Coalition of Alcohol and Drug Educators

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Cannabis Debates and Cannabis Debacles:

Part 1:

Serious Downstream Implications of Cannabis Neurotoxicity and Genotoxicity

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Public education on cannabis is obviously paramount. Cannabis disinformation is our greatest threat.

CANNABIS DEBATES AND CANNABIS DEBACLES: SERIOUS DOWNSTREAM IMPLICATIONS OF CANNABIS NEUROTOXICITY AND GENOTOXICITY

THE PIECE BY DR GODLEE REMINDS US ON THE ONE HAND THAT WEIGHTY DECISIONS ARE BEING MADE ON THE BASIS OF FLAWED AND INCOMPLETE EVIDENCE AND ON THE OTHER THAT MUCH OF WHAT WE HAVE SEEN TILL NOW IN RELATION TO THE EPIDEMIOLOGY OF CANNABIS HAS OCCURRED IN A LOW CANNABIS USE ENVIRONMENT, A PROTECTED SITUATION WHICH IS DIRECTLY DUE TO CANNABIS'S HITHERTO ILLEGAL STATUS, WHICH BEARS LITTLE RESEMBLANCE TO THE HIGH-USE HIGH-POTENCY PRODUCTS AND CONSUMPTION PATTERNS WHICH ARE PRESENTLY EMERGING ON BOTH SIDES OF THE 49TH PARALLEL IN NORTH AMERICA.

Our research group has taken a novel approach which looks for correlates at the population health level of findings which have been made in important and repeated epidemiological studies. As shown below numerous and emphatic confirmations of such laboratory and study findings in relation to cannabis have been found at the population health level. Such repeated confirmations imply careful pause at the national and international policy level.

The 2019 World Drug Report from the United Nations office of Drugs and Crime demonstrates in detail that the presently emerging cannabis epidemic in USA is one of increased intensity of use more than increased numbers of users. The National Survey of Drug Use and Health (NSDUH) shows a rise in lifetime use of cannabis 2006-2017 of 9% compared to an 80% rise in those using cannabis daily or almost daily. When combined with the high potency forms of cannabis and hashish oil presently widely available in North America, this portends a tsunami of serious downstream sequelae. Most published cannabis epidemiology is only marginally relevant to this new high-use high-potency era.

NSDUH quantifies several parameters of mental health including any mental illness, serious mental illness and suicidal thinking against national drug use across both time and space. Close temporospatial association has been demonstrated in unpublished explorations of all three indices with cannabis use and cannabinoid exposure. Such findings confirm at the level of population health the many published studies linking cannabis consumption to numerous measures of serious mental health outcomes including depression, bipolar disorder, anxiety and schizophrenia.

It was recently shown that the autism epidemic in USA is rising exponentially related to the increased use of cannabis whilst the use of most other drugs has fallen (NSDUH) and that the incidence of autism is predicted to be 60% higher in cannabis liberal states than states where cannabis is not legal by 2030[1,2]. Such findings imply that the adverse mental health outcomes well described in adults are even more serious in children and confirm epidemiologically the many experimental studies showing interference with brain development by multiple pathways. Such children will likely never have the opportunity to develop normally – as they never were.

Colorado is known as one of the US leaders in cannabis liberalization. It is less well known that an extra 11,753-20,152 major congenital abnormalities occurred din Colorado from 2000-2014 (depending on whether one uses the September 2018 Colorado birth defects data or the October 2018 data), and particularly features 104% rise in spina bifida, 71% rise in microcephalus and 123% rise in atrial septal defect, 45% rise in all cardiovascular defects, 35% rise in major central nervous system defects and 34% rise in

chromosomal anomalies including a 25% rise in Down's syndrome [3]. Indeed the emergence of very elevated rates of atrial septal defect in Kentucky, Colorado, Hawaii and many US cannabis-liberal states suggests the emergence of yet another cannabis related congenital defect (CDC data). This in turn suggests our presently described list of over 20 cannabis-associated birth defects is itself incomplete and likely to expand dramatically in coming years.

All seven studies to examine the relationship between cannabis use and gastroschisis have been positive with an odds ratio of about 3.0 [4]. A recent important CDC study documented impressive racial differences in gastroschisis incidence [5]. If one assigns the baseline incidence of gastroschisis in children of African-American teenager mothers (9.0/100,000 live births) to unity, then the incidence of gastroschisis in infants born to non-Hispanic white mothers is twice as common (17.1) and in American Indian / Alaska Natives is three times as common (26.0). These relativities disappeared quickly at older maternal ages consistent with a differential environmental teenage exposure rather than a truly genetic explanation. These changes directly parallel the historical rates of teenage cannabis use in these racial groups as quantified by the Youth Risk Behaviour Survey, the Monitoring the Future Survey and the National Longitudinal Alcohol Survey in USA. A mechanism was recently described whereby interference in late gestational uterine blood flow around the time of birth can cause preeclampsia in the mother and other external sequalae [6].

Cannabis use in parents has been previously linked with childhood leukaemias and sarcomas which are some of the major cancers of childhood [7]. Unsurprisingly then one notes a 52% rise in all childhood cancer from 1975-2017 based in CDC Surveillance Epidemiology and End Results (SEER) data. As noted above the use of other drugs has fallen across this time. Cannabis has been shown to be reproductively toxic by many routes including interfering with cell division and mitosis and damaging to many parts of the epigenomic machinery [8 9]. Indeed the presence of DNA fragments in the cytoplasm has been shown to be potently stimulating to the innate immune system in a cell autonomous manner which in turn damages the genome. This explains the frequently cited increase in the degree of malignancy of cannabis related cancers, and their occurrence in much younger patients, which were previously not understood. Again the rates of all pediatric cancer in African-Americans is about 60% that occurring in Americans of Caucasian heritage, which again parallels lower rates and lower intensity of cannabis use in African-American communities – a situation which is presently in a state of flux.

Four of four studies examining the relationship between testicular cancer and cannabis use have all been strongly positive with an odds ratio of around 3 [7 10]. Unsurprisingly there has been a 66% rise in the rate of all-age testicular cancer from 3.8 to 6.3 cases /100,000 (CDC SEER Data).

Dr Godlee's call to watch carefully the unfolding milieu in North America is timely and salient. However we need to do so with open eyes and carefully and impartially evaluate what we are really seeing judged against the important metrics of earlier eras when cannabis use was less prevalent. Detailed and sophisticated space-time investigations are required. We find it paradoxical – and probably unjustifiable – that at a time when scientific knowledge is so advanced and epidemiological methods are so complex that confusion reigns supreme in this area and the field is overripe with disinformation.

We welcome the call for continued careful surveillance but feel that while so many concerning findings continue to be uncovered studious caution is the only responsible approach. Sophisticated spatial geostatistical investigations are urgently mandated.

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Cannabis Debates and Cannabis Debacles:

Part 2:

Oocytes: Non-renewable National Genomic Resource – and Prostacyclin Rules

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CANNABIS DEBATES AND CANNABIS DEBACLES: CANNABIS DAMAGES OOCYTES A NON-RENEWABLE NATIONAL GENOMIC RESOURCE – AND PROSTACYCLIN RULES

MY CLINIC IN AUSTRALIA IS CONNECTED WITH DOZENS AND DOZENS OF CHILDREN AT VARIOUS POINTS ON THE AUTISTIC DISORDER SPECTRUM (ASD). THIS WOULD NOT BE UNUSUAL IN A PEDIATRIC NEUROLOGY CLINIC OR IN A CLINIC SPECIALIZING IN THE TREATMENT OF SUCH CHILDREN.

What is unusual about my clinic is that I we have a special interest in the treatment of drug dependency syndromes. Oddly, with some recent exceptions [10-13] the literature on the relationship of drug exposure to the development of subsequent autism is relatively sparse. Whilst no drugs are good for neonatal brain development, tobacco, alcohol, opioids and cannabinoids are known to negatively impact brain development with long term outcomes consistent with many features of the ASD spectrum. Cocaine is not a factor in Australia as its use in our parts is rare. Cannabis use is holoendemic amongst our drug dependent patients with lifetime use rates of over 95%.

One of my cases concerns me very greatly. A lady of 25 years of age vehemently describes and insists that she smoked only a couple of cones of cannabis per week for two years. She was not using other drugs at this time in her life. Two years after complete cessation of all drugs except tobacco she gave birth to a child, now five years old, who obviously has several features of autism. Why?? What mechanism could exist which two years later could impact brain development to such an extent at a time when cannabinoids themselves must have long left her system? What would be the population implications of such a case rolled out across a nation? Could such a process underlie the present exponential growth in ASD cases across USA and in many places in the developed world [10 12]?

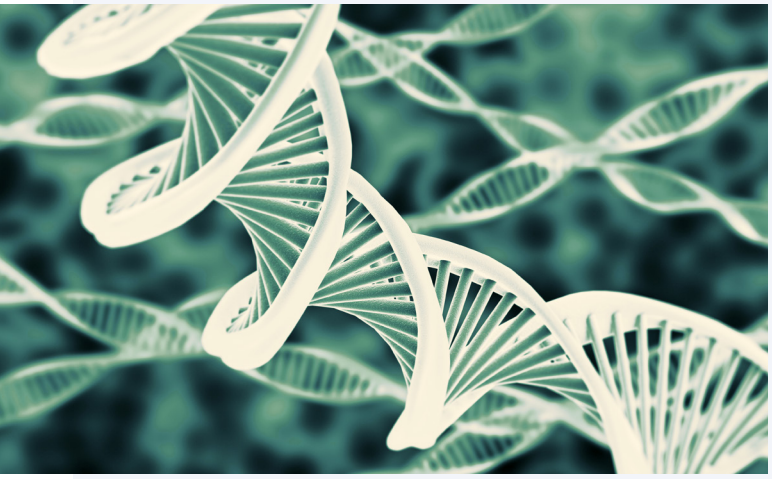
The classical experiments of Morishima reported by NIDA in 1984 leave very little to the imagination in relation to the genotoxic effects of cannabis on developing oocytes. Morishima showed that 20% of oocytes were lost after just the first cell division following cannabis exposure, and the news got worse in subsequent divisions [14]. Apparently the oocytes were not able to cope with the genotoxic stress induced by cannabis exposure. Cannabis is known to induce DNA damage by several mechanisms including

damage to chromosomes at the time of cell division, dramatic reductions in histone formation which form the core of the nucleosomes around which DNA is twined and are crucially involved in signalling to the transcription and epigenetic machinery to regulate gene expression, alteration of DNA methylation and many other processes [15-19]. And genotoxic stress of many types is known to trigger DNA checkpoints and interfere with the normal process of meiotic and mitotic cell division; and are also known to trigger ageing and cellular senescence pathways.

The implications of stimulated senescence in human gametes have not been clearly thought out.

A momentary consideration of the differing biology of gametic reproduction in the two sexes is pertinent. Every medical student is taught that infant females are born with 1,000,000 oocytes in their ovaries, a number which falls to 400,000 by the time of menarche and she loses 20-50 with each menstrual cycle until ovarian exhaustion some time before menopause.

This monotonic decline in the oocyte pool caused by their non-replacement directly implies that any genotoxic damage suffered by the developing oocyte would be FIXED in place, and just as we learned through studying mechanisms of chromothripsis and epigenomics, any cells not fatally damaged – which many would be - could pass on these effects to subsequent cell divisions, and potentially the developing embryo. In males the biology is very different, with 1500 sperm formed each second and an estimated 3 million million over a 60 year reproductive lifetime. Genotoxic damage sustained by males [17 20] would therefore have to be passed on by mechanisms involving cell division – of which there are many including chromosomal fragmentation, oxyradical DNA adduct formation particularly of the base guanine, and extensive DNA methylation and epigenomic damage of many types.



Can oocytes repair DNA damage? The answer to this question is not straightforward. It was classically taught that human oocytes have deficient DNA repair mechanisms related to the dramatically reduced availability of DNA repair proteins in contrast to oocytes of other species such as mice and monkeys [21-24]. If so this implies that genomic damage would necessarily be passed along. However more recent studies suggest that oocytes have more DNA repair capacity that previously thought [25]. However by analogy with epigenomic and chromothripsis studies it seems most unlikely that human oocytes can completely repair their genomic / epigenomic damage particularly in the context of Morishima's work demonstrating extensive and severe genotoxicity, chromosomal bridging, chromoplexy and obvious macroscopic chromosomal damage.

Such considerations lead to the appalling conclusion that oocytes suffering the very considerable genotoxic / epigenotoxic damage imposed by cannabinoids – including cannabidiol [20] – can be irreversibly damaged and some of these damaged gametes will pass their genetically scrambled misinformation to subsequent embryos. Similar considerations apply to males albeit by well described mechanistic pathways which include cell division.

In this sense oocytes in particular can be conceptualized as a non-renewable genomic resource, and a key component of our national gene-environmental interactive heritage.

One of the less appreciated findings of the stunning paper on the genotoxic effects of cannabis on mice and humans sperm by Murphy et. al. was the finding that cannabis exposure in both species reduces prostacyclin by epigenetic mechanisms [17]. The thromboxane – prostacyclin axis has been known for several decades to control the balance between vasoconstriction and platelet adhesiveness on the one hand and vasodilatation and platelet disaggregation on the other. Both are highly potent agents active at the nanomolar level and tightly control vasomotor tone and the coagulation state or "stickiness" of the blood. Prostacyclin is a key vasodilator and regulator of microvascular integrity. It is known to have a powerful and potent effect on maintaining the patency of vessels of sub-millimeter diameter.

Dr Nora Volkow, Director of NIDA has expounded on the links between cannabis use and the cardiovascular disorders of myocardial infarction and stroke in adults [26 27]. Cannabinoids acting via type 1 cannabinoid receptors (CB1R's), the dominant cannabinoid receptor in the body, have been shown to strongly induce proinflammatory including arteritic states [28 29]. Cannabis has also been shown to upregulate thromboxane at the proteomic level [30]. The recent demonstration that cannabis epigenetically suppresses prostacyclin production offers a further major mechanistic basis for cannabinoid vasotoxicity. It also establishes a major point of cross-talk between cannabinoid and prostaglandin proinflammatory signalling which is clinically relevant.

This becomes of clinical significance when the association of cannabis with gastroschisis and multiple other cardiovascular disorders is considered [19 31-35].

The links between maternal cannabis use and gastroschisis have been described elsewhere [19 33-35]. Fascinatingly geographical microclusters of gastroschisis in Canada, California and Australia have also been described [36-39] suggesting that some environmental exposure is occurring within a tight geographical radius which is damaging foetal development. Gastroschisis is increasingly believed to be due to a vascular accident in the development of the anterior abdominal wall which interferes with its growth and closure. Whether these geographically confined epicentres relate to local cannabis dealerships has not been definitively geospatially demonstrated in Canada and California, but the possibility seems particularly intriguing. The Australian gastroschisis outbreak was first noted in 2011 and continues to occur ongoing in the national epicentre of our cannabis industry the Northern Rivers area of New South Wales.

If cannabis is linked with both vasospasm and a thrombogenic state then the fate of embryonic anterior abdominal wall closure, which normally occurs about the tenth or twelfth week of foetal development, would seem to be inevitably imperiled.

Epigenomic damage is believed to be inheritable for three to four generations, or about the next hundred years. Such considerations take the cannabis debate out of the arena of civil liberties and place it firmly in the field of gene-environmental impact and national genomic heritage.

Were cannabis to be linked just with mental illness, just with autistic spectrum disorder, just with 28 congenital defects or just with a 50% rise in TOTAL pediatric cancers then there should be no debate on any measures which increase its use, access or availability. That it has been linked with all four areas, in the context of its many other known harms – respiratory, driving, impaired developmental trajectory, reduction in IQ, hippocampal shrinkage, brain disconnection and immunopathies - implies directly that the cannabis legalization debate itself is non-viable and profoundly and inherently misleading.

What is required is improved public education to dispel the widespread myths, and set the truth at liberty and give it legs to set the world's people free wherever they reside in the beautiful way the truth has always done. Can we rise to the challenge??

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Can we rise to the challenge??”

REFERENCES - PART 1.

1. Reece A. S., Hulse G.K. Effect of Cannabis Legalization on US Autism Incidence and Medium Term Projections. *Clinical Pediatrics: Open Access* 2019;4(2):In Press. doi: DOI: 10.24105/2572-0775.4.154 . [published Online First: May 3rd 2019]

2. Reece A. S., Hulse G.K. Epidemiological Associations of Various Substances and Multiple Cannabinoids with Autism in USA. *Clinical Pediatrics: Open Access* 2019;4(2):In Press. doi: 10.24105/2572-0775.4.155 [published Online First: May 3rd 2019]

3. Reece A. S., Husle G.K. Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends *Clinical Pediatrics* 2019;In Press

4. Reece A. S., Hulse G.K. Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends *Clinical Pediatrics* 2019;In Press

5. Short TD, Stallings EB, Isenburg J, et al. Gastroschisis Trends and Ecologic Link to Opioid Prescription Rates - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2019;68(2):31-36. doi: 10.15585/mmwr.mm6802a2

6. Robertson SA. Preventing Preeclampsia by Silencing Soluble Flt-1? *N Engl J Med* 2019;380(11):1080-82. doi: 10.1056/NEJMcibr1817501

7. Reece A.S. Chronic Toxicology of Cannabis. *Clinical Toxicology* 2009;In Press(Accepted 28/05/09.)

8. Reece AS, Hulse G.K. Impacts of Cannabinoid Epigenetics on Human Development: Reflections on Murphy et. al. "Cannabinoid Exposure and Altered DNA Methylation in Rat and Human Sperm" *Epigenetics* 2018; 13: 1208-1221. Epigenetics 2019;In Press

9. Reece AS, Hulse GK. Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity. *Mutat Res* 2016;789:15-25. doi: 10.1016/j.mrfmmm.2016.05.002

10. Reece A. S., Hulse G.K. Explaining Contemporary Patterns of Cannabis Teratology. *Clinical Pediatrics* 2019;4(1):1000146. doi: 10.4172/2572-0775.1000146 [published Online First: 20th February 2019]

Published on https://www.bmj.com/content/366/bmj.l4507/rapid-responses

REFERENCES - PART 2.

11. Reece A. S., Hulse G.K. Effect of Cannabis Legalization on US Autism Incidence and Medium Term Projections. *Clinical Pediatrics: Open Access* 2019;4(2):In Press. doi: DOI: 10.24105/2572-0775.4.154 . [published Online First: May 3rd 2019]

12. Reece A. S., Hulse G.K. Epidemiological Associations of Various Substances and Multiple Cannabinoids with Autism in USA. *Clinical Pediatrics: Open Access* 2019;4(2):In Press. doi: 10.24105/2572-0775.4.155 [published Online First: May 3rd 2019]

13. Reece A.S., Hulse G.K. Gastroschisis and Autism: Dual Canaries in the Californian Coal Mine. *JAMA 2019*;In Press [published Online First: 2019]

14. Morishima A. Effects of cannabis and natural cannabinoids on chromosomes and ova. *NIDA Res Monogr* 1984;44:25-45.

15. Tahir SK, Zimmerman AM. Influence of marihuana on cellular structures and biochemical activities. *Pharmacology, biochemistry, and behavior* 1991;40(3):617-23.

16. Tilak SK, Zimmerman AM. Effects of cannabinoids on macromolecular synthesis in isolated spermatogenic cells. *Pharmacology* 1984;29(6):343-50. [published Online First: 1984/01/01]

17. Murphy SK, Itchon-Ramos N, Visco Z, et al. Cannabinoid exposure and altered DNA methylation in rat and human sperm. *Epigenetics* 2018 doi: 10.1080/15592294.2018.1554521

18. Reece A. S., Husle G.K. Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends *Clinical Pediatrics* 2019;In Press

19. Reece AS, Hulse GK. Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity. *Mutat Res* 2016;789:15-25. doi: 10.1016/j.mrfmmm.2016.05.002

20. Russo C, Ferk F, Misik M, et al. Low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) cause DNA damage and chromosomal aberrations in human-derived cells. *Archives of toxicology* 2018 doi: 10.1007/s00204-018-2322-9

21. Mihalas BP, Redgrove KA, McLaughlin EA, et al. Molecular Mechanisms Responsible for Increased Vulnerability of the Ageing Oocyte to Oxidative Damage. *Oxid Med Cell Longev* 2017;2017:4015874. doi: 10.1155/2017/4015874

22. Feng R, Sang Q, Kuang Y, et al. Mutations in TUBB8 and Human Oocyte Meiotic Arrest. *New England Journal of Medicine* 2016;374(3):223-32. doi: doi:10.1056/NEJMoa1510791

23. Pfender S, Kuznetsov V, Pasternak M, et al. Live imaging RNAi screen reveals genes essential for meiosis in mammalian oocytes. *Nature* 2015;524(7564):239-42. doi: 10.1038/nature14568

24. Wang X, Liu D, He D, et al. Transcriptome analyses of rhesus monkey preimplantation embryos reveal a reduced capacity for DNA double-strand break repair in primate oocytes and early embryos. *Genome Res* 2017;27(4):567-79. doi: 10.1101/gr.198044.115

25. Stringer JM, Winship A, Liew SH, et al. The capacity of oocytes for DNA repair. *Cell Mol Life Sci* 2018;75(15):2777-92. doi: 10.1007/s00018-018-2833-9

26. Volkow ND, Baler RD, Compton WM, et al. Adverse Health Effects of Marijuana Use. *New England Journal of Medicine* 2014;370(23):2219-27. doi: doi:10.1056/NEJMra1402309

27. Volkow ND, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med* 2014;371(9):879. doi: 10.1056/NEJMc1407928

28. Menahem S. Cardiovascular Effects of Cannabis Usage. In: V.R. P, ed. Handbook of Cannabis and Related Pathologies: Biology, Pharmacology and Treatment. New York: Academic Press 2017:481-85.

29. Pacher P, Steffens S, Hasko G, et al. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol* 2018;15(3):151-66. doi: 10.1038/nrcardio.2017.130

30. Wang J, Yuan W, Li MD. Genes and pathways co-associated with the exposure to multiple drugs of abuse, including alcohol, amphetamine/methamphetamine, cocaine, marijuana, morphine, and/or nicotine: a review of proteomics analyses. *Molecular neurobiology* 2011;44(3):269-86. doi: 10.1007/s12035-011-8202-4

31. Reece A. S., Hulse G.K. Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends *Clinical Pediatrics* 2019;In Press

32. Reece AS, Hulse G.K. Impacts of Cannabinoid Epigenetics on Human Development: Reflections on Murphy et. al. "Cannabinoid Exposure and Altered DNA Methylation in Rat and Human Sperm" *Epigenetics* 2018; 13: 1208-1221. Epigenetics 2019;In Press

33. Reece A.S. Chronic Toxicology of Cannabis. *Clinical Toxicology* 2009;In Press(Accepted 28/05/09.)

34. Reece AS. Known Cannabis Teratogenicity Needs to be Carefully Considered. *British Medical Journal* 2018;362:k3357. [published Online First: 4th August 2018]

35. Reece AS, Norman A, Hulse GK. Cannabis exposure as an interactive cardiovascular risk factor and accelerant of organismal ageing: a longitudinal study. *BMJ Open* 2016;6(11):e011891. doi: 10.1136/bmjopen-2016-011891

36. Anderson JE, Cheng Y, Stephenson JT, et al. Incidence of gastroschisis in california. *JAMA Surgery* 2018 doi: 10.1001/jamasurg.2018.1744

37. Bassil KL, Yang J, Arbour L, et al. Spatial variability of gastroschisis in Canada, 2006-2011: An exploratory analysis. *Canadian journal of public health* 2016;107(1):e62-7. doi: 10.17269/cjph.107.5084

38. McMillan M. Birth Defects Exceed NSW Average. Northern Star Newspaper, 3rd June 2011. Lismore: Northern Star, 2011.

39. Expert Review Panel Appointed to New South Wales Health. Review of Gastroschisis on the NSW North Coast. In: From New South Wales Health Department Center for Record Linkage DC, Dr Lee Taylor, ltayl@doh.health.nsw.gov.au „ ed. Sydney: New South Wales Health Department, , 2011:1-11.

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