2018 "SIDS Sudden Infant and Early Childhood Death: The past, the present and the future"

17. Although not specifically asked by Counsel Assisting to review the above, I consider it important to do so in order to understanding current thinking around the role of cytokine response and infection. It is from a well-accepted statement on current ideas and thinking in SIDS and has been referenced in evidence by Professor Horne.

18. This book chapter, in my opinion, correctly identifies 'mild infection' as a trigger for a probable cause of SIDS. It provides clarity with respect to how mild infection can cause an inappropriate inflammatory response (which was clearly identified in our prospective study of SIDS and ALTE's, see the Hunter Region study attached to my first report).

19. The above mentioned chapter includes a comprehensive review of genetic studies of cytokines (known to be mediators in the inflammatory response). The chapter looks at SNP's (i.e. isolated base mutations) of a range of cytokines such as IL-6, TNFα, IL-10 etc. It is evident from that chapter that no significant abnormality has been found. This is not surprising as cytokines are only mediating an abnormal immune response without

themselves necessarily being responsible for it. This is not to say that a disturbed genetic change in a particular cytokine may not be contributing to the inflammatory response, once a more targeted approach is used to identify specific genetic loci.

a. By way of analogy: If you know there is a particular flathead fish in Sydney Harbor where there is a proximate adjoining sewer outlet that is delivering hepatitis virus into the water, and that fish contracts the virus, you are most unlikely to catch that specific fish by randomly throwing in a line into Sydney Harbour. This is similar to attempting to find a cytokine genotype specific for SIDS without knowing where it likely may be. Knowledge of the driving force behind the cytokine change is required.

b. The term "genomic wide studies" will catch every fish in the Harbour but without necessarily knowing which fish has the hepatitis. It becomes problematic to take this approach when you are uncertain about the correct location of the underlying problem.

20. In my opinion based on my clinical and laboratory expertise, I have no confidence that any of the genetic studies of cytokines or genome wide studies will provide a single cytokine with respect to resolving questions about the deaths in the Folbigg family. Focus on complicated laboratory studies easily detracts from the strong clinical data about genetic relationships involving SIDS and ALTE's, which have a direct relationship to the Folbigg case. This is not to say that genetic factors are not centrally important, but rather, the technologies utilised are little more than a fishing expedition at this stage. This is an area of major technological advance, and large research efforts, and I have no doubt that further scientific studies will

further refine the area of investigation, and may provide greater understanding and clarity in future.

Professor Robert Clancy

27 March 2019