IN THE CORONERS COURT
OF VICTORIA
AT MELBOURNE

Court Reference: COR 2015 4937

FINDING INTO DEATH WITHOUT INQUEST

Form 38 Rule 60(2)
Section 67 of the Coroners Act 2008

Findings of:	Paresa Antoniadis Spanos, Coroner
Deceased:	Graeme Harold Griffiths
Date of birth:	26 February 1950
Date of death:	26 August 2015
Cause of death:	Severe neurtropenic sepsis and multi-organ failure secondary to severe mucositis and probable DPD deficiency in the setting of T3 rectal carcinoma
Place of death:	Frankston

I, PARESA ANTONIADIS SPANOS, Coroner,

having investigated the death of GRAEME HAROLD GRIFFITHS without holding an inquest:

find that the identity of the deceased was GRAEME HAROLD GRIFFITHS

born on 26 February 1950

and that the death occurred on 26 August 2015

at Peninsula Private Hospital, 525 McClelland Drive, Frankston, Victoria 3199

from:

I (a) SEVERE NEUTROPENIC SEPSIS, MULTI-ORGAN FAILURE

I (b) SEVERE MUCOSITIS, PROBABLE DPD DEFICIENCY

I (c) T3 RECTAL CARCINOMA

Pursuant to section 67(1) of the **Coroners Act 2008**, I make findings with respect to **the following circumstances**:

1. Mr Griffiths was a 65-year-old retired banker specialising in insolvency who was living with his wife of 16 years, Doris, in Portsea at the time of his death. He was a keen sailor, diver and fisherman. Prior to being diagnosed with cancer, Mr Griffiths was fit and healthy and had had no major illnesses.

DIAGNOSIS OF RECTAL CARCINOMA & PLANNED TREATMENT

2. In July 2015, Mr Griffiths undertook a routine faecal occult blood test which returned an abnormal result. His general practitioner, Dr Adrian Murrie of Sorrento Medical Clinic, provided a referral for a colonoscopy which, once conducted, found evidence of an invasive, moderately-differentiated colorectal adenocarcinoma (rectal lesion).

3. On 22 July 2015, Mr Griffiths and his wife consulted colorectal surgeon Eric Torey for an opinion about treatment options. While Mr Torey was initially hopeful that the lesion was detected early and would therefore not require pre-operative chemotherapy treatment, a rectal MRI performed that afternoon showed that the lesion was present in the rectum and had invaded the bowel wall and into adjoining lymph nodes. The lesion was therefore graded as a Stage 3 (T3N2M0)[1] locally advanced rectal cancer. Mr Griffiths was referred to medical oncologist Dr Simone Steel.

4. On 3 August 2015, Mr Griffiths and his wife consulted Dr Steel. Mr Griffiths reported being in good health generally, although he admitted that in the past he had had intermittent perirectal bleeding which was not associated with other symptoms such as obstruction or pain,

[1] The American Joint Committee on Cancer's 'Cancer Staging System' defines rectal cancer by the extent of tumour spread through the wall of the bowel (T stage), spread to local and regional lymph nodes (N stage) and spread to other organs (M stage).

and there was no family history of malignancy. Dr Steel conducted a complete CT chest, abdomen and pelvis scan which did not detect distant metastases.

5. According to Dr Steel, she had a long discussion with Mr Griffiths and his wife about treatment options and the rationale for combined chemo-radiotherapy treatment that she ultimately recommended. Mr Griffiths agreed to take the chemotherapy agent, capecitabine[2] 1500mg twice daily, an oral form of the more commonly used intravenous 5 fluorouracil [5-FU].[3] Dr Steel provided information about the side effects[4] of chemotherapy, referred Mr Griffiths to radiation oncologist Dr Marcus Foo for an opinion on concurrent radiotherapy and made a plan to review him in three weeks to monitor his progress on chemotherapy and organise repeat blood tests.

6. On 10 August 2015, Mr Griffiths and his wife consulted Dr Foo, who discussed possible treatment options with them and concluded that long course preoperative pelvic chemo-radiotherapy would be of greatest benefit. A plan was made to treat Mr Griffiths with radiation together with capecitabine, which Mr Griffiths commenced on 12 August 2015.

CIRCUMSTANCES PROXIMATE TO DEATH

7. On 13 August 2015, Mr Griffiths woke up with nausea, lack of appetite and low energy levels. According to Mrs Griffiths, he also started experiencing back pain, which by the end of the day was quite debilitating.[5] Over the following two days, Mr Griffiths developed ulcers in his mouth and his back pain worsened. On or about 15 August 2015,[6] Mr Griffiths telephoned Dr Steel and advised her of these symptoms.[7] Mr Griffiths later consulted Dr Murrie who provided him with a prescription for Endone for pain relief.

8. On 19 August 2015, Mr Griffiths consulted radiation oncologist Dr Mario Guerreri as Dr Foo was unavailable. He complained of painful mucositis[8] and skin reactions. Dr Guerreri telephoned Dr Steel, who advised him that Mr Griffiths should cease taking capecitabine. He

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[2] Capecitabine is a pro-drug of 5-FU which is metabolised to 5-FU by the liver.
[3] 5-FU is a cytotoxic nucleoside analogue which when metabolized by normal and malignant cells, results in genetic damage leading to cell death. It is used to treat many forms of cancer, particularly gastrointestinal cancers.
[4] According to Mrs Griffiths, in this initial consultation Dr Steel mentioned some side effects, including a rare chance of heart attack, and provided her husband with a patient information sheet from the eviQ website which did not address potential fatal complications of taking capecitabine. However, in correspondence to the Coroners Prevention Unit dated 13 April 2016, Dr Steel asserted that she explained to Mr Griffiths and his wife the two rare side effects of capecitabine – coronary spasm and the possibility of harbouring an enzyme deficiency that made it difficult to metabolise the drug.
[5] Statement of Doris Griffiths, dated 16 May 2016.
[6] In correspondence to the Court from various parties, the date Mr Griffiths telephoned Dr Steel has been stated as varying between 15 and 17 August 2015.
[7] According to Mrs Griffiths, Dr Steel advised her husband to take Panadol or to see his general practitioner [GP] regarding the pain. However, in correspondence dated 23 September 2015, Dr Steel states that she offered Mr Griffiths an admission to PPH which he declined, preferring to see his GP instead.
[8] Painful inflammation and ulceration of the mucous membranes lining the digestive tract, usually as an adverse effect of chemotherapy and radiotherapy treatment for cancer.

was offered a hospital admission but declined because, according to Dr Steel, he did not feel sufficiently unwell and chose to remain an outpatient and continue radiotherapy. He was provided with advice on mouth care.

9. On 20 August 2015, Mr Griffiths presented to Dr Foo for radiation. According to Mrs Griffiths, by this time her husband had oozing ulcers around his mouth and tongue and found it difficult getting from the car to the clinic due to dwindling energy levels. Dr Foo, concerned by these symptoms, contacted Dr Steel and arranged for Mr Griffiths to be admitted to Peninsula Private Hospital [PPH] that evening.

10. On arrival at PPH, Mr Griffiths was assessed by the nursing team and gave a history of diarrhoea for the past four days and a loss of appetite and nausea for more than five days. He was considered medically stable and commenced on intravenous fluids, analgesia and mouth washes to prevent infection.

11. On 21 August 2015, Mr Griffiths was reviewed by Dr Steel. She observed him to be stable from a haemodynamic perspective, with no signs of infection or sepsis. A full blood examination showed a normal total white cell count and neutrophil count. As Mr Griffiths had grade three mucositis, he was continued on intravenous fluids and pain relief.

12. On 23 August 2015, locum oncologist Dr Katherine Geddes noted a decline in Mr Griffiths' white cell count. Later that day, his condition had declined further, presumably due to sepsis, and intravenous antibiotics were commenced in addition to granulocyte-colony stimulating factor [GCSF] to stimulate white cell growth. At about 7:00pm, Mr Griffiths was observed to have syncope and hypotension and was responding poorly to IV antibiotics. A Medical Emergency Team [MET] call was made and once he was stabilised he was transferred to the Intensive Care Unit [ICU] for ventilation, intubation and support of his blood pressure.

13. On 24 August 2015, Dr Steel reviewed Mr Griffiths again, noting that he most likely had a dipyrimidine dehydrogenase [DPD] deficiency[9] and was therefore unable to metabolise capecitabine. Her impression was that Mr Griffiths had enterocolitis[10] and neutropenic sepsis.[11]

14. Mr Griffiths continued to deteriorate despite antibiotic and GCSF treatment. When his abdomen became distended, he was taken to theatre for an exploratory laparotomy in an

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[9] DPD is an enzyme which is involved in the metabolism of uracil and thymine. It is also responsible for metabolising approximately 85% of administered 5-FU and capecitabine. The prevalence of DPD deficiency if thought to vary from 3-5% of the population having a partial loss of function to a prevalence of 0.2% of the population having a complete loss of function.

[10] Inflammation of the entire small and large intestines.

[11] Systemic infection (septicaemia) due to extremely low white cell count (secondary to chemotherapy).

attempt to identify the source of infection. Inter-operatively, one to two litres of fluid was drained but no pelvic abnormality was evident and the surgeon was unable to identify a perforation or other likely source of infection.

15. On 26 August 2015, Mr Griffiths was diagnosed with multi-organ failure. In light of his continued deterioration despite maximal support, discussions ensued between Mr Griffiths' family and his treating clinicians and the decision was made to withdraw active treatment. Mr Griffiths was treated palliatively thereafter and kept comfortable until he died at 11:20am.

16. ICU consultant Dr Sachin Gupta completed a death certificate and formulated the cause of Mr Griffiths' death as severe neutropenic sepsis, multi-organ failure in the setting of severe mucositis, and probable DPD deficiency and T3 rectal carcinoma.

REPORT OF MR GRIFFITHS' DEATH & THE CORONIAL INVESTIGATION

17. On 25 September 2015, Mrs Griffiths reported her husband's death to the Coroner and expressed concerns about the clinical management and care provided by Dr Steel and staff at Peninsula Private Hospital. As the report was received a month after Mr Griffiths' death, it was not possible for his body to be examined by a forensic pathologist at the Victorian Institute of Forensic Medicine and so the investigation of his death has not been informed by any forensic medical examination on the coroner's behalf.

18. Without doing justice to the anguish expressed by Mrs Griffiths at the death of her husband, the primary concerns she raised about his clinical management were that Dr Steel had not explained the potentially fatal consequences of DPD deficiency and failed to test Mr Griffiths for DPD deficiency prior to commencing him on capecitabine. Additionally, Mrs Griffiths asserted that the severity of her husband's adverse reaction to capecitabine was not recognised promptly and so treatment was delayed, and that this may have adversely affected his clinical course.

19. Leaving aside whether Mr Griffiths' death should have been reported to the Coroner by PPH in the first instance, Section 14(2) of the *Coroners Act 2008* [the Act] empowers coroners to investigate if a death is or may be a "reportable death."[12] An exhaustive definition of what constitutes a reportable death appears in section 4 of the Act.[13] Relevantly, section 4(2)(a)

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[12] Sections 14 and 15 of the *Coroners Act* 2008 prescribe when a Coroner may and when he or she must investigate a death. Section 16 of the Act enables a Coroner to determine whether a death is a reportable death and proscribes further investigation if a death is not a reportable death (or appears to have occurred 100 years earlier).

[13] The *Coroners Act 2008,* like its predecessor the *Coroners Act 1985*, requires certain deaths to be reported to the Coroner for investigation. Apart from a jurisdictional nexus with the State of Victoria [s.4(1)], the definition of a reportable death in section 4 includes deaths that appear to have been unexpected, unnatural or violent or to have resulted, directly or indirectly, from accident or injury [s. 4(2)(a)], those arising during a medical procedure or occurring unexpectedly after a medical procedure where the death may be causally related to the procedure [s. 4(2)(b)] and the

provides that reportable deaths include those that appear to have been "unexpected, unnatural or violent or to have resulted, directly or indirectly, from an accident of injury"[14] and section 4(2)(b) includes deaths that occur during a medical procedure or following a medical procedure where the death is or may be causally related to the medical procedure and a registered medical practitioner would not, immediately before the procedure was undertaken, have reasonably expected the death.

20. At my request, the HMIT of the Coroners Prevention Unit[15] reviewed Mr Griffiths' medical records and Dr Gupta's death certificate and advised that the death was likely the result of a rare toxic reaction to a chemotherapy drug rather than the natural progression of a disease process. On the basis of that advice, I concluded that Mr Griffiths' death was both unnatural and unexpected and therefore determined that his death was a reportable death within the meaning of the Act and a coronial investigation was initiated.[16] Alternatively, the death resulted from the administration of the drug (a medical procedure) and would not have been *reasonably* expected prior to the administration of the drug.[17]

21. At my request, the HMIT examined Mr Griffiths' medical records from Peninsula Private Hospital, his consultations with Dr Steel and additional material provided by Dr Steel and Mrs Griffiths and provided some preliminary advice about his clinical management and care. I subsequently commissioned an expert opinion from oncologist, Professor John Zalcberg of The Alfred Hospital and the Department of Epidemiology and Preventative Medicine at Monash University.

EXPERT OPINION – PROFESSOR ZALCBERG

22. Professor Zalcberg, an oncologist specialising in the field of gastro-intestinal cancers, was asked to provide an appraisal of the clinical management and care provided to Mr Griffiths in light of current practice in Australia,[18] expert advice about the availability of DPD deficiency

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death of a person who immediately before death was in the custody or care of the state [s. 4(c)-(f)] or whose identity is unknown [s.4(2)(g)] or where a death certificate has not been or is unlikely to be signed [s.4(2)(h)].

[14] The *Coroners Act 2008,* like its predecessor the *Coroners Act 1985*, requires certain deaths to be reported to the Coroner for investigation. Apart from a jurisdictional nexus with the State of Victoria, the definition of a reportable death in section 4 includes deaths that appear *to have been unexpected, unnatural or violent or to have resulted, directly or indirectly, from accident or injury* and the *death of a person who immediately before death was a patient within the meaning of the Mental Health Act 1986".*

[15] The Coroners Prevention Unit (CPU) was established in 2008 to strengthen the prevention role of the Coroner. The CPU assists the Coroner to formulate prevention recommendations and comments, and monitors and evaluates their effectiveness once published. The CPU is staffed by independent, highly skilled investigators, researchers and health care clinicians.

[16] Therefore falling within the terms of section 4(2)(a) of the Act.

[17] Therefore falling within the terms of section 4(2)(b) of the Act.

[18] The materials on which Prof Zalcberg's report was based included Mr Griffiths' medical records, Dr Steel's statement, correspondence between Dr Steel and AHPRA and between Dr Steel and the Director of Clinical Services at

testing in Australia and whether or not current practice addresses the need to test for DPD deficiency before commencing chemotherapy and/or deciding on the type of chemotherapy to be offered. I will outline Prof Zalcberg's opinions in relation to each of these matters in turn.

Mr Griffiths' Clinical Management

23. According to Professor Zalcberg, version 2.2016 of the National Comprehensive Cancer Network Guidelines [NCCN Treatment Guidelines][19] suggests that for T (any) N 1-2 tumours, treatment options include concurrent chemotherapy and radiotherapy, radiotherapy alone or chemotherapy alone. However, in Australia and in most United States centres, most clinicians would choose to use a five to six week course of radiotherapy with either concurrent 5-FU or oral capecitabine chemotherapy pre-operatively to treat a patient with a more advanced version of stage three rectal cancer, as in Mr Griffiths' case. Therefore, in Prof Zalcberg's opinion, Dr Steel's decision to treat Mr Griffiths with capecitabine in conjunction with radiation was consistent with standard practice in the field.

24. The expert observed that patients should always be informed of all the risks of chemotherapy including the risk of death. However, in his experience, given that such events are fortunately quite rare and provided they are described before a course of therapy is recommended, they rarely alter a patient's wish to receive optimal, potentially curative, treatment. Moreover, explanations about specific but rare causes of adverse outcomes (as opposed to the outcomes themselves) are not generally seen as obligatory from a clinical perspective particularly when there is no practical alternative – no way of predicting serious problems – other than to forewarn patients to act appropriately if significant side effects are experienced.

25. Prof Zalberg noted that in Mr Griffiths' case there were conflicting statements about whether the risk of DPD deficiency was discussed.[20] As the adverse effects are no different to the side effects of chemotherapy that occur in the absence of DPD deficiency, it is not clear how information about a theoretical but finite risk of DPD deficiency would have assisted Mr Griffiths or his wife in their decision-making, given clear instructions about appropriate actions to take if an adverse reaction occurred. Prof Zalcberg noted that Mr Griffiths and his wife responded appropriately to the emergence of his adverse effects/sequelae of DPD deficiency.[21]

Peninsula Private Hospital, correspondence from and the statement made by Mrs Griffiths and correspondence between Mrs Griffiths and Associate Professor Rosemary Harrup, Chair of the Medical Oncology Group of Australia.

[19] National Comprehensive Cancer Network, 2016 'NCCN Clinical Practice Guidelines in Oncology: Colon Cancer', version 2.2016.

[20] Prof Zalcberg's Expert Report, page 7.

[21] Prof Zalcberg's Expert Report.

26. Prof Zalcberg noted the telephone calls between Mr Griffiths and Dr Steel three and five days after commencing capecitabine and the nature and severity of the symptoms he reported. He also considered Mrs Griffiths' evidence that her husband had been reassured by these communications and Dr Steel's account that she had suggested a hospital admission, which Mr Griffiths had declined. Prof Zalcberg opined that a face-to-face review when Mr Griffiths had contacted his oncologist for a second time, on about 17 August 2015, may have provided Dr Steel with a better idea of the severity of his symptoms, especially as by then he had been prescribed Endone by his general practitioner to manage pain.

27. Like Dr Steel, Professor Zalcberg considered that by the time Mr Griffiths was admitted to PPH, his symptoms were sufficiently serious to suggest that he had some form of intolerance to 5-FU-based chemotherapy, such as is seen when patients have a DPD deficiency. The expert noted that Mr Griffiths was administered broad spectrum intravenous antibiotics and given GCSF to increase his neutrophil count among other appropriate measures initiated to understand the cause of Mr Griffiths' deterioration and to try to reverse his septic shock and ongoing hypotension. Prof Zalcberg concluded that Mr Griffiths' symptoms were managed appropriately in hospital.

28. Although Prof Zalcberg did not consider that Mr Griffiths' death was preventable in all the circumstances, he made a number of recommendations aimed at optimizing cancer care and preventing similar deaths in future.

DPD Deficiency Testing & Current Australian and International Clinical Practice

29. DPD deficiency is a metabolic disorder in which there is absent or significantly decreased activity of dihydropyrimidine dehydrogenase, an enzyme involved in the metabolism of uracil and thymine. Individuals with a DPD deficiency may develop life-threatening toxicity following exposure to 5-FU or capecitabine.[22] There are at least four well-described genetic variants of the DPD gene, which encodes the DPD enzyme, that are linked to excessive toxicity to 5-FU and its oral equivalent.

30. Prof Zalcberg observed that the prevalence of DPD deficiency is thought to vary from 3-5% of the population having a partial loss of function to a prevalence of 0.2% of people having complete loss of function.[23] Mortality rates among individuals with a partial DPD deficiency are in the order of 10% while very severe toxicity occurs in over 30% of patients. In the very

[22] The normal breakdown of 5-FU occurs in the liver and is mediated by the rate-limiting enzyme DPD. DPD breaks down approximately 85% of administered 5-FU. Capecitabline is an orally available pro-drug of 5-FU which is metabolised to 5-FU by the liver and, in turn, metabolised by DPD. See Prof Zalcberg's expert report.
[23] Prof Zalcberg's Expert Report.

small number of individuals with complete loss of DPD function, it is *generally considered that any exposure to 5-FU is more likely than not to be fatal.*[24]

31. A commercially-provided genetic test is available in Australia but according to Prof Zalcbeerg its availability is not well-known among oncologists. The cost of the test is not reimbursed through Medicare and the turn-around time for a result is currently too slow for the test to be considered practical prior to treating patients with 5-FU.

32. Genetic tests for DPD deficiency are complex to interpret and an abnormal result does not necessarily mean that a patient will experience serious adverse events if administered 5-FU. When DPD deficiency is identified, the consequent need to reduce the 5-FU dose or eliminate the drug from the chemotherapy options entirely, risks providing suboptimal treatment for the cancer given that some patients may not experience life-threating toxicity.

33. Due to the complexity of genetic testing for DPD deficiency, measures of DPD enzyme function have been developed. These functional assays measure the ratio of uracil to dihydrouracil, a conversion process that requires normally functioning DPD levels. In Australia, this test is only performed in a single research laboratory in Newcastle, rather than an accredited commercial pathology laboratory, and the tests are only performed every few weeks making pre-treatment testing unfeasible.

34. Prof Zalcberg advised that it was not routine practice around Australia – nor in most major centres internationally – to routinely test for DPD deficiency prior to the administration of 5-FU.[25] Although some national health trusts in the UK and some centres in France and The Netherlands are starting to conduct DPD deficiency testing prior to commencing treatment, the extent of these emerging practices is unclear. Indeed, neither European Guidelines[26] nor the USA's Federal Drugs Administration [FDA][27] mandate measurement of DPD deficiency prior to the clinical use of 5-FU.

Recent Developments

35. Professor Zalcberg advised that since Mr Griffiths' death, an oral antidote for severe 5-FU toxicity has been developed by American pharmaceutical company Wellstat and approved for use by the US FDA. Marketed as Vistogard, the antidote may be used for any serious adverse event which is thought to be related to intolerance to 5-FU, but it must be administered as soon as possible after severe toxicity is recognised, ideally within 24-48 hours.

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[24] Prof Zalcberg's Expert Report, page 5.
[25] Prof Zalcberg's Expert Report, page 6.
[26] Such as the recently released, 'Consensus Guidelines for the Management of Patients with Metastatic Colorectal Cancer' developed by the European Society of Medical Oncology. See Prof Zalcberg's Expert Report, page 6.
[27] Prof Zalcberg's Expert Report, page 5.

CONCLUSIONS

36. I find that Mr Griffiths, late of Point Nepean Road in Portsea, died at Peninsula Private Hospital in Frankston on 26 August 2015 and that the cause of his death was severe neurtropenic sepsis and multi-organ failure secondary to severe mucositis and probable DPD deficiency in the setting of T3 rectal carcinoma.

37. The available evidence, including Professor Zalcberg's evidence about current oncology practice in Australia, does not support a finding that there was any want of clinical management and care on the part of Dr Steel and other clinicians involved in Mr Griffiths' treatment that caused or contributed to his death.

COMMENTS

Pursuant to section 67(3) of the *Coroners Act* 2008, I make the following comments connected to the death:

38. In 2015, there was no readily available and reliable way to predict DPD deficiency, DPD testing prior to treatment with 5-FU was not the standard of care in Australia or internationally and nor was the oral antidote to 5-FU available in Australia. Mr Griffiths' death was therefore *not preventable* in the way that that term is understood in this jurisdiction.

39. The investigation of Mr Griffiths' death, and particularly the detailed expert report provided by Professor Zalcberg, has revealed evidence of the emerging use of pre-5-FU treatment DPD testing overseas has highlighted opportunities for prevention of similar deaths in Australia in the future.

RECOMMENDATIONS

Pursuant to section 72(2) of the *Coroners Act* 2008, I make the following recommendations connected to the death:

40. That the Medical Oncology Group of Australia [MOGA] consider whether testing for DPD deficiency should be standard care for patients proposed to be commenced on 5-FU chemotherapy treatment.

41. That the Federal and Victorian Governments expedite the agreement for a single national repository for the oral antidote to 5-FU, Vistogard.

42. That the Peter MacCallum Cancer Centre agree to establish and maintain a national repository for Vistogard.

I direct that a copy of this finding be provided to the following:

Mrs Doris Griffiths

Dr Simone Steel, Peninsula Health

Professor John Zalcberg, Monash Health

Peter MacCallum Cancer Centre

Royal Australasian College of Physicians

Medical Oncology Group of Australia

Therapeutic Goods Administration

Federal Government of Australia, Minister for Health, the Honourable Greg Hunt

Victorian Government, Minister for Health, the Honourable Jill Hennessy

Signature:

PARESA ANTONIADIS SPANOS
CORONER
Date: 20 November 2017

Cc: Manager, Coroners Prevention Unit