THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

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THE NEW ZEALAND MEDICAL JOURNAL
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This Issue in the Journal

Great expectations: use of molecular tests and computerised prognostic tools in New Zealand cancer care
Deborah M Wright, Rob McNeill, Arend E H Merrie, Cristin G Print

There is an international drive to improve the survival of patients with cancer by tailoring treatment more precisely to the individual's tumour; 'personalised medicine'. Personalised medicine may include consideration of important clinical and pathological factors, e.g. tumour stage, and, increasingly, consideration of the molecular characteristics of individual tumours. We surveyed New Zealand cancer clinicians and discovered that molecular tests and computerised prognostic tools are used by many clinicians and influence the treatment provided to cancer patients. In addition we found that most clinicians predict that the impact and influence of these technologies will increase over the next 10 years. This has important clinical and economic implications for New Zealand's cancer control strategy.

Clinical trials in New Zealand—an update
Vickie Currie, Andrew Jull

An average of 180 clinical trials per year were conducted 2005–2009, up from an average of 111 per year in 1998–2003. Early phase trials accounted for much of the increase, probably because of an increase in the number of early phase units in New Zealand. Most commercial trials were compliant with the Committee of Medical Journal Editors (ICMJE) requirement to register trials, but non-commercial trials were not so compliant.

Short and long term outcomes of oesophagectomy in a provincial New Zealand hospital
Fadhel Al-Herz, David Healey, Tarik Sammour, Josese Turagava, Bruce Rhind, Mike Young

Oesophagectomy (resection of the oesophagus) is a very complex surgical procedure associated with a significant morbidity and mortality rate. There is very little published data from New Zealand, with no published data from a non-Tertiary New Zealand hospital. Data from 68 patients who underwent oesophagectomy at Palmerston North Hospital were analysed. Survival outcomes of oesophageal resection in this provincial New Zealand hospital were comparable to published series from national and international tertiary centres.

Arcobacter species in diarrhoeal faeces from humans in New Zealand

Owen Mandisodza, Elizabeth Burrows, Mary Nulsen

Arcobacter species used to be classified as campylobacters but differ in a number of properties. Overseas studies have shown that arcobacters can be found in healthy, and occasionally, sick animals as well as in poultry and other meats, shell fish, seawater, fresh water and the environment. Our study found two *Arcobacter* species, *A. butzleri* and *A. cryaerophilus*, in 0.9% of 1380 patients with diarrhoea from the Hawke's Bay region of New Zealand. A number of these patients had persistent or watery diarrhoea but one-third were also infected with another enteric pathogen. Arcobacters are considered emerging enteric pathogens but further studies would be valuable in determining their overall importance in disease of humans.

Is late-night salivary cortisol a better screening test for possible cortisol excess than standard screening tests in obese patients with Type 2 diabetes?

Elna Ellis, Paul K L Chin, Penelope J Hunt, Helen Lunt, John G Lewis, Steven G Soule

One of the rare causes of diabetes mellitus and obesity is having excessive production of cortisol, a steroid hormone. There are two routine tests available to check patients for excess cortisol, including: a 24 hour urine collection; or a blood test. A newer test involves checking for cortisol levels in saliva, which is potentially a more convenient test. Our study showed that the salivary cortisol test was inferior to the other two tests, and the urine collection test was the best.

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Detecting and treating prostate cancer: a surgeon's perspective

Nicholas C Buchan

PSA testing has become a "hot" topic in recent years and the debate has only become stronger since the publication of the early results of the European and American Prostate cancer screening trials.[1–3] Such is the debate and interest in the topic that it has even overflowed into the popular press with recent articles published in North and South and Scientific American.[4,5]

Unfortunately the debate has left many confused and uncertain of the role of PSA in prostate cancer management. Much of the debate has surrounded the role of PSA testing in population based screening in *asymptomatic* men. The key tenants of the debate have surrounded whether or not there is an overall survival benefit and if this survival benefit is outweighed by the potential for harm from the diagnosis of so called "insignificant" cancers and the morbidity of treatment.

This very real concern about over treatment is well recognised and accepted by those treating prostate cancer and there has been a significant paradigm shift over the last 5 years towards aggressive treatment of intermediate and high risk disease and away from intervention in low risk disease. This "uncoupling" of the link between diagnosis and active treatment will go some way to reducing the harm from over treatment. Another strategy to reduce this harm is to develop new biomarkers that have accurate prognostic value in predicting the course of the disease process in individual patients.

The article published in this issue of the *NZMJ* by Lance Ng and colleagues[6] titled *Beyond PSA: are new prostate cancer biomarkers of potential value to New Zealand doctors?* is an excellent summary of the landscape of investigation into prostate cancer biomarkers. Currently there are no markers that closely rival PSA in clinical practice, but this is a field in constant evolution.

One of the key difficulties for any prostate cancer researcher is the long latency period between diagnosis of prostate cancer and sequelae of the disease. This means that any studies being conducted with overall survival and cancer specific survival as endpoints need at least 15 years to mature. If a biomarker was developed that was also able to determine response to treatment this would greatly speed up the development and investigation of new prostate cancer treatments especially at the early, potentially curable stages of the disease.

Currently a significant amount of investment has gone into drug development at the end stages of the disease, partly because it is easier to measure outcomes later in the disease process as the latency period is significantly reduced. Whatever opinion you have on prostate cancer population screening in *asymptomatic* men everyone agrees that prostate cancer has a significant impact on the New Zealand population.

Prostate cancer is the third leading cause of male cancer deaths in New Zealand.[7] There is no doubt that we need to get smarter about the concept of screening in general.

Risk assessment tools may play a central role in the future when considering whether to biopsy men with an elevated PSA. Such tools enable both the clinician and patient to quantify the risk of finding prostate cancer on biopsy and most importantly the specific risk of finding high-grade prostate cancer.[8]

A limited list of factors such as age, comorbidity, prostate volume, family history, ethnicity and previous biopsy status have been identified to modify risk and are important for consideration in routine practise.[9,10]

As the debate surrounding PSA screening has raged what has been lost in translation is that PSA remains an invaluable test in *symptomatic* men as well as in the follow up of men treated for prostate cancer. As a clinician treating prostate cancer on a daily basis, unfortunately it is common for me to hear from patients and General Practitioners alike that they thought that PSA, as a test is "a waste of time". It is important that this misconception and extrapolation of the prostate cancer screening data to *symptomatic* men be rectified.

It is the right of all male New Zealanders to be well informed about the benefits and drawbacks of PSA testing and it is our responsibility as clinicians to enable them in making a risk assessment based on the most currently available data. Moreover it is the right of all New Zealand males to have a PSA test if they so choose.

Competing interests: None declared.

Author information: Nicholas C Buchan, Urological Surgeon, Christchurch Public Hospital, Urology Associates, and Canterbury Urology Research Trust Board, Christchurch

Correspondence: Nicholas C Buchan, Urological Surgeon, Christchurch Public Hospital, PO Box 4345, Christchurch, New Zealand. Email: nick@urology.co.nz

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Great expectations: use of molecular tests and computerised prognostic tools in New Zealand cancer care

Deborah M Wright, Rob McNeill, Arend E H Merrie, Cristin G Print

Abstract

Background Use of molecular tests and computerised prognostic tools designed to individualise cancer care appears to be rapidly increasing in New Zealand. These tests have important clinical and health economic implications, but their impact on cancer care has not been fully assessed.

Aim To determine cancer clinicians' use of and expectations for molecular tests and computerised prognostic tools.

Method Online survey of clinicians managing cancer in New Zealand.

Results 137 clinicians participated, 31% used molecular tests and 57% used computerised prognostic tools. These technologies affected clinical decisions made by a quarter of participants. Over 85% of participants believed that the impact of molecular tests and computerised prognostic tools would increase over the next decade and that a stronger evidence base would support their use.

Conclusions Molecular tests and computerised prognostic tools already influence treatment provided to many New Zealand cancer patients. Clinicians who participated in this survey overwhelmingly expect the use of these tests to increase, which has important clinical implications since there is little high quality prospective data assessing the ability of these tests to improve patient outcomes. Expanded use of these often-expensive tests also has economic implications. The role of these technologies needs to be considered in the context of a wide-ranging cancer control strategy.

There is an international drive to improve outcomes for patients with cancer by individualising cancer treatment using technologies including molecular tests (MT) and computerised prognostic tools (CPT).[1,2] MT utilise molecular information, for example variations in DNA sequence or RNA expression levels, to diagnose disease or to predict susceptibility or treatment outcome. CPT use computerised statistical models to combine large datasets with individuals' clinical details to infer individualised prognoses.

MT and CPT designed to aid clinical decision making for patients with a range of malignancies have been described.[3] Molecular tests available in New Zealand (NZ) include: MammaPrint[4] and Onco*type* DX,[5] which use gene expression analysis to derive a recurrence risk score for patients with early breast cancer; *FLT3*, *NPM1* and *CEBPA* mutation analysis which provide prognostic information for patients with cytogenetically normal acute myeloid leukaemia (CN-AML) and are recommended in World Health Organization (WHO) guidelines;[6,7] *KRAS* mutation analysis, which predicts response to cetuximab, an unfunded treatment for metastatic colorectal cancer;[8] *UGT1A1* mutation analysis to predict irinotecan toxicity;[9] *EGFR* mutation

analysis to predict response to gefinitib and erlotinib for patients with non-small cell lung cancer.[10]

In NZ we also have free online access to a number of CPT including Adjuvant!, which estimates recurrence risk and treatment benefit for patients with breast, colon or lung cancer.[11] Further details of these examples of MT and CPT are given in Table 1.

Table 1 Examples of molecular tests and computerised prognostic tools currently available in New Zealand for the care of patients with cancer

Molecular test	Type of cancer	Clinical significance	Method of detection	Sensitivity	Specificity	Ref
Onco*type* DX	Breast	21-gene test used to assign a tripartite recurrence risk score for ER-positive, lymph node negative breast cancers using a continuous variable algorithm.	qRT-PCR	77%	55%	12
MammaPrint	Breast	70-gene test use to assign dichotomous 'high' or 'low' risk of metastatic recurrence from a continuous variable.	Microarray	90%	42%	13
FLT3 mutation analysis	CN-AML	Internal tandem duplication is associated with constitutional activation of the *FLT3* tyrosine kinase receptor and shorter disease free survival.	PCR	–	–	7
NPM1 mutation analysis	CN-AML	*NPM1* mutations are associated with improved prognosis in the absence of *FLT3* mutation	PCR	–	–	7
CEBPA mutation analysis	CN-AML	*CEBPA* mutations are associated with improved prognosis.	PCR	–	–	7
KRAS mutation analysis	Metastatic CRC	*KRAS* mutation predicts lack of response to anti-EGFR- antibodies (e.g. cetuximab)	PCR	49%	93%	8
UGT1A1 mutation analysis	Metastatic CRC	Presence of the *UGT1A1*28* mutation predicts risk of severe neutrophenia in patients treated with irinotecan.	PCR	23%	92%	9
EGFR mutation analysis	Non-Small Cell Lung Cancer	EGFR activating mutations predict response to EGFR tyrosine kinase inhibitors (e.g. gefinitib and erlotinib)	PCR	77%	93%	14
Adjuvant! for breast cancer	Breast cancer	Uses clinicopathological data to predict overall and disease free survival, and the impact of endocrine therapy and polychemotherapy.	Web-based computerised prognostic tool	70%	57%	12

CN-AML=cytogenetically normal acute myeloid leukaemia; CRC=colorectal cancer; ER=(o)estrogen receptor; qRT-PCR=quantitative reverse transcription polymerase chain reaction.

The utilisation of MT and CPT during the management of patients with solid organ and haematological malignancy is likely to have a significant impact on clinical

practice and health economics in NZ, however it has not been evaluated to date. The intent of this study is to determine the awareness and specific utilisation of MT and CPT amongst NZ cancer clinicians treating solid organ and haematological malignancy, and to ascertain their predictions for the impact of these technologies over the next 10 years.

Methods

An anonymous online questionnaire was used to survey clinicians who treat patients with cancer in NZ.

The questionnaire was implemented using LimeSurvey software (Carsten Schmitz, Germany), a free open source survey application. It comprised 185 questions in three sections. Most questions in sections one and two had fixed 'click button' answer options and a free text 'other' option; where a numeric answer was required a free text box or slide rule was provided.

In section 3, participants were shown clinical scenarios relating to their area of specialty. The scenarios presented situations in which molecular tests are purported to assist with clinical decision-making: stage II breast cancer, stage II colon cancer and CN-AML in remission after chemotherapy. Participants were invited to leave free text comments at the end of each section of the survey.

The questions presented to each participant were determined by their previous responses such that each participant saw only those questions relevant to their clinical practice. The questionnaire took approximately 15 minutes to complete.

Please visit http://www.bioinformatics.auckland.ac.nz/doc/project_data/Supplemetary_figure_and_tables_FINAL.docx to view the questionnaire in full and all supplementary figures and tables. The University of Auckland Human Participants Ethics Committee granted ethical approval for this study.

Medical and radiation oncologists, haematologists, pathologists and general surgeons practicing in NZ at specialist and trainee level were invited to participate by email via their professional societies and colleges. All trainees were enrolled in college-approved training programmes. Reminder emails were sent out 2 and 4 weeks after the initial invitation. Participation was incentivised with an iPad (Apple Inc., California, USA), won by a participant selected using a random number generator.

The survey was conducted over 11 weeks, from 17th May to 1st August 2010. Responses from clinicians practicing outside NZ were excluded from analysis, as were incomplete responses that did not include details of the participant's specialty and seniority. Data analysis was carried out using PASW Statistics 18.0 (IBM Corp., NY, USA), Excel 2008 version 12.2.9 (Microsoft Corp., Washington, USA) and VassarStats (faculty.vassar.edu/lowry/VassarStats.html). Relationships between independent categorical variables were analysed using the chi-square test for independence of association, relationships between non-independent variables were analysed using McNemar's test. Where multiple tests were performed the Bonferroni correction was used. A P value of <0.05 was held to be significant and $P<0.01$ as highly significant.

Results

Survey participants - 739 clinicians were invited to participate in the survey. 186 clinicians accessed the online questionnaire; 137 completed it (Figure 1). Participants represented all invited specialties and included both specialists and trainees (Table 2). Specialists were significantly under represented relative to trainees ($P<0.01$); pathologists were significantly under represented relative to other specialties ($P<0.05$ for both pathology specialists and trainees). Participants worked in secondary, tertiary, academic and private practice settings.

Figure 1. Participation in a survey investigating utilisation of molecular tests and computerised prognostic tools

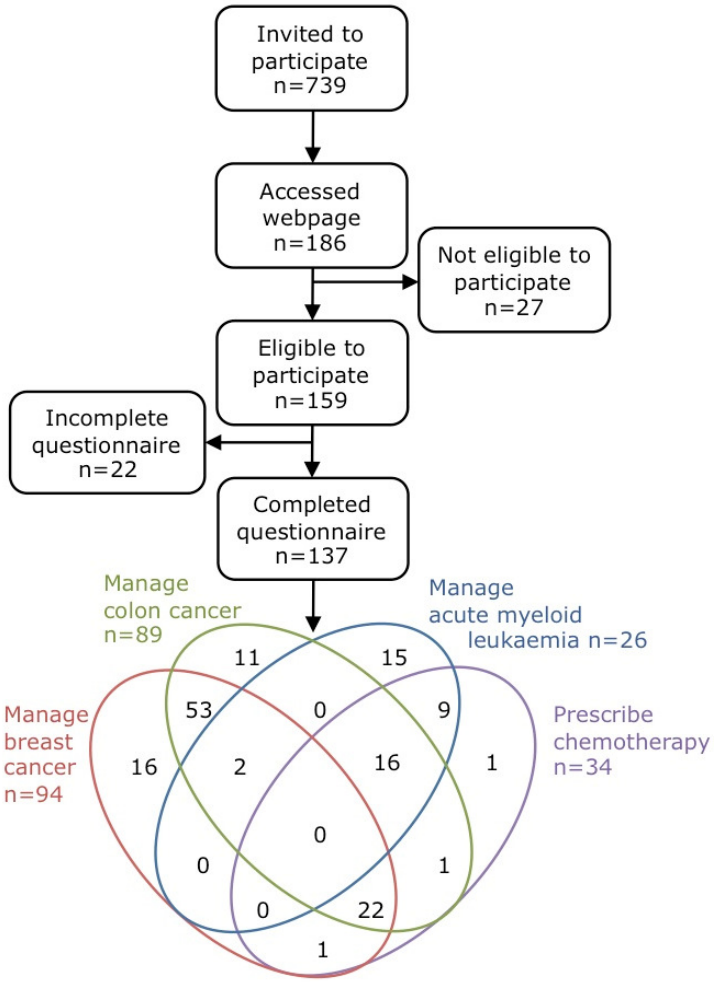

Table 2. Seniority and specialty of survey participants

Seniority	Specialty	Number of participants (n=137)	Number of clinicians invited to participate (n=739)	Participation rate (%)
Specialists	General surgery	26	140	(19)
	Medical oncology	17	71	(24)
	Radiation oncology	15	45	(33)
	Haematology	15	61	(25)
	Pathology	11	217	(5)
Registrars/Fellows	General surgery	27	69	(39)
	Medical oncology	11	23	(48)
	Radiation oncology	4	17	(24)
	Haematology	4	17	(24)
	Pathology	7	79	(9)

Current practice—A greater proportion of participants were aware of MT than CPT (92% vs. 69%, *P*<0.01*)* (Table 3). Awareness of MT by specialists vs. registrars showed no statistically significant difference (6% and 10%, respectively), however specialists were significantly less likely to be aware of CPT than registrars (60% vs. 81%, P <0.05). Fewer participants had ever used MT than CPT (43 vs. 78, *P*<0.01). Of participants aware of MT, 59/126 (47%) reported that they had never used MT relevant to their clinical practice. Of participants aware of CPT, 12/94 (13%) reported that they had never used CPT relevant to their clinical practice.

Table 3. Awareness and utilisation of molecular tests and computerised prognostic tools amongst New Zealand cancer clinicians

Variables	Molecular tests n=137		Computerised prognostic tools n=137	
Not aware of any tools/tests n (%)	11	(8)	43	(31)
Aware of tools/tests n (%)	126	(92)	94	(69)
Utilisation by those aware of tools/tests				
Never used them	83		16	
Previously used them	7		13	
Currently used them	36		65	

Table 4 presents data on factors that limited the use of those MT and CPT most commonly used in NZ. Supplementary Tables 1 and 2 present this data for all of the MT and CPT included in the survey.

Factors reported to limit the use of MT and CPT varied. For example, awareness of both the CPT Adjuvant! and the MT Onco*type* DX was high (78% and 86%) amongst participants who managed breast cancer (n=94) but while the use of Onco*type* DX was most commonly limited by cost, use of Adjuvant! was most commonly limited by lack of clinical time (Table 4).

For participants who prescribed chemotherapy, both the cost of mutation analysis and, in some instances, the cost of unfunded medications (e.g. cetuximab) limited their uptake of MT.

Table 4. Factors that limited the use† of molecular tests and computerised prognostic models for the management of patients with cancer in New Zealand

	Oncotype DX (n=94)		**FLT3 mutation analysis** (n=26)		***KRAS* mutation analysis** (n=34)		**Adjuvant! for breast cancer** (n= 94)	
	Current or previous user (n=10)	Never used (n=24)	Current or previous user (n=22)	Never used (n=4)	Current or previous user (n=16)	Never used (n=18)	Current or previous user (n=70)	Never used (n=24)
No limiting factor(s) identified n(%)	0 (0)	0 (0)	14 (64)	0 (0)	1 (6)	0 (0)	24 (34)	0 (0)
Not aware of tool n(%)	–	25 (30)	–	2 (50)	–	10 (56)	–	13 (54)
Other limiting factor identified n(%)	10 (100)	59 (70)	8 (36)	2 (50)	15 (94)	8 (44)	46 (66)	11 (46)
Limiting factors:								
Cost[a]	9	36	3	0	14	5	–[b]	–[b]
Time	1	2	1	0	0	0	24	1
Not relevant to my practice	0	17	0	1	1	3	2	7
Internet access[c]	–	–	–	–	–	–	16	1
Concern about evidence base	0	13	1	0	0	0	16	0
Doesn't add information	0	6	0	1	0	0	7	1
Limited availability[d]	–	9	–	–	4	1	–	–
Patient age[e]	–	–	5	–	–	–	–	–
Medicolegal concerns	0	3	0	0	0	0	3	0
Other	2	4	1	0	0	0	6	3

†Current use defined as use within preceding 6 months. Responses for Onco*type* and Adjuvant! for breast cancer are from participants who managed patients with breast cancer (n=94); for *FLT3* mutation analysis from participants who managed acute myeloid leukaemia (n=26); for *KRAS* mutation analysis from participants who prescribed chemotherapy (n=34). More than one limiting factor could be selected for each test by each participant.
– response not offered. [a]Cost of the test to the patient or the health system, [b]This tool is available free of charge, [c]Limited internet access in clinical settings, [d]Availability of the test or, in the case of *KRAS* testing, lack of access to / availability of cetuximab (not funded in the public health system at time of survey), [e]Test not used for older patients for whom certain management strategies would not be offered.

At the time of the survey 80% of participants managing breast cancer (75/94) were aware of the prognostic MT Onco*type* DX and MammaPrint; Onco*type* DX was currently being used by six, MammaPrint by two. Of the 26 participants managing CN-AML, 92% had heard of *FLT3*, *NPM1* or *CEBPA* mutation analysis; *FLT3, NPM1* and *CEBPA* mutation analysis were currently being used by 22 (85%), 15 (41%) and two (8%) of these clinicians, respectively. Thirty-four participants

prescribed chemotherapeutic agents of whom 29 (85%) had heard of *KRAS*, *UGT1A1*, or *EGFR* testing. Twelve (35%), one (3%) and four (12%) of these clinicians currently used *KRAS*, *UGT1A1* and *EGFR* mutation analysis, respectively.

Table 5. Impact of molecular tests and computerised prognostic tools on the management of patients with cancer in New Zealand

	Oncotype DX (n=6)		*FLT3* mutation analysis (n=22)		*KRAS* mutation analysis (n=12)		Adjuvant! for breast cancer (n=59)	
How often have you used this tool/test in the last 6 months? Median(IQ range)	1.5	(1–2)	3	(2–3)	5	(3–6)	12	(7–35)
For what proportion of eligible patients do you use this tool/test? Median(IQ range)	5	(5–6)	90	(63–95)	23	(5–95)	85	(45–95)
What is the primary function of this tool/test in your practice? n(%)								
Explaining management options	1	(17)	3	(14)	5	(42)	42	(71)
Clinical decision making	4	(66)	17	(77)	2	(16)	16	(27)
Assessing clinical trail eligibility	–	–	2	(9)	5	(42)	–	
Other	1	(17)	0	(0)	0	(0)	1	(2)
Does this test affect your clinical decisions? n(%)								
Yes	3	(50)	19	(87)	10	(84)	28	(48)
No	0	(0)	2	(9)	1	(8)	22	(37)
Other	3	(50)	1	(4)	1	(8)	9	(15)
Does use of this tool/test improve patient outcomes in your practice?[a] n(%)								
Yes	–		15	(68)	8	(67)	43	(73)
No	–		3	(14)	1	(8)	7	(12)
Other	–		4	(18)	3	(25)	9	(15)

Current use defined as use within preceding 6 months. Responses are from participants who currently used these computerised prognostic tools and molecular tests.

-Answer not offered for this question. [a]Outcomes could include, for example, reduction in side effects by avoiding treatment (e.g. allogeneic stem cell transplantation) as well as overall and disease free survival. IQ, interquartile range.

Participants were asked to comment on the influence these tools had on their practice (Table 5). For 19 participants *FLT3* mutation analysis affected their clinical decisions; 16 were more likely to offer allogeneic stem cell transplantation, two were more likely to suggest deferring treatment and one was more likely to offer chemotherapy. For 10 participants *KRAS* mutation analysis, which predicts response to cetuximab, affected their clinical decisions; six reported that it resulted in offering fewer patients treatment with this drug and two that they offered more patients treatment with cetuximab.

Twenty-eight participants reported that Adjuvant! for breast cancer affected their clinical decisions; 18 considered adjuvant therapy for fewer patients and 10 for more.

Overall, MT were more likely than CPT ($P<0.01$) to affect the clinical decisions of participants currently using them. However, because fewer participants used MT than CPT, the global effect of MT and CPT on clinical decisions was similar; 33/137 participants reported that MT affected their clinical decisions, 35/137 participants reported that CPT did so.

Estimated value of molecular tests—The median estimated value of hypothetical tests that provided reliable patient-specific recurrence and response data was $1000 (Table 6). The majority of participants concluded that such a test could save the health service money, with no significant difference between the scenarios offered.

Table 6. Participants estimated the value of hypothetical molecular tests in response to clinical scenarios, and whether such tests could reduce health costs

Scenario	How much do you think this test is worth?		Do you think this test could save patients, the health system or insurers money?					
	NZ$		Yes		No		Don't know	
50 year old woman with stage IIA, grade 2, ER/PR +ve, HER2 -ve breast cancer. Wide local excision, radiotherapy, endocrine therapy. Molecular test to predict risk of disease recurrence and response to specific chemotherapeutic agents. (n=94)	1000	(500–2000)	66	(70)	11	(12)	17	(18)
Middle aged patient with colon cancer. Definitive resection with primary anastomosis. Stage II (pT3, pN0, M0). Molecular test to predict risk of disease recurrence and response to specific chemotherapeutic agents. (n=89)	900	(500–1625)	57	(64)	18	(20)	14	(16)
Previously well 40-year-old patient with AML. Achieved complete remission with induction chemotherapy. Options include consolidation chemotherapy or stem cell transplant. Molecular test to predict risk of disease relapse and response to specific chemotherapeutic agents. (n=26)	1000	(500–1000)	20	(78)	2	(7)	4	(15)

Estimates of test worth are median value in NZ$ (interquartile range). All other data are number of participants (percentage). AML=acute myeloid anaemia.

Predictions for the future – All participants (n=137) were asked to predict the change in impact of MT and CPT on the care of patients with cancer over the next decade. Over 85% of participants, whether or not they currently used these tests and tools, predicted that they would have a greater influence and a stronger evidence base within the next 10 years (Table 7).

Table 7. Predicted change in the influence and impact of molecular tests and computerised prognostic tools on the management of patients with cancer over the next 10 years

Variables	Molecular tests (n=137)						Computerised prognostic tools (n=137)					
	Less		No change		More		Less		No change		More	
Frequency of use n(%)	0	(0)	1	(1)	136	(99)	1	(1)	8	(6)	128	(93)
Quality of evidence base n(%)	0	(0)	4	(3)	133	(97)	1	(1)	10	(7)	126	(92)
Influence on decision making n(%)	0	(0)	3	(2)	134	(98)	0	(0)	18	(13)	119	(89)
Ability to improve patient outcomes n(%)	0	(0)	8	(6)	129	(94)	1	(1)	18	(13)	118	(86)

Discussion

This study has elucidated the use of molecular tests (MT) and computerised prognostic tools (CPT) by 137 clinicians treating patients with solid organ and haematological malignancy in NZ, the factors that limit their uptake and their predicted impact over the coming decade. For each point below we will first draw conclusions from our data and then discuss the potential role of MT and CPT in NZ cancer care.

Survey response rate—The 'click through' response rate to our survey was 25% (186/739); most clinicians who visited the survey completed it (137/186, 72%). However the figure of 186 responders to 739 invitations may significantly underestimate response due to difficulties in accurately determining the number of eligible participants. Some members of the relevant colleges and professional societies are members of more than one organisation (e.g. haematologists may be members of both RACP and RCPA), others are currently practicing overseas and are likely to have determined that they were ineligible to participate prior to accessing the survey's website. Participation was unevenly distributed amongst the invited specialities; a significantly smaller proportion of invited pathologists participated than clinicians invited other specialties.

In order to maximise participation we utilised strategies that have been found effective including reminder notices and incentivisation;[15] participation was modest nonetheless. Studies have found that clinicians have the lowest survey response rate of all health care providers,[16] with Australasian physicians less likely to participate than their international colleagues.[17] It has also been shown that response rates to electronic surveys vary widely, from 0.1%[18] to 83%,[19,16] but tend to be lower than to postal surveys.[18] Reviews of survey-based research have commented that surveys with low response rates can provide useful and representative data.[16] We are therefore confident that our data is a helpful contribution to this field.

Current use—We found that MT and CPT currently influence the treatment offered to a significant number of patients with cancer in NZ; our data suggests that the care of up to 80% of patients with CN-AML is impacted by the use of *FLT3* mutation analysis and that the care of up to 40% of women with early breast cancer is impacted

by the use of the CPT Adjuvant!. 67-73% of participants who used these technologies believed that they positively impact patient outcomes. Overall a greater number of participants were aware of MT than were aware of CPT, but CPT were more commonly used.

It is interesting to speculate on the factors that may explain this difference. We propose that awareness of MT may be enhanced by the larger number of publications about them than about CPT (8,600 versus 159 PubMed-referenced publications in 2010) and by the effort of manufacturers to raise the profile of some expensive MT within Australasia.

The MT discussed in this paper range in cost from around $300 per patient for *FLT3* mutation analysis testing (Canterbury Health Laboratories, http://www.labnet.co.nz/testmanager/) to around $4500 per patient for MammaPrint (personal communication with Ronald van Klaveren, Agendia, March 2011). In contrast we suggest that the greater uptake of CPT may be because they are often available free of charge and can be accessed using computer hardware and software commonly available in clinical settings.

Use of MT and CPT may also be influenced by their inclusion in current clinical guidelines. For example *FLT3* testing for patients with CN-AML is recommended in the current WHO guidelines[6] and was used by 85% of participants who treat this malignancy. In contrast, MammaPrint, which was used by only 2% of participants who manage breast cancer, is not mentioned in NZ's Early Breast Cancer Guidelines.[20]

64 to 78% of participants estimated that the use of hypothetical MT might reduce healthcare costs even at prices that would significantly increase the cost of pathological assessment.[21] In the USA, industry-associated studies have previously calculated that use of MammaPrint[22] and Onco*type* DX[23] may indeed reduce healthcare costs. However, some may argue that assessing the economic value of MT in NZ may be premature before more robustly establishing their ability to improve patient outcomes.[24,25]

Future use—Nearly all clinicians forecast that MT and CPT will be used more frequently and will have a greater influence on clinical decisions within the next decade. Participants predicted that this increased impact and influence would be supported by a stronger evidence base and greater ability to improve patient outcomes. Less than 1% of respondents believed that these tools would become less important over the next 10 years.

Discussion of the role of MT and CPT in NZ cancer care—This survey showed that clinicians are currently using MT and CPT to make clinical decisions about patients with cancer in NZ and have great expectations for their increasing contribution over the next 10 years. It also suggested that a subset of clinicians saw the relative lack of research into the effect of MT or CPT on patient outcomes as limiting MT or CPT uptake. MammaPrint, Onco*type* DX and other MT that have not yet completed prospective trials are currently influencing patient care in this country.[26-28] The NZ Cancer Control Strategy supports an evidence-based approach to the management of patients with malignancy.[29] Therefore, we would like to suggest that high quality research evaluating the effects of MT and CPT on patient outcome

should be a priority. This view is backed by overseas studies, which have found that some MT have worrying variations in their technical use,[30] that others are marketed before a convincing evidence base has been assembled[31] and that the clinical evaluation of some MT and CPT has lagged behind the technological leaps that have allowed these tests to be used.[32,33]

Defining the role of MT and CPT in NZ cancer care requires input from a wide range of clinical specialists and scientists. Pathologists were under-represented amongst survey respondents, yet their involvement in a multidisciplinary effort to integrate traditional histopathology with developments in the molecular understanding of cancer can not be overestimated.[34] For example, Cummings *et al* stress that new MT will only produce maximal clinical benefit for patients with breast cancer if they are used by pathologists as an adjunct to their existing armamentarium.[35]

In conclusion, our survey suggested that MT and CPT already influence treatment provided to NZ cancer patients and that NZ cancer clinicians overwhelmingly expect their use and influence to increase. This has important clinical and health economic implications for NZ. Although these technologies may represent exciting opportunities to improve cancer care and patient outcomes it seems important that their use is supported by high quality evidence and that research is undertaken into their effects on both patient outcome and future health resource utilisation.

As with any health care intervention, MT and CPT cannot be considered in isolation, but rather should be considered as elements of a co-ordinated strategy that includes primary prevention, early referral, screening, and optimal specialist management to improve the quality of cancer care in NZ.

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Author information: Deborah M Wright, PhD Student;[1,2] Rob McNeill, Senior Lecturer;[3] Arend EH Merrie*, Colorectal Surgeon, Honorary Clinical Senior Lecturer;[2,4] Cristin Print*, Associate Professor of Pathology.[1,5]

[1]Department of Molecular Medicine and Pathology, University of Auckland, Auckland.

[2]Department of Surgery, University of Auckland, Auckland.

[3]School of Population Health, University of Auckland, Auckland.

[4]Colorectal Unit, Department of Surgery, Auckland City Hospital, Auckland.

[5]Bioinformatics Institute, University of Auckland, Auckland.

*Joint Senior Authors.

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Correspondence: Dr Deborah Wright, Department of Molecular Medicine and Pathology, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, 1142, New Zealand. Fax: +64 (0)9 3737492; email: deborah.wright@auckland.ac.nz

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Clinical trials in New Zealand—an update

Vickie Currie, Andrew Jull

Abstract

Aims To describe clinical trial activity in New Zealand for the period 2005–2009 and estimate the number of trials that were listed on World Health Organization-compliant trials registers.

Methods Clinical trials were identified from the annual reports (2005–2009) of the six Health and Disability Ethics Committees. To be included, trials must have been referred to as phase I, II, III or IV trials; or included key descriptors in the title; or have been known to the authors as randomised controlled trials. Key trial characteristics were obtained from searching trials registers or through contact with the investigators.

Results 900 clinical trials were approved in the period 2005–2009 (average 180 per year). The Multi Region ethics committee received most of the applications (379, 42%) followed by the Northern X (190, 21%) and Northern Y (151, 17%). 621 (69%) trials were late phase trials (average 124 per year) and 279 (31%) were early phase trials (average 56 per year). Most trials involved a drug (651, 72%). Trials that recruited infants, children or adolescents accounted for just 68 trials (8%). The most frequent conditions targeted were cancer (163, 18%), cardiovascular disease (125, 14%) and respiratory disease (83, 9%). 532 (59%) trials were commercially sponsored and 335 (37%) were non-commercial. Merck Sharp & Dohme were the single most frequent commercial sponsor (50, 9% of commercial trials) and the Health Research Council the single most frequent non-commercial sponsor (70, 21% of non-commercial trials). 758 (84%) trials could be identified as being listed on a WHO-compliant trials registry. Non-commercially sponsored trials had lower rates of registration (278, 83%) than commercially sponsored trials (480, 90%).

Conclusions Clinical trial activity in New Zealand has increased compared with the period 1998–2003 and early phase activity accounted for most of the increase. There has been a dramatic rise in trials registration and the commercial sector has been more compliant with the International Committee of Medical Journal Editors' statement on trials registration than the non-commercial sector.

In 2010 the New Zealand Health Select Committee investigated the clinical trial landscape in order to consider ways to better coordinate nationwide approaches, remove barriers, streamline processes and measure performance.[1] Several submissions to the Health Select Committee noted the lack of any routinely collected or reported metrics on clinical trial activity in New Zealand. Information regarding clinical trial activity in New Zealand is scarce with no information published since a previous report by one of the authors in 2005.[2]

Measures of clinical trial activity can facilitate accurate estimates of the economic value of the activity, enable comparisons to be made between levels of trial activity

and known areas of disease burden, and identify the impact of policy and process changes. Thus it seems desirable that clinical trial activity be aggregated, if not routinely, then at least with some regularity.

No clinical trial can proceed without ethics committee review and the Health and Disability Ethics Committees publish annual reports on their website that list the studies submitted for their consideration. These details, although limited, are generally sufficient to determine whether a study was a clinical trial. The original intent of this investigation was to describe trial activity from 2004, but the reorganisation of ethics committees adversely affected the reporting for that year.

Therefore, the aim of this study was to describe clinical trial activity in New Zealand 2005–2009 and estimate compliance to the International Committee of Medical Journal Editors' (ICMJE) statements on trials registration.[3 4]

Methods

Annual reports from the six Health and Disability Ethics Committees in New Zealand for the years 2005–2009 were downloaded from the Committees' website. The reports were handsearched by one of the authors (VC) to identify applications for ethical approval for clinical trials.

To be included, trials must have been referred to as phase I, II, III or IV trials; or have contained the key descriptors randomised trial, controlled trial, double blind, placebo or trial in the title; or have been known to the authors to be randomised controlled trials. Pilot studies were only included if they were randomised pilot trials. Where there was uncertainty as to whether an application related to a trial, further information was sought from the applicant or obtained by internet searching.

Trials were not included if the application had been declined or withdrawn. The ethics committee reports were independently reviewed by the second author (AJ) to ensure complete data collect.

Information was extracted from the reports on the year of application, the committee from which approval was sought, the phase of the trial, the type of intervention, the condition being targeted, the population group sought for the trial, trial registration and the sponsor or funder. Trial registers that met the World Health Organization (WHO) Minimal Registration Data Set were searched either through the WHO International Clinical Trials Registry Platform or by directly accessing the register (*clinicaltrials.gov*, the Australia New Zealand Clinical Trials Registry or Current Controlled Trials).

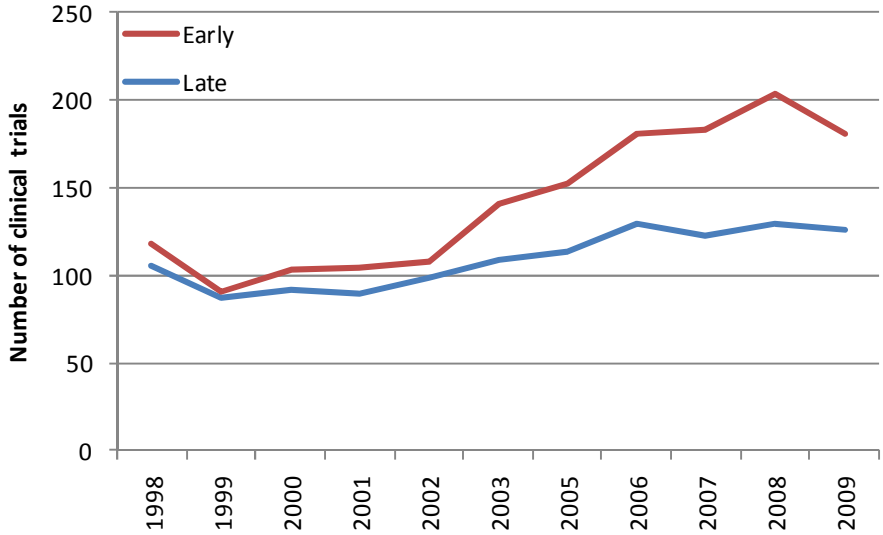
Early phase trials were those identified as phase I, II or pilot randomised controlled trials. Phase I or II trials need not have used random allocation. Late phase trials were those that self-identified as phase III or IV trials and must have used random allocation. If the phase of the trial was unable to be identified from internet searches or the trial title, it was categorised as late phase. Each trial was assigned to one of 26 condition categories. If a trial fell into two or more categories it was coded according to the greatest perceived contribution to one category.

A random sample of 10% of the data extract was independently reviewed by a second author (AJ) to ensure accuracy of content and agreement with condition categorisations. Although agreement was 93%, all condition categorisations were then reviewed by the second author for accuracy and consistency.

Results

Ethical approval was sought for 900 clinical trials conducted in New Zealand between January 2005 and December 2009. Trial activity increased within the 5-year period: there were 152 trials in 2005, 181 trials in 2006, 183 trials in 2007, 203 trials in 2008 and 181 trials in 2009 (Figure 1) giving an annual average of 180 trials per year. The trials were predominantly late phase (621 trials, 69%, average 124/year) with 279 trials (31%, average 56/year) being described as phase I or phase II clinical trials (61 and 189 respectively) or pilot randomised trials (29).

Figure 1. Contribution (cumulative) of early and late phase trials 2005–2009 compared to data from previous report 1998–2003.[2] Note data not available for 2004



The multi-region ethics committee received the largest proportion of applications in the 5-year period, with 379 (42%) of trials falling under this committee's jurisdiction (table 1). Northern X reviewed 190 applications (21%), Northern Y reviewed 151 applications (17%), Central reviewed 71 applications (8%), Upper South reviewed 61 applications (7%) and Lower South reviewed 48 applications (5%).

A similar pattern was evident with both early and late phase trials, which were most frequently reviewed by the multi-region ethics committee (Early: 112, 40%. Late: 267, 43%), followed by the Northern X (Early: 65, 23%. Late: 125, 23%) and Northern Y committees (Early: 44, 16%. Late: 107, 17%). The pattern varied slightly with the Upper South (Early: 29, 10%. Late: 32, 5%), Central (Early: 20, 7%. Late: 51, 8%), and Lower South committees (Early: 9, 3%. Late: 39, 6%). Early phase trials increased from 25% of trial activity in 2005 to 30% of trial activity in 2009, with peak activity in 2008.

758 (84%) trials could be identified as listed on a WHO-compliant trials register, with *clinicaltrials.gov* being the most frequent site of registration (498, 55%) followed by the Australia and New Zealand Clinical Trials Register (250, 28%). The percentage of trials registered was highest at 88% (134) in 2005, but fell in the following years to 82% (148) in 2006, 84% (154) in 2007, 82% (167) in 2008 and 86% (155) in 2009. 278 (83%) of non-commercial trials and 480 (90%) of commercial trials were registered; the only year non-commercial trials exceeded commercial trials being registered was in 2005 (Table 3).

Table 1. Clinical trials by year and phase for each ethics committee

Region	2005 N (%)		2006 N (%)		2007 N (%)		2008 N (%)		2009 N (%)	
	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Multi-region	16 (42)	47 (41)	19 (37)	54 (42)	32 (53)	57 (46)	25 (34)	59 (46)	20 (36)	50 (40)
Northern X	7 (18)	33 (29)	12 (23)	22 (17)	16 (27)	23 (19)	17 (23)	23 (18)	13 (24)	24 (19)
Northern Y	5 (13)	19 (17)	10 (19)	18 (14)	8 (13)	25 (20)	13 (18)	21 (16)	8 (15)	24 (19)
Central	3 (8)	5 (4)	6 (12)	10 (8)	3 (5)	9 (7)	5 (7)	10 (8)	3 (5)	17 (13)
Upper South	7 (18)	5 (4)	4 (8)	12 (9)	1 (1)	3 (2)	7 (9)	5 (4)	10 (18)	7 (6)
Lower South	–	5 (4)	1 (2)	13 (10)	–	6 (5)	7 (9)	11 (9)	1 (2)	4 (3)
Total	38 (25)	114 (75)	52 (29)	129 (71)	60 (33)	123 (67)	74 (36)	129 (64)	55 (30)	126 (70)
	152		181		183		203		181	

Table 2. Clinical trials by year approved and condition

Variables	2005 N (%)	2006 N (%)	2007 N (%)	2008 N (%)	2009 N (%)	Total N (%)
Cancer +	35 (23)	32 (18)	30 (16)	34 (16)	32 (18)	163 (18)
Cardiovascular ++	24 (16)	33 (18)	26 (14)	28 (14)	14 (8)	125 (14)
Respiratory	10 (7)	22 (12)	17 (9)	18 (9)	16 (9)	83 (9)
Gastroenterology	17 (11)	4 (2)	15 (8)	16 (8)	12 (7)	64 (7)
Diabetes	10 (7)	11 (6)	18 (10)	11 (5)	12 (7)	62 (7)
Neurology	5 (3)	8 (4)	7 (4)	7 (3)	10 (6)	37 (4)
Mental health	5 (3)	8 (4)	4 (2)	7 (3)	9 (5)	33 (4)
Anaesthesia/pain	4 (3)	6 (3)	7 (4)	8 (4)	8 (4)	33 (4)
Haematology (non-cancer)	3 (2)	5 (3)	7 (4)	7 (3)	6 (3)	28 (3)
Rheumatology	3 (2)	7 (4)	7 (4)	6 (3)	5 (3)	28 (3)
Women's health	8 (5)	1 (1)	7 (4)	1 (1)	7 (4)	24 (3)
Ophthalmology	6 (4)	3 (2)	2 (1)	4 (2)	8 (4)	23 (3)
Infectious diseases	2 (1)	4 (2)	6 (3)	3 (2)	7 (4)	22 (2)
Emergency/critical care	2 (1)	4 (2)	6 (3)	4 (2)	5 (3)	21 (2)
General/vascular surgery	1 (1)	6 (3)	3 (2)	7 (3)	4 (2)	21 (2)
Orthopaedics	2 (1)	5 (3)	4 (2)	5 (3)	4 (2)	20 (2)
Neonatology	3 (2)	4 (2)	2 (1)	5 (3)	2 (1)	16 (2)
Dermatology	1 (1)	1 (1)	1 (1)	7 (3)	2 (1)	12 (1)
Renal	–	–	3 (2)	4 (2)	4 (2)	11 (1)
Urology	1 (1)	3 (2)	2 (1)	3 (2)	2 (1)	11 (1)
Dental	–	2 (1)	3 (2)	3 (2)	2 (1)	10 (1)
Gerontology	2 (1)	1 (1)	1 (1)	2 (1)	–	6 (1)
Immunology	–	1 (1)	1 (1)	1 (1)	2 (1)	5 (1)
Transplant	2 (1)	2 (1)	1 (1)	–	–	5 (1)
Other *	2 (1)	3 (2)	1 (1)	6 (3)	4 (2)	16 (2)
Unknown	4 (3)	5 (3)	1 (1)	5 (2)	4 (2)	19 (2)
Total	**152 (17)**	**181 (20)**	**183 (20)**	**203 (23)**	**181 (20)**	**900 (100)**

[+] Included haematological cancers; [++] Included cardiac surgery and interventional cardiology; [*] Included herbal, dietary, injury prevention, education, physiotherapy, sports science, sleep disorder, and health services delivery interventions and other endocrine diseases.

Table 3. Trial registration, by year, for non-commercial and commercial trials (excluding 33 trials where sponsorship could not be determined)

Registered	2005 N (%)		2006 N (%)		2007 N (%)		2008 N (%)		2009 N (%)	
	Public	Industry	Public	Industry	Public	Industry	Public	Industry	Public	Industry
Yes	55 (98)	79 (92)	57 (84)	91 (88)	47 (76)	107 (92)	61 (79)	106 (88)	58 (81)	97 (92)
No	1 (2)	7 (8)	11 (16)	13 (12)	15(24)	10 (8)	16 (21)	14 (12)	14 (19)	8 (8)
Total	**142**		**172**		**179**		**197**		**177**	

The sponsor could be identified in 867 (96%) trials either directly from the annual report or from a trials register. 532 (59%) trials were funded by industry or other private sponsors (commercially sponsored) and 335 (37%) by public research funders, government agencies or research charities. The largest single commercial contributor to trial activity was Merck with 50 trials (9% of commercial activity), followed by Roche (48, 9%), GSK (41, 8%) and Novartis (28, 5%).

The largest single non-commercial sponsor was the Health Research Council of New Zealand, providing funding for 70 trials (21% of non-commercial activity). Universities (both New Zealand and overseas universities) were the sponsor for 41 trials (12%), while district health boards or other health providers sponsored 37 trials (11%), and government ministries or other government agencies sponsored 17 trials (5%). The remaining 170 trials (51% of non-commercial activity) were sponsored by research trusts or charities within New Zealand and from overseas.

The largest single condition category investigated was cancer followed by cardiovascular disease (including stroke) and respiratory diseases (table 2). The target populations recruited were adults in 631 trials (70%), infants in 29 trials (3%), children in 22 trials (2%) and adolescents in 7 trials (1%).

Ten trials (1%) targeted both children and adolescents, while 60 trials (7%) allowed all ages entry (20) or had age criteria that allowed a mix of children, adolescents and adults to be recruited but within specified age ranges (40). The target population could not be identified in the remaining 141 trials (16%).

The intervention was a drug in 651 (72%) trials compared with a process such as education, training or service delivery in 108 (12%) trials, a procedure such as radiation therapy or surgery in 55 (6%) trials, and a device in 49 (5%) trials. The interventions in the remaining 37 (4%) trials included dietary interventions, alternative therapies or were unable to be determined.

Discussion

The number of trials undertaken in New Zealand in 2005-2009 has increased to an average of 180 trials per year, up from an average of 111 per year in 1998-2003.[2] Growth that appeared to have started in 2003 has been sustained. Much of the increase is due to early phase activity, with 300% increase in activity from an average of 14 trials per year in 1998-2003. The proportion of trials that could be identified as being listed on a WHO-compliant register has also increased to 84%, up from 32% in 2003.[2]

Internationally, this study remains the only nationwide stock take of all clinical trial activity, with the exception of a similar exercise undertaken in by one of the authors in 2004.[2] The national organisation of the health and disability ethics committees, an overarching operating standard, with standardised national application form and annual reporting facilitates such a stock take. Other national surveys have been limited to non-commercial trials only or examined clinical trial registers for specific country codes.[5 6]

This study demonstrates once more that ongoing monitoring of trial activity in New Zealand is possible, especially if information currently reported by ethics committees is used. Such an activity could be undertaken be the relevant ministries, such as the Ministry of Health or the Ministry of Research, Science and Technology. With very little added effort, information that clearly identifies ethics applications as pertaining to a clinical trial, the phase of the trial, whether it is registered or not and where, could be included in the ethics committees' annual reports for aggregation by a ministry.

New Zealand is thought to provide an environment conducive to increasing clinical trial activity: it is a resourceful and innovative society, has a reputation for conducting world class research, and can produce results on time, with added cost benefits when the New Zealand dollar is weak against other currencies.[7] These factors are reflected New Zealand's contribution to clinical trial publications per million population over the last 60 years (791/million), which puts New Zealand at number three after Sweden and Denmark.[8]

Similarly, New Zealand's biomedical research publications per million population 1990–2000 (309.2) are on par with that of the United Kingdom (310.4) although well short of Sweden (714.3) and the USA (451.2).[9] Although it is not possible to compare all clinical trial activity, the average number of non-commercial trials conducted in New Zealand during 2005–2009 that were non-commercially sponsored was 67 per year, comparable to the 66.5 per year conducted in the United Kingdom during 1980–2002.[5] There is no doubt that New Zealand is a small player in clinical trial activity, but it does punch above its weight.

The increase in trials being registered from 32% in 2003 to 84% in 2005–2009 can only be ascribed to the announcement by the ICMJE that trials seeking publication in member journals had to be prospectively registered on a register compliant with the WHO Minimal Registration Data Set.[4] Previous attempts to encourage registration, such as legislative requirements in trials for life-threatening or serious conditions, had little effect.[10] That 100% of trials conducted in New Zealand were not registered cannot be explained by the increase in early phase activity. Industry appears to be more compliant with trials registration than the non-commercial sector and the commercial sector accounts for the greater proportion of early phase trials in New Zealand (38% of commercial trials compared to 22% of non-commercial trials).

Although industry was hesitant to ascribe voluntarily to trials registration, citing commercial sensitivity,[11] our findings suggest industry has overcome such reservations. The report of the health select committee inquiry into improving the environment for clinical trials recommended that trials conducted in New Zealand be registered with the Australia New Zealand Clinical Trials Register (ANZCTR).[12] However, a possible barrier has arisen as the Health Research Council (HRC) is no longer assisting with funding the ANZCTR, even though the HRC recommends

registering on the ANZCTR. Alternative sources of public funding from New Zealand are needed if this register is to be maintained.

Clinical trials are defined by the WHO as being "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."[3] As such the WHO expectation is that any trial from phase I onwards should be registered, although that consideration was relaxed by the ICMJE 2005 statement.[4]

Ethics committees have a role in continuing improvement in trials registration. The current national application form does ask if it is intended to register a clinical trial, but there is no hint of necessity. If ethics committees were to require trial registration prior to releasing ethical approval, non-commercial sector performance would improve. Such an improvement would be unlikely to influence approval times for commercially-sponsored trials given industry's already excellent record in trials registration.

This study was subject to three limitations. First, the number of clinical trials for which ethical approval was sought may have been underestimated despite our best efforts. If a study did not include adequate descriptors to identify it as a trial or could not be identified as such from internet searching it was excluded from selection. Second, we did not determine where the trial took place. While locality organisations are included for each trial approval in the ethics committees' reports, it was not always possible to determine where the trial was undertaken from such locality reports and thus the information was not collated for analysis. However, we have reported information by ethics committee, which allows some approximation of trial activity at a regional level. Third, the ethics committee annual reports do not specify if trials progress from approval to completion. While this study details applications for ethical approval for trials, it therefore does not definitively detail the number of trials initiated in New Zealand, as some trials may have failed to recruit participants.

Conclusion

There has been an increase in clinical trial activity since 2005 and much of this increase is due to increased early phase activity. There has been a dramatic increase in the proportion of trials registered, with commercially-sponsored trials being more compliant with registration. Ethics committees could improve the compliance of the non-commercial sector with trials registration by requiring evidence of trial registration prior to providing ethical approval.

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Author information: Vickie Currie, Summer Scholar, Faculty of Medicine and Health Sciences, University of Auckland; Andrew Jull, Associate Professor, School of Nursing and Senior Research Fellow, Clinical Trials Research Unit, School of Population Health, University of Auckland

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Correspondence: Andrew Jull, Associate Professor, School of Nursing, University of Auckland, Private Bag 92019, Auckland, New Zealand. Fax: +64 (0)9 3767158; email: a.jull@auckland.ac.nz

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THE NEW ZEALAND MEDICAL JOURNAL
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Short and long term outcomes of oesophagectomy in a provincial New Zealand hospital

Fadhel Al-Herz, David Healey, Tarik Sammour, Josese Turagava, Bruce Rhind, Mike Young

Abstract

Background Oesophagectomy is a complex procedure associated with a significant morbidity and mortality rate. There is very little published data from New Zealand, with no published data from a non-Tertiary New Zealand hospital. We aimed to evaluate the outcomes of oesophagectomy at a single provincial hospital in New Zealand.

Method Retrospective review of clinical records of all patients who underwent oesophagectomy at Palmerston North Hospital (a level II provincial New Zealand public hospital) between 1993 and 2010 was performed. Demographic data, operative details, postoperative recovery parameters, survival data, pathological data, and details of adjuvant treatment were collected.

Results Data from all 68 patients who underwent oesophagectomy were included. Mean age was 63.6 ± 10.9 years, and 69% of patients were male. Mean operating time was 438.37 ± 101.8 min, and mean intraoperative blood loss was 934.5 ± 790.2 ml. Median intensive care unit stay was 7 (1–29) days, and total day stay was 17.5 (4–60) days. Tracheostomy was performed in 20 patients (29.4%). Anastomotic leak occurred in 7 patients (10.3%), chylothorax in 6 patients (8.8%) and cardiopulmonary complications in 34 patients (50.0%). The all cause in-hospital mortality rate was 4.4%. Overall survival at 30 days was 98.5%, at 1 year was 78.3% and at 5 years was 30.3%.

Conclusion Survival outcomes of oesophagectomy in this provincial New Zealand hospital are comparable to published series from national and international tertiary centres.

Oesophagectomy is a potentially curative treatment for patients with resectable oesophageal cancer, and is the mainstay of treatment for adenocarcinoma in patients without metastatic disease.[1] The procedure is, however, associated with considerable morbidity,[2] and despite advances in surgical technique and adjuvant therapy, 5-year survival rates in all published series remain at or below 40%.[3–7]

A multitude of factors influence survival rates after curative oesophageal resection. These include: patient selection criteria, tumour location, surgical technique, perioperative care practices, adjuvant therapy protocols, and various population factors.[4,7,8]

The impact of hospital and surgeon volume on operative mortality has also been well reported.[9–11] As a result of this, referral of patients suitable for oesophagectomy to dedicated specialised centres has been advocated, in keeping with international trends

towards centralisation and specialisation of low-volume complex surgery.[12–14] However, there is currently no evidence that volume has any influence on long-term survival or improvement in quality of life after oesophagectomy.[15] In addition, it has been noted that volume alone is insufficient to define centres of excellence, and that a lowest recommended annual volume has not actually been defined.[15]

In New Zealand, geographical and population barriers to centralisation have meant that oesophagectomy continues to be performed in some non-tertiary centres. A single case series published from a tertiary centre has demonstrated equivalent outcomes for oesophagectomy in New Zealand compared with international data;[16] however, there is currently no published data from a non-tertiary hospital.

Palmerston North Hospital (PNH) is a level II provincial hospital servicing the city of Palmerston North (population 75,000) and the Manawatu province of the lower central North Island of New Zealand (population 160,000). It is the only secondary level hospital in the Manawatu region, and one of six national Regional Cancer Treatment Service centres, providing specialist intensive care, medical and surgical subspecialty services for a larger population of up to 500,000.

The aim of this study is to evaluate the outcome of oesophagectomy at PNH.

Methods

Patients—All patients who underwent an oesophagectomy at PNH between 1st January 1993 and July 2010 were included in this study (clinical records prior to 1993 are not available, as a significant number, particularly of deceased patients, have been deliberately destroyed in accordance with national clinical records guidelines). There were no exclusion criteria.

Data collection—Retrospective review of patient clinical records, the Otago Audit System electronic database[21] (prospectively maintained by the Department of General Surgery since 1993), as well as Operating Theatre and Department of Pathology electronic records was performed by two investigators (F.A., D.H.). Data collected included demographic data, intraoperative parameters, postoperative outcomes, pathological / histological data, details of adjuvant and neo-adjuvant therapy, and survival data.

Statistics—Results were tabulated and analysed using SPSS® for Windows® version 17.0 (Lead Technologies Inc, Chicago, Illinois, USA). Continuous variables were tested using the Shapiro-Wilk test for normality and the results presented as Mean (Standard Deviation) for parametric data and Median (Range) for non-parametric data.

Results

Patients—Sixty-eight patients underwent surgery for oesophagectomy between January 1993 and July 2010 in PNH. Mean patient age was 63.3 years, and 69.1% of the patients were male (Table 1).

Fifty-two patients (76.5%) presented with pathology sited in the distal third of the oesophagus, and the remaining with pathology in the middle third of the oesophagus. Sixty-five patients underwent an Ivor-Lewis oesophagectomy; 1 underwent Ivor-Lewis oesophagectomy with pancreatectomy; 1 underwent oesophagectomy via abdominal and right thoracotomy with oesophago-jejunal anastomosis (because of previous total gastrectomy), and 1 underwent left thoraco-abdominal oesophagestrectomy.

Table 1. Baseline patient parameters

Variables	N (%)
Age (Mean in years, SD)	63.6 (10.9)
Sex	
Male	47 (69.1%)
Female	21 (30.9%)
BMI (Mean in kg/m^2, SD)	25.9 (7.4)
ASA score	
I	6 (8.8%)
II	43 (63.2%)
III	19 (27.9%)
Previous major abdominal surgery	24 (35.3%)

SD: Standard Deviation.

Intraoperative data—Four surgeons performed all the operations, with one surgeon (M.Y.) performing 35 operations, and another (B.R.) performing 31 operations. The other two surgeons performed one oesophagectomy each during this period. Mean operating time was 438.4 ± 101.8 min and mean intraoperative blood loss was 934.5 ± 790.2 ml (Table 2).

Median intraoperative blood transfusion requirement was 2 units (0–8), and mean intravenous fluid requirement was 6.6 ± 1.4 L. Eight patients had intraoperative complications: 5 patients had a splenic injury (all requiring splenectomy), 1 patient had a liver injury (treated conservatively with packing and a re-look laparotomy on day 1, and 2 patients developed an intraoperative acute coronary syndrome.

Table 2. Intraoperative parameters

Variables	N (%)
Operation	
Ivor-Lewis oesophagectomy	65 (95.5%)
Oesophagectomy + splenectomy + pancreatectomy	1 (1.5%)
Oesophagectomy + oesophago-jejunal anastamosis	1 (1.5%)
Thoraco-abdominal oesophagectomy	1 (1.5%)
Operative intent	
Cure	64 (94.1%)
Palliation	4 (5.9%)
Operation time (Mean in min, SD)	438.7 (101.8)
Blood loss (Mean in ml, SD)	934.5 (790.2)
Blood transfused (Red cells, Median in units, Range)	2 (0–8)
Intravenous fluids (Mean in L, SD)	6.6 (1.4)
Intraoperative complications	
Splenic injury	5 (7.4%)
Liver injury	1 (1.5%)
Acute coronary syndrome	2 (2.9%)
Total (per patient)	8 (11.8%)

Postoperative data—Median intensive care unit stay was 7 days (1–29), and median time to extubation was 3 days (0–23, Table 3). Twenty (29.4%) patients required

tracheostomy. Mean intravenous fluid infusion in the first 24 hours was 10.4 ± 2.1 L, median time of total parenteral nutrition administration was 7.5 days (0–33), and median time of jejunal or nasogastric enteric feeding administration was 0.5 days (0–47). The median total hospital stay was 17.5 (4–60) days.

Table 3. Postoperative recovery parameters.

Parameter	Value
Intravenous fluids 1st 24hours (Mean in L, SD)	10.4 (2.1)
Days in ICU (Median, Range)	7 (1–29)
Day extubated (Median, Range)	3 (0–23)
Total days intubated (Median, Range)	4 (0–23)
Tracheostomy required	20 (29.4%)
Days on TPN (Median, Range)	7.5 (0–33)
Days on enteric feed (Median, Range)	0.5 (0–47)
Day oral fluids started (Median, Range)	8 (0–55)
Day oral solid food started (Median, Range)	11 (0–57)
Day stay (Median, Range)	17.5 (4–60)
Major postoperative complication	
Anastomotic leak	7 (10.3%)
Chylothorax	6 (8.8%)
Other intra-abdominal	3 (4.4%)
Sub-phrenic abscess	1
Stomach perforation	1
Mesenteric ischaemia	1
Cardiopulmonary	34 (50.0%)
Pneumonia	25
ARDS	2
Pulmonary embolism	1
Congestive cardiac failure	1
Myocardial infarction	3
Cardiac Arrhythmia	4
Cerebrovascular Event / Stroke	1
Prolonged unexplained hypotension	1
Acute renal failure	2 (2.9%)
Costal osteomyelitis	2 (2.9%)
Central line sepsis	1 (1.5%)
Total (per patient)	39 (57.54%)
Minor postoperative complication	
Atrial Fibrillation	20
Wound infection	3
Urinary tract infection	2
DVT	1
Early anastomotic stricture	4
Foot drop	1
Total (per patient)	25 (36.7%)
Re-operation	6 (8.8%)
Re-admission to ICU	10 (14.7%)

ICU=Intensive Care Unit; SD=Standard Deviation.

An anastomotic leak occurred in seven patients (10.3%), chylothorax in six patients (8.8%) and cardiopulmonary complications in thirty-four patients (50.0%, Table 3).

Six patients (8.8%) required reoperation to resolve major postoperative complications, and ten patients (14.7%) required re-admission to ICU after they had been discharged to the general surgical ward. Minor early / inpatient postoperative complications occurred in 25 patients (36.7%).

Pathology—Fifty-one patients (75.0%) had adenocarcinoma diagnosed on histology, 11 (16.2%) had squamous carcinoma, 2 patients (2.9%) had adeno-squamous carcinoma, 2 patients (2.9%) had Barrett's disease with high grade dysplasia but no invasive cancer, 1 (1.5%) had a gastrointestinal stromal tumour, and 1 (1.5%) had a non-invasive neuroendocrine tumour. Further details on staging and adjuvant/ neoadjuvant therapy for the 64 patients with confirmed invasive cancer are presented in Table 4.

Table 4: Pathology and adjuvant/neoadjuvant therapy for patients with invasive carcinoma (n=64)

Variables	N (%)
Differentiation	
Well	12 (18.8%)
Moderate	32 (50.0%)
Poor	16 (25.0%)
Not available	4 (6.3%)
Lymph nodes (Mean, SD)	
Total nodes	13.1 (8.7)
Positive nodes	3.3 (5.9)
T	
T1	12 (18.8%)
T2	11 (17.2%)
T3	40 (62.5%)
T4	1 (1.6%)
N	
N0	32 (50.0%)
N1	32 (50.0%)
M	
M0	61 (95.3%)
M1	3 (4.7%)
Preoperative Chemotherapy / Radiotherapy	
Chemotherapy	17 (26.6%)
Radiotherapy	2 (3.1%)
Nil	45 (70.3%)
Postoperative Chemotherapy / Radiotherapy	
Chemotherapy	10 (15.6%)
Radiotherapy	19 (29.7%)
Chemotherapy + Radiotherapy	1 (1.6%)
Nil	34 (53.1%)

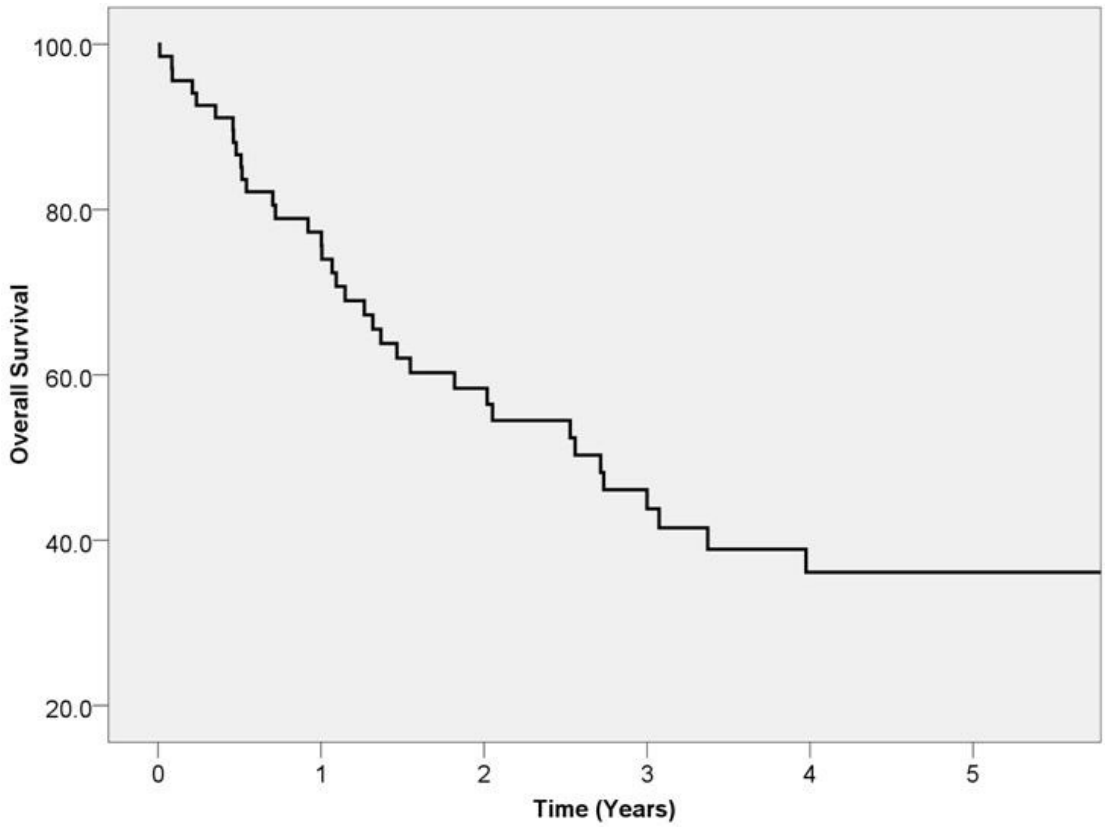
Survival—There were 3 postoperative in-hospital deaths. One patient died secondary to systemic sepsis after a clinical anastomotic leak, 1 patient had a global mesenteric embolic event on day 4, and 1 patient died after a myocardial infarction on day 31. Thus the total in-hospital survival rate was 95.6%.

For patients with a confirmed diagnosis of invasive carcinoma on the resection specimen, the 1 year survival rate was 77.2% and the 5 year survival rate was 30.3% (Table 5). A Kaplan-Meier survival curve is shown in Figure 1. The survival rate for the entire patient cohort (including patients with non-invasive disease) was marginally higher.

Table 5. Survival for patients with invasive carcinoma (n=64).

Variables	Percentage
30 days (n=64)	98.4%
1 year (n=57)	77.2%
2 years (n=50)	56.0%
3 years (n=42)	42.9%
4 years (n=40)	32.5%
5 years (n=33)	30.3%

Figure 1. Kaplan-Meier survival graph for patients with invasive carcinoma (n=64)



Discussion

We have conducted a retrospective study looking at the short and long-term outcomes of oesophagectomy in a secondary level provincial New Zealand hospital. The results

demonstrate outcomes that are generally comparable with current national and international data.[2,5,6,9–11,15–20]

The 5-year overall survival rate in this study was 30%, which compares favourably with the published 5 year rate of 23% by Omundsen et al (the only published oesophagectomy case series from a tertiary New Zealand hospital).[16] The trend is similar for survival at 1 year (77.2% vs 54.5%); and 3 years (42.9% vs 35%) as well.[16]

The apparent differences in survival rate could be explained by a number of factors. In our series only 1 patient (1.6%) was diagnosed with a stage T4 tumour, versus 12 patients (18%) in the Omundsen study.[16] It is unclear whether this difference is due to patient selection or earlier detection. In addition, a higher percentage of patients in our series were given neo-adjuvant chemotherapy compared with the relatively low rates in the Omundsen series.[16] This is probably because their data set pre-dates publication of the MAGIC trial of neo-adjuvant therapy for oesophago-gastric adenocarcinoma.[21]

Since publication of the MAGIC trial recommendations, use of neo-adjuvant chemotherapy has probably increased in New Zealand.[22] Certainly, since early 2007, Palmerston North Hospital's Regional Cancer Treatment Service has adopted the MAGIC protocol for neoadjuvant therapy for bulky stage II and III oesophageal or gastric adenocarcinoma (as evident on preoperative imaging) in otherwise fit patients.[21].

The postoperative complication rate in our study is relatively high. Although the anastomotic leak rate of 10.3% is within the accepted range for this procedure, a relatively high proportion of patients developed postoperative cardiopulmonary complications (50.0%) compared to other published series.[9, 11, 15, 16, 20, 23] One possible explanation for this finding is the relatively prolonged intubation time experienced by these patients (3 days).

Indeed, the long intensive care unit stay (7 days) is not only a reflection of the lack of a dedicated high dependency unit in PNH, but also the high rate of utilisation of a tracheostomy for ventilation (which anecdotally is a practice peculiar to the PNH intensive care unit). However, it has been previously shown that early extubation may significantly reduce the rate of postoperative cardiovascular complications, and from a resource utilisation perspective it is clear that an early extubation policy should be advocated.[24-26]

Another possible reason for the high cardiopulmonary complication rate is the highly positive intraoperative and postoperative fluid balance. Patients received on average 2 units of blood and 6.6 L intravenous fluids intraoperatively, despite an estimated blood loss of less than 1 L. In addition, the total volume of intravenous fluids administered in the first 24 hours was 10.4 L.

There is now clear evidence that a policy of relative fluid restriction is advantageous in terms of cardiopulmonary complications after major abdominal surgery, and specifically after oesophagectomy.[17, 27, 28] Taking these practices one step further, a recent case-control study by Munitiz et al demonstrates significant advantages using a clearly defined enhanced recovery perioperative protocol in the management of patients undergoing oesophagectomy.[17]

As part of this protocol, all patients were extubated in the operating theatre or immediately on arrival in the intensive care unit, and a policy of negative fluid balance over the first 4 days was adhered to. As a result, pulmonary complications were significantly reduced from 23% to 14% (P=0·025).[17] These modifications in perioperative management are being discussed at PNH, with view to implementation, at the time of writing of this manuscript.

Despite the relatively higher postoperative cardiopulmonary complication rate in our study, it should be noted that the in hospital mortality rate in our series was relatively low at 4.4%.[9,11,15,16,20,23] Thus, the impact of hospital volume on short and long term survival was not readily apparent.

The major limitation of the current study is the retrospective nature of the data collection. In addition, mortality data was derived from the Palmerston North Hospital Clinical Records Department rather than the New Zealand Births and Deaths Registry. Nonetheless, all deaths notified by the New Zealand Births and Deaths registry are cross-referenced automatically with the Palmerston North Hospital Clinical Records Department, and therefore we can assume that survival data is accurate. Another weakness of this study is that disease-specific mortality and cancer recurrence rates could not be established.

Conclusion

Outcomes of oesophagectomy in this provincial New Zealand hospital are comparable to published series from national and international tertiary centres.

Competing interests: None declared.

Author information: Fadhel Al-Herz, Surgical Registrar, Department of Surgery, Palmerston North Hospital, Palmerston North; David Healey, Surgical Registrar Department of Surgery, Palmerston North Hospital, Palmerston North; Tarik Sammour, Research Fellow, Department of Surgery, South Auckland Clinical School, Faculty of Medical and Health Sciences, University of Auckland; Josese Turagava, Surgical Registrar Department of Surgery, Palmerston North Hospital, Palmerston North; Bruce Rhind, General Surgeon Department of Surgery, Palmerston North Hospital, Palmerston North; Mike Young, General Surgeon, Department of Surgery, Palmerston North Hospital, Palmerston North

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Correspondence and reprint requests: Dr Tarik Sammour, Research Fellow, Department of Surgery, South Auckland Clinical School, Private Bag 93311, Middlemore Hospital, Otahuhu, Auckland, New Zealand. Fax: + 64 (0)9 6264558; email: sammour@xtra.co.nz

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Arcobacter species in diarrhoeal faeces from humans in New Zealand

Owen Mandisodza, Elizabeth Burrows, Mary Nulsen

Abstract

Aim To determine the prevalence, genetic diversity and antimicrobial susceptibility of *Arcobacter* spp in faecal samples from humans with diarrhoea in New Zealand.

Methods An enrichment method was used to isolate *Arcobacter* spp from diarrhoeal human faeces submitted to a community laboratory in Hawke's Bay. The identity of isolates was confirmed by PCR and their diversity was determined by pulsed field gel electrophoresis (PFGE). Antibiotic susceptibility was established with E test strips.

Results *Arcobacter* spp were isolated from 12 of 1380 diarrhoeal faecal samples examined (0.9%), including 7 *A. butzleri* and 5 *A. cryaerophilus*. Additional enteric pathogens were detected in four of these diarrhoeal faecal samples. All the *Arcobacter* isolates were genetically distinct and susceptible to ciprofloxacin. Most were also susceptible to erythromycin (92%) but fewer to tetracycline (67%) and ampicillin(50%).

Conclusion *A. butzleri* and *A. cryaerophilus* cause a small proportion of cases of diarrhoea in humans resident in New Zealand.

Arcobacter species, formerly classified as aerotolerant *Campylobacter species*, are widely distributed in production animals, pets, wild animals, and the environment. Colonised animals, particularly poultry, frequently show no symptoms but, on occasions, *Arcobacter* spp. have been implicated in abortions, mastitis and diarrhoea.[1,2] *Arcobacter* spp are also common in foods such as meats and shell fish, and fresh water.[1,2]

Three of the 12 species, *A. butzleri, A. cryaerophilus* and *A. skirowii* have been isolated from humans with diarrhoea or other gastrointestinal symptoms,[1,3] in particular, watery or persistent diarrhoea.[4–7] *A. butzleri* was the only pathogen detected in an outbreak of recurrent abdominal cramps in 10 children aged 3 to 7 years in an Italian school.[8]

Occasionally *A. butzleri*[9-11] and *A. cryaerophilus*[12,13] have been isolated from patients with bacteraemia but *Arcobacter* species have also been isolated from faecal samples from healthy humans.[7,14-16]

Arcobacter spp. have recently been detected in a high proportion of chicken meat samples purchased in Palmerston North, New Zealand[17] so the aim of this study was to investigate their prevalence in the faeces of humans with diarrhoea in one region of New Zealand.

Materials and Methods

All faecal samples sent to a community laboratory in Hawke's Bay, New Zealand, for diagnosis of gastrointestinal infection, between October, 2007 and June, 2008, were cultured for *Arcobacter* spp. after they had had been sampled for routine screening of pathogens.

For the initial enrichment, 1 g of faeces was emulsified in 9 mL of *Arcobacter* broth (Oxoid Ltd, UK) and incubated at 28°C for 48 hrs in a microaerobic atmosphere with gas packs (AnaeroPack System™, Mitsubishi Gas Chemicals, Japan). This was then subcultured onto *Arcobacter* selective agar, containing *Arcobacter* broth (28g L^{-1}), Oxoid No. 1 agar (12g L^{-1}), plus the following antimicrobial agents supplied by Aldrich Sigma NZ: cefoperazone (16mg L^{-1}), trimethoprim (64mg L^{-1}), novobiocin (32mg L^{-1}). amphotericin B (10mg L^{-1}), 5-fluorouracil (100mg L^{-1}).

Agar plates were incubated for 48 hrs in a microaerobic atmosphere. Preliminary identification was based on colony morphology and Gram reaction of the isolates from pure culture, by oxidase test using oxidase strips (Oxoid Ltd, UK), and by dark-field microscopy for darting motility. Presumptive isolates of *Arcobacter* spp, subcultured onto 5% sheep blood agar, were preserved on Microbank porous beads system (Pro-Lab Diagnostic) and stored at -80°C for later molecular characterization.

Routine faecal screening included culture for *Salmonella, Shigella, Campylobacter*, *Yersinia* and *Aeromonas* species. Selected stools were also examined for *E. coli* O157 and/or rotavirus. If requested, a *Helicobacter pylori* faecal antigen test, a *Cryptosporidium* plus *Giardia* species antigen test and microscopic examination for parasites were also done. Clinical data on positive samples was derived from laboratory records. Reference strains of *A. butzleri* (ATCC 49616) and *A. cryaerophilus* (ATCC 43158 and ATCC49942) were obtained from the Institute of Environmental Science and Research Limited (ESR), Wellington, New Zealand. Ethical approval was provided by the Central Ethical Committee (HDEC CEN/07/04/026).

The minimum inhibitory concentration (MIC) of ampicillin, tetracycline, ciprofloxacin and erythromycin was determined for *Arcobacter* spp. grown for 48 hrs on blood agar and suspended in saline to a density equivalent to 1.0 McFarland standard. For each antibiotic-isolate combination, a Mueller Hinton agar plate enriched with 5% sheep blood (Fort Richard, NZ) was spread with 100µL of the suspension, overlaid with an MIC Evaluator strip (Oxoid, UK) and incubated at 28°C for 48 hrs in a microaerobic environment. The MICs were classified as susceptible, intermediate or resistant according to the criteria used in the 1997-2006 NARMS report for *Campylobacter* for tetracycline, erythromycin and ciprofloxacin and for *Salmonella, Shigella* and *E. coli* O157 for ampicillin.[18]

Multiplex polymerase chain reaction (m-PCR) was performed as described by Houf et al (2000),[19] except that loading buffer was omitted, the $MgCl_2$ concentration was increased from 1.3 to 1.5 mmol L^{-1} and one to two colonies of suspected *Arcobacter*, grown for 48 h on 5% sheep blood agar plates at 27±2°C microaerobically, were added directly to the reaction mix which was then heated to 94°C for 3 min prior to amplification in a GeneAmp PCR System 2400 (Biosystems, Singapore) Amplified products were separated by electrophoresis in 1.5% agarose. Gels were stained with ethidium bromide and inspected visually under UV light. DNA from *A. butzleri* (ATCC 49616), and *A. cryaerophilus* (ATCC 43158) type strains were included as positive controls.

For PFGE, frozen-stored isolates of *Arcobacter* were streaked onto 5% sheep blood agar plates and grown microaerobically for 48–72 hours at 27±2°C. Colonies were suspended in 2 mL of phosphate buffered saline (PBS) to a final optical density (OD) of 1.00 ± 0.20. Suspended cells (400 mcL) were mixed with 20 mcL of proteinase K (20 mg mL^{-1}) (Amresco, USA) and equal volumes of 1% Seakem Gold agarose (Cambrex Bioscience, USA) prepared in 0.5× TBE buffer. The mixture was transferred to Chef disposable plug moulds (Bio-Rad, USA) and allowed to solidify at room temperature. Plugs were incubated at 55°C in 5 mL of lysis buffer (50 mM Tris, 50 mM EDTA and 1% Sarcosyl) and 25 mcL of proteinase K for 3 hours.

Treated plugs were washed once with 10-15 mL of MilliQ (MQ) water and four times with 10-15 mL of TE buffer (10 mM Tris and 1 mM EDTA) for 10-15 min at 55°C. About 2 mm of the plug was digested with *Eag*I (New England Biolabs, USA) at 37°C for four hours. The restriction fragments were separated by electrophoresis in 1% of Seakem Gold agarose (Cambrex Bioscience, USA) using a CHEF Mapper (Bio-Rad, USA).

The gels were run using the following conditions: Initial switch time 0.1 seconds, final switch time 90 seconds, run time 20 hours, angle 120°, gradient 6V/cm, temperature 14°C and ramping factor linear.

The gels were stained for 10 minutes in ethidium bromide solution, destained with sterile water and visualised using the Gel-DOC 2000 software (Bio-Rad, USA).

Results

From 1380 diarrhoeal faecal samples, 16 isolates were presumptively identified as *Arcobacter* spp. but only 12 (0.9%) were positive by multiplex PCR.

Table 1. Details of patients whose faeces yielded *Arcobacter* spp

Isolate	Age (yrs)	Sex	Symptoms	Appearance of faeces	*Arcobacter* spp isolated	Other enteric pathogens detected
1	32	M	Diarrhoea lasting 1 week	Diarrhoeic	*butzleri*	None
2	32	M	NR[1]	NR	*butzleri*	None
3	46	F	Persistent diarrhoea lasting 1 week	Loose	*butzleri*	None
4	53	M	Persistent diarrhoea	Loose	*butzleri*	*Helicobacter pylori* antigen positive
5	72	M	NR	Semi-formed	*butzleri*	None
6	76	M	Diarrhoea and vomiting	Soft	*butzleri*	*Aeromonas hydrophila*
7	78	M	?Diarrhoea	Loose	*butzleri*	None
8	2	F	Diarrhoea	Loose	*cryaerophilus*	None
9	31	F	NR	Watery	*cryaerophilus*	None
10	40	F	NR	Loose	*cryaerophilus*	*Blastocystis hominis*
11	56	F	?Diarrhoea	Semi-formed	*cryaerophilus*	*Helicobacter pylori* antigen positive
12	71	F	?Diarrhoea	Semi-formed	*cryaerophilus*	None

[1]NR: none recorded

A. butzleri was cultured mainly from males and *A. cryaerophilus* from females (Table 1) and the difference between the two sexes is statistically significant (p=0.015). Four patients had an additional pathogen detected, namely *Helicobacter pylori* (two), *Blastocystis hominis* and *Aeromonas hydrophila.* All except one of the patients were adults, with ages ranging from 31 to 78 years. Three patients had persistent diarrhoea but, information was not provided for another four.

PFGE indicated that the *Arcobacter* isolates from diarrhoeal faeces were different from each other (data not shown) and also from those from poultry meat previously isolated in Palmerston North.[17]

All of the *Arcobacter* isolates were susceptible to ciprofloxacin and all but one susceptible to erythromycin. That *A. butzleri* isolate was resistant to ampicillin and tetracycline with intermediate resistance to erythromycin (Table 2). Three additional *Arcobacter* isolates showed intermediate resistance to tetracycline. Only half the isolates were susceptible to ampicillin.

Table 2. Antimicrobial susceptibility of Arcobacter spp. isolated from the faeces of patients with diarrhoea

Isolate	*Arcobacter* species	Ciprofloxacin (mg/L) Sens≤1[1]	Erythromycin (mg/L) Sens≤8[1]	Tetracycline (mg/L) Sens≤4[1]	Ampicillin (mg/L) Sens≤8[1]
1	*butzleri*	0.12	4	4	4
2	*butzleri*	0.06	4	4	8
3	*butzleri*	0.06	2	2	32
4	*butzleri*	0.25	8	8	8
5	*butzleri*	0.12	8	8	64
6	*butzleri*	0.25	16	16	32
7	*butzleri*	0.25	4	4	64
8	*cryaerophilus*	0.12	8	8	8
9	*cryaerophilus*	0.06	1	1	64
10	*cryaerophilus*	0.12	2	2	8
11	*cryaerophilus*	0.12	1	1	4
12	*cryaerophilus*	0.25	2	2	16

[1] The resistance break points were ≥4 mg/L for ciprofloxacin, ≥32 mg/L for erythromycin, ≥16 mg/L for tetracycline and ≥32 mg/L for ampicillin.[18]

Discussion

The isolation of *A. butzleri* and *A. cryaerophilus* from 0.9% of diarrhoeal faecal samples collected in Hawke's Bay, New Zealand is consistent with the 1% isolation rate of *A. butzleri* reported for diarrhoeal stools in France[11] but higher than the 0.14% reported for *A. butzleri* and *A. cryaerophilus* in both Belgium[7] and Denmark.[20]

Culture-based methods yielded *A. butzleri* from 2.4% of faecal samples collected from Thai children with diarrhoea[21] but the use of PCR to detect *Arcobacter* spp. directly from faeces has generally yielded a higher proportion of positive results, e.g. 7.5% for *A. butzleri*, 3.5% for *A. cryaerophilus* and 2% for *Arcobacter skirowii* for patients hospitalised with diarrhoea or other gastrointestinal disorders in South Africa[15] and 8% for *A. butzleri* from patients with travellers' diarrhoea who had visited Mexico, Guatemala or India.[22] By contrast, *A. butzleri* was detected in only 1.2% of diarrhoeal stools by means of PCR in another study in France.[23]

However the real significance of *Arcobacter* isolation is difficult to determine since several pathogens have been detected in a number of these patients. In the present study, one third had a second pathogen detected (Table 1) which is comparable with the 20% of patients with *A. butzleri* plus another enteric pathogen reported by Vandenberg et al (2004).[7] The latter group also found that 16% of patients with *A. butzleri* in their faeces had an underlying disease and 20% of the *A. butzleri* isolates were from asymptomatic patients. Of 16 patients with travellers' diarrhoea with *A. butzleri* detected, 15 also harboured either enterotoxigenic *Escherichia coli* (ETEC) or *Campylobacter* sp.[22]

Likewise 20 of 33 patients with *Arcobacter* spp. hospitalised in South Africa had one to three other gastrointestinal pathogens detected.[15] *Arcobacter* spp. have also been detected in faeces collected from asymptomatic patients, including 7 abattoir workers in Switzerland[14] and 26% of healthy subjects in Italy.[16] Interestingly the latter group

found an increased carriage rate of *Arcobacter* spp. (79%) in older people with type 2 diabetes but no gastrointestinal disorders.

Other bacterial species isolated from the 1380 diarrhoeal faecal samples examined for *Arcobacter* spp. in the current study were: *Campylobacter* (15.1%), *Salmonella* (2.6%), *Aeromonas* (2.2%), *Yersinia* (1.9%) and *Shigella* (0.1%) (S. Wallace, personal communication). Thus *Arcobacter* spp. (0.9%) were more common than *Shigella*, much less common than *Campylobacter* spp and roughly similar in frequency to the other enteric bacterial pathogens.

Two studies found that *A. butzleri* was more common in the faeces of females than males[7,8] and one found the opposite[15] but the differences in all studies were small. Another group isolated *A. cryaerophilus* from the faeces of 1.4% of healthy men who worked in abattoirs.[14] Thus it is likely that the unequal distribution of the two *Arcobacter* species across the sexes shown in Table 1, although statistically significant, is not biologically meaningful.

Based on results from single isolates, *Arcobacter* spp. have been described as antibiotic resistant.[9,24] However, the observation that all the isolates in this study were susceptible to ciprofloxacin (Table 2) is consistent with reports that 89 to 100% are susceptible to ciprofloxacin.[11,25–27] Likewise, erythromycin susceptibility (92%, Table 2) and 87 to 100%[27-29] is common among *Arcobacter* spp. By contrast, the relatively low proportion of isolates susceptible to tetracycline in this study (67%, Table 2) differs from the 100% susceptibility reported for isolates from the USA,[27] Japan,[29] and Thailand[26] but resistance to ampicillin is common worldwide.[9,28,30]

We conclude that *A. butzleri* and *A. cryaerophilus* do occasionally cause diarrhoea in New Zealanders which may be persistent or watery. However their real significance as emerging enteric pathogens, both in New Zealand and overseas,[1] is unclear. Their ability to colonise healthy animals and survive on meats[1,17] and in the environment does mean human exposure is likely to be common but further studies would be useful to better establish the virulence of *Arcobacter* spp. for humans before recommending that laboratories routinely test for these bacteria.

Competing interests: None declared.

Author information: Owen Mandisodza, Medical Laboratory Scientist, Hawke's Bay Hospital Laboratory, Hastings; Elizabeth Burrows, Technician, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Palmerston North; Mary Nulsen, Associate Professor, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Palmerston North

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Correspondence: Mary Nulsen, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11222, Palmerston North 4442, New Zealand. Fax: +64 (0)6 3505714; email: M.F.Nulsen@massey.ac.nz

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Is late-night salivary cortisol a better screening test for possible cortisol excess than standard screening tests in obese patients with Type 2 diabetes?

Elna Ellis, Paul K L Chin, Penelope J Hunt, Helen Lunt, John G Lewis, Steven G Soule

Abstract

Aim To compare the performance, in terms of specificity for cortisol excess, of late-night salivary cortisol with 24-hour urine-free cortisol (24hr UFC) and overnight 1mg dexamethasone suppression test (1mg DST) in a group of obese T2DM patients.

Methods Forty obese patients with T2DM without clinical features of Cushing's syndrome were recruited. Plasma, urinary and salivary cortisol were measured directly by an enzyme-linked immunosorbent assay using monoclonal antibodies. The specificities of the three tests using various cutoffs were calculated and compared, employing the assumption that none of the patients had hypercortisolism.

Results The patients had a mean age and BMI of 56 years (range 31–75) and 37kg/m^2 (31–56) respectively. All 40 provided late-night salivary cortisol samples. Thirty-eight patients completed all three tests. Two patients only completed two screening tests. The specificities of late-night salivary cortisol (cutoff 10nmol/L), 24hr UFC (400nmol) and 1mg DST (50nmol/L) were 70% (95% CI 53–83%), 90% (76–97%) and 72% (55–85%) respectively. The specificity of late-night salivary cortisol was significantly less than 24hr UFC (P=0.039) but not 1mg DST (P>0.99).

Conclusion Late-night salivary cortisol has a poor specificity for cortisol excess in obese patients with T2DM with 24hr UFC showing significantly better specificity in our population.

Overt Cushing's syndrome is associated with a high prevalence of impaired glucose tolerance (60%) and Type 2 diabetes (15–20%), reflecting multiple adverse effects of glucocorticoids on glucose homeostasis.[1] These include increased hepatic gluconeogenesis, peripheral insulin resistance and finally a suppressive effect of glucocorticoids on beta-cell function. Furthermore, patients with Type 2 diabetes (T2DM) often have several clinical features of Cushing's syndrome, including central weight excess, hypertension and hyperglycaemia, raising the question of whether cortisol excess is more common in patients with T2DM than in a control population.[2]

An early prospective study by Catargi et al of 200 overweight inpatients with poorly controlled T2DM (HbA1C>8%) reported a 2% prevalence of occult Cushing's syndrome and concluded that systematic screening for cortisol excess might be warranted in this group.[3] Apart from a 9.4% prevalence of subclinical Cushing's syndrome later reported by Chiodini et al,[4] subsequent studies have generally found a low prevalence of Cushing's syndrome in patients with T2DM (0–1%), arguing against routine screening.[5–8]

Salivary cortisol is in equilibrium with biologically-active-free plasma cortisol and has a circadian rhythm which mirrors plasma cortisol. The measurement of late night salivary cortisol has been promoted as a non-invasive screening test for cortisol excess with 92–100% sensitivity and 93–100% specificity for the diagnosis of Cushing's syndrome.[9–12] However recent Endocrine Society guidelines caution that 'the influence of gender, age and coexisting medical conditions on late night salivary cortisol concentrations has not been fully characterised.'[13]

Previous studies utilising measurement of plasma and 24-hour urine cortisol (24hr UFC) have suggested that patients with T2DM, particularly those with microvascular complications, have activation of the hypothalamic-pituitary-adrenal (HPA) axis.[14–16] There is however limited and conflicting data regarding the utility of late night salivary cortisol to screen for cortisol excess in the setting of T2DM.

A study by Liu et al suggested that a raised bedtime salivary cortisol (>10nmol/L) was relatively uncommon in 141 patients with T2DM without Cushing's syndrome (3%).[17] Conversely, Mullan et al recently reported that 23% of 201 consecutive T2DM patients without evidence of Cushing's syndrome had a raised bedtime salivary cortisol (>10nmol/L).[8]

We hypothesised that bedtime salivary cortisol would be more specific than conventional tests, namely the overnight 1mg dexamethasone suppression test (1mg DST) and 24hr UFC, in screening for Cushing's syndrome in patients with T2DM. Thus we aimed to clarify the diagnostic performance of bedtime salivary cortisol compared with the 1mg DST and 24hr UFC in this patient group.

Since we were interested in examining the specificity of the various screening tests in the context of T2DM, we systematically excluded patients who had clinical features suspicious for cortisol excess.

Methods

Inclusion and exclusion criteria—We prospectively recruited 40 patients from the Christchurch Diabetes Centre outpatient clinic.

Inclusion criteria for the study were

- T2DM,
- Age 20–75 years, and
- Obesity (body mass index, BMI>30kg/m^2).

Exclusion criteria were

- Clinical features suspicious of Cushing's syndrome—namely proximal muscle weakness, easy bruising or broad (>1cm) violaceous striae,
- Use of oral, inhaled or topical steroids within the last 3 months,
- Oestrogen replacement,
- Current use of enzyme-inducing drugs,
- Shift workers,
- Depression (on antidepressants or under active clinical management for depression),
- Heavy alcohol intake (>14 or 21 standard drinks per week for women and for men respectively), and
- Hospitalisation for an acute condition within the previous month and
- Pregnancy.

Testing protocol—Baseline clinical and demographic data were recorded. Patients performed the three tests in the order listed with supervision by an endocrinology research nurse:

- Five consecutive bedtime salivary cortisol samples (normal <10nmol/L as per our previous report).[18] A minimum of 1ml of saliva was collected into a plastic container (Salivette®) on five consecutive evenings before retiring to bed and prior to brushing/flossing their teeth.
- A 24-hour urine collection for creatinine and cortisol (normal <400nmol).[19]
- A 1mg-DST (normal <50nmol/L).[13]

Steroid assays—Plasma, urinary and salivary cortisol were measured directly by an enzyme-linked immunosorbent assay (ELISA) using monoclonal antibodies.[20] For saliva and urine the cortisol was extracted with dichloromethane prior to ELISA whereas plasma cortisol was measured by a direct ELISA. The salivary cortisol assay has a limit of detection (LOD) of 3nmol/L, interassay coefficient of variation (CV) of 12.6% for the "low control" (mean cortisol value 7 nmol/L) and 7.4% for the "high control" (mean cortisol value 22 nmol/L). The urinary cortisol assay has a LOD of 22nmol/L and interassay CV of 8.5–13.3% over the range of 99 to 217nmol/L. The plasma cortisol assay has a LOD of 55nmol/L and interassay CV of 6.9–8.5% over the range of 98 to 1007nmol/L).

Statistical analyses—Test specificity was defined as:

$$Specificity(\%) = \frac{True\ negatives}{True\ negatives + False\ positives} \times 100$$

Specificity was calculated based on the assumption that all included patients did not have Cushing's syndrome.

McNemar's Chi-squared test was used to compare the performance of the screening tests, in terms of specificity for Cushing's syndrome. The 95% confidence interval (95% CI) of each test's specificity was calculated using the binomial distribution.

The relationships between BMI, HbA1C and salivary cortisol, 1mg-DST and 24hr-UFC were examined by Spearman's rank correlation coefficient. GraphPad Prism version 5.04 for Windows (GraphPad Software, San Diego, California USA) was used to generate the graphs.

The study was approved by the New Zealand Upper South B Regional Ethics Committee, and informed written consent was obtained from all patients.

Results

Demographic data

Forty patients with T2DM were studied, 15 male and 25 female, with mean age 56 years (31–75), BMI 37kg/m^2 (31–56) and HbA1C 8.6% (6.2–11.6). Overall glycaemic control was suboptimal with only 6 subjects (15%) having HbA1C ≤7% and 9 (23%) ≤7.5%.

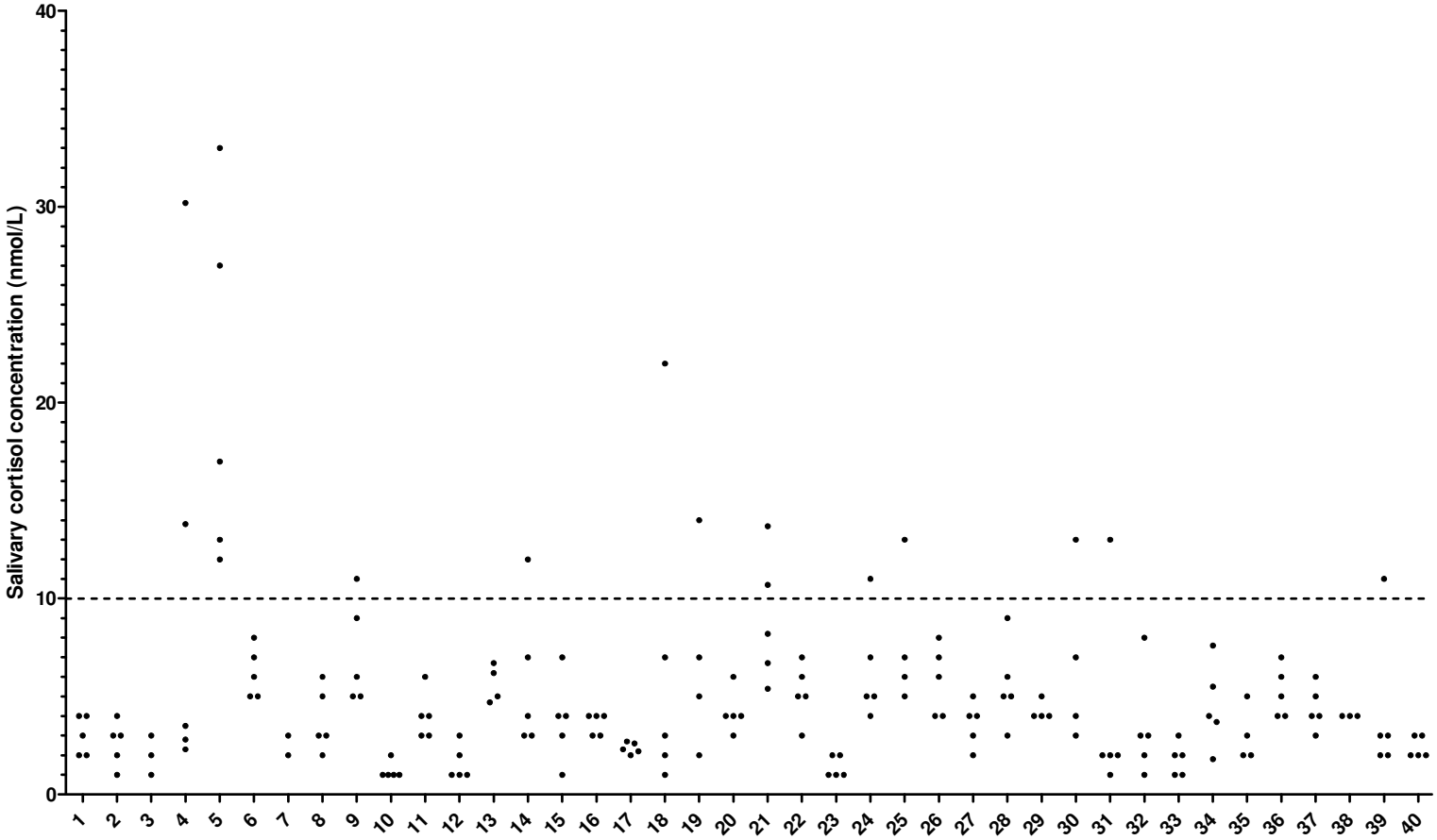
Biochemical data

Salivary cortisol—32 subjects (80%) provided 5 bedtime salivary samples, a further five (12.5%) provided 4 samples, two provided 3 samples (5%) and a single patient provided only 2 samples (2.5%). Applying the 10nmol/L cutoff for bedtime salivary cortisol, 12/40 had at least one salivary cortisol result ≥10nmol/L—a false positive rate of 30% or specificity of 70% (95% CI 53–83%) (see Figure 1).

Seven of the 12 patients with one or more raised salivary cortisol results had only a single salivary cortisol minimally raised in the10–15nmol/L range and had both normal 1mg DST and 24hr UFC. Table 1 details the results of the remaining 5

subjects (with at least one salivary cortisol >15nmol/L or 10–15nmol/L with another abnormal test result).

Figure 1. Salivary cortisol concentrations



Note: Each dot represents one result (n=187 for 40 patients); Broken horizontal line represents cutoff (see text).

Table 1. Biochemical data of five obese patients with Type 2 diabetes, no clinical features of Cushing's syndrome with (1) at least one raised salivary cortisol >15nmol/L, or (2) at least one salivary cortisol between 10–15nmol/L with another abnormal test result (abnormal results in bold)

Age (yr)	BMI (kg/m^2)	HbA1C (%)	Salivary cortisol (nmol/L)†	1mg DST cortisol (nmol/L)‡	24hr UFC (nmol)§ [24h creat (mmol)]	Repeat salivary cortisol† (nmol/L)	Repeat 24hr UFC§ (nmol) [24h creat (mmol)]	48hr DST cortisol* (nmol/L)
46	39	10.1	3.5, 2.8, 2.3, **30.2, 13.8**	**90**	234 [6.9]	1.9, 6.8, 1.7, 1.6, 2	364 [14.7]	
54	39	11.1	**12, 27, 13, 33, 17**	**118**	380 [7.9]			**73**
68	33	7.5	2, 7, 1, 3, **22**	**63**	**485** [10.6]			11
58	30	6.5	8.2, 6.7, **10.7**, 5.4, **13.7**	27	**414** [17.3]		**611** [16.9]	
51	31	11.2	**13**, 6, 5, 7	**59**	253 [9.2]			

† normal salivary cortisol <10nmol/L

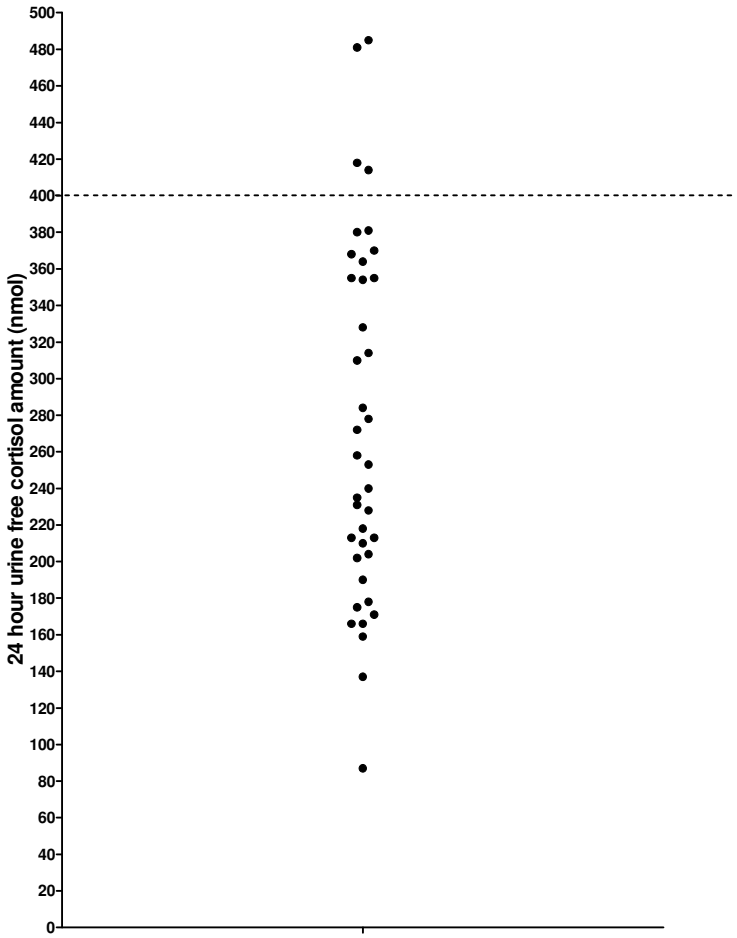
‡ normal morning cortisol after 1mg DST <50nmol/L

§ normal 24-hour UFC <400nmol

* normal cortisol after 48hr low dose Dexamethasone <50nmol/L

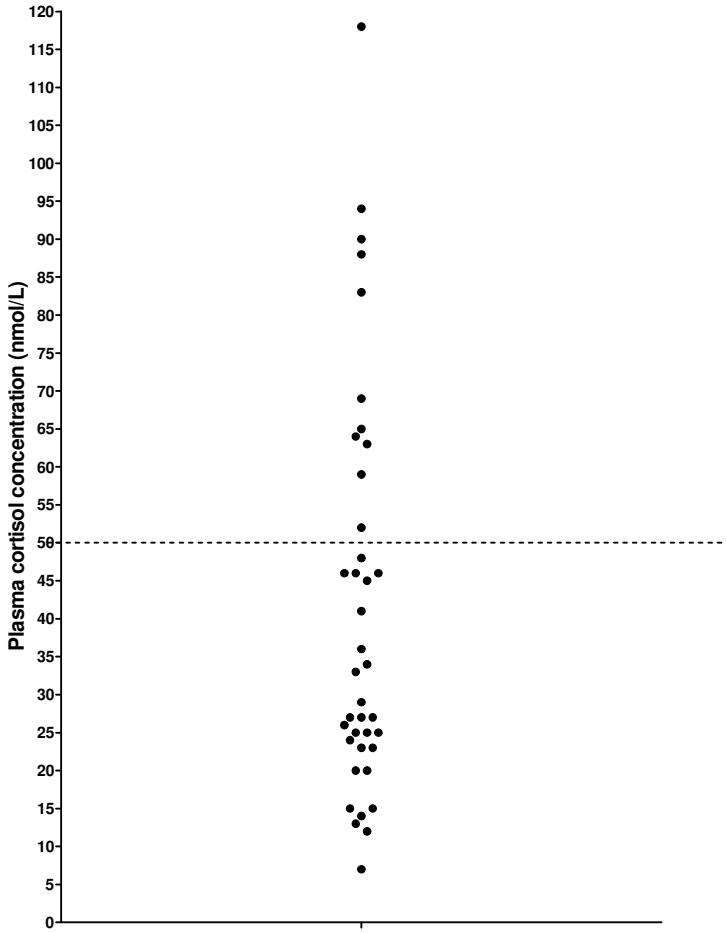
24hr UFC and 1mg DST—39 subjects completed a 24-hour urine collection and the 1mg DST. The specificity of the 1mg DST using the conventional cutoff of <50nmol/L was only 72% (95% CI 55-85%). The 24hr UFC had a specificity of 90% (95% CI 76-97%) using the cutoff <400nmol (see Figures 2 and 3).

Figure 2. 24-hour urine-free cortisol amounts



Note: Each dot represents one result (n=39 for 39 patients); Broken horizontal line represent cutoff (see text).

Figure 3. Plasma cortisol concentrations post-1mg dexamethasone suppression test



Note: Each dot represents one result (n=39 for 39 patients)Broken horizontal line represents cutoff (see text).

Overall, the specificity of salivary cortisol was inferior to 24hr UFC (P=0.039) but not 1mg DST (P>0.99). The difference in specificity between 24hr UFC (cutoff <400nmol) and 1mg DST (cutoff <50nmol/L) was not statistically significant (P=0.146).

Relationship between cortisol results and demographic data

There was no significant relationship between BMI, HbA1C and either the mean salivary cortisol, 1mg DST or 24hr UFC. There was a significant positive correlation between the mean salivary cortisol and 1mg DST cortisol (r=0.36, P=0.02) but not with 24hr UFC (r=0.19, P=0.2).

Discussion

Bedtime salivary cortisol is promoted as an accurate diagnostic test for Cushing's syndrome in view of the close correlation of salivary cortisol with free circulating cortisol, the ease of sample collection and the stability of salivary cortisol at room

temperature.[9–12] The reported test sensitivity and specificity are between 95 and 98%, suggesting that bedtime salivary cortisol is an ideal screening test for Cushing's syndrome.[1] However the utility of bedtime salivary cortisol in the setting of T2DM remains contentious with the prevalence of raised salivary cortisol (>10nmol/L) in the two available studies reported as 3% and 23% respectively.[8,17]

Our study was designed to determine the specificity of bedtime salivary cortisol in obese patients with T2DM in the real world setting and aimed to answer the clinical question: how likely is it that a raised bedtime salivary cortisol in an obese patient with T2DM is a false positive result? We thus selected patients who did not have clinical features suspicious of Cushing's syndrome and performed standard screening tests for cortisol excess (bedtime salivary cortisol, 1mg DST and 24hr UFC) to compare the specificity of the tests in this context.

Our results indicate that the specificity of bedtime salivary cortisol using the cutoff of <10nmol/L (70%) was inferior to 24hr UFC using the cutoff of <400nmol (90%, P=0.039) but not 1mg DST using the conventional cutoff of <50nmol/L (72%, P>0.99).

Several previous studies have examined the activity of the HPA axis in patients with T2DM. Early reports found no alteration of the HPA axis in T2DM[21,22] although several more detailed recent studies have consistently described increased HPA axis activity as reflected by an elevation of basal ACTH, basal and post-dexamethasone cortisol, 24-hour urinary and salivary cortisol.[15,17,23–25] Furthermore, in a study of 190 patients with T2DM, Oltmanns et al[26] described a positive relationship between diurnal salivary cortisol concentrations and HbA1C, as well as fasting and postprandial glucose. Oltmanns speculated that the stimulatory effect of cortisol on hepatic gluconeogenesis may exacerbate hyperglycaemia and ultimately promote the development of diabetes-related complications.[26] This hypothesis is supported by cross-sectional studies which revealed a relationship between increased HPA axis activity and several diabetes complications, in particular carotid atherosclerosis, diabetic retinopathy and polyneuropathy.[14,27,28] Although correlations observed in cross-sectional studies do not prove causation, a putative mechanism for HPA axis activation is a reduction in parasympathetic tone, which may result in disproportionate sympathetic activation of the HPA axis.[29]

Our study, similar to recent reports, suggested activation of the HPA axis in a group of generally poorly controlled T2DM patients (mean HbA1C 8.6%) with a relatively high prevalence of false positive screening tests for cortisol excess (30% by bedtime salivary cortisol, 28% by 1mg DST and 10% by 24hr UFC) when applying cutoffs derived from a healthy reference population. The high rate of false positive screening tests for cortisol excess in our patient population, in whom Cushing's syndrome was not felt to be clinically likely, suggests that to confidently diagnose Cushing's syndrome in the setting of T2DM requires the use of normative data derived from a control population of patients with T2DM rather than from healthy controls.

In contrast to the earlier report of a positive association between glycaemic control and cortisol secretion,[26] our study did not reveal any correlation between HbA1C and several measures of cortisol secretion, possibly due to the limited number of subjects enrolled and the relatively narrow range of HbA1C results.

The overlap of clinical features in patients with Cushing's syndrome and centrally obese patients with T2DM has raised the question whether routine screening for cortisol excess is warranted in the context of obese patients with T2DM. This issue has been studied by several groups who have reported a variable prevalence of Cushing's syndrome ranging from 0–9.4% (Table 2).[3-8] Of note, the prevalence of 9.4% reported by Chiodini et al[4] referred to subclinical hypercortisolism, a biochemical diagnosis defined by failure of suppression of cortisol following 1mg DST with either a raised 24hr UFC, suppressed plasma ACTH or raised midnight cortisol. This remarkably high prevalence may be a reflection of the patient population studied (inpatients admitted for poor glycaemic control) and the use of test criteria determined in a healthy control population. On the basis of the relatively low reported prevalence of Cushing's syndrome in most screening studies (0–3%), consensus expert opinion is that systematic screening for Cushing's syndrome in obese patients with T2DM is not warranted.[13]

There are several limitations to our study. Obviously, the results of the study are highly dependent on the cortisol "cutoff" levels used to define an abnormal result. Whilst our cutoff for salivary cortisol was derived from an 'in-house' reference population, the other normal ranges were derived from the published literature rather than our own control population, which may have affected the results. Further, the specificity of the overnight DST in this setting of obesity may have been improved with the use of a higher dose of dexamethasone.[30]

It is also relevant that in our study each participant had several measurements of salivary cortisol compared with only one measurement of urine cortisol excretion and a single 1mg DST, potentially increasing the chance of a spurious salivary result. Additionally, the accuracy of 24-hour urine samples is also questionable because the compliance with urine collection instructions is known to be notoriously variable. Another concern is that we assumed that the included patients did not have Cushing's syndrome, based on the absence of clinical features. However, some of the five subjects with clearly abnormal results (as defined in Table 1) may have had mild Cushing's syndrome at the time of the study. We have not formally re-evaluated the patients but are not aware that any of these five patients have subsequently developed overt Cushing's syndrome 2 to 4 years following study completion. Alternatively, these patients may have had other conditions associated with elevated cortisol that were not part of our exclusion criteria, such as obstructive sleep apnoea.

In conclusion, in a population of obese patients with poorly controlled T2DM selected for the absence of specific features of cortisol excess, bedtime salivary cortisol has a high false positive rate (30%). This suggests that the test has limited specificity in this clinical context and raises questions regarding the utility of bedtime salivary cortisol as a screening test for Cushing's syndrome in patients with T2DM.

Based on our data, 24hr UFC has the lowest rate of false positive results. We cannot comment on test sensitivity, as we did not study a population with proven Cushing's syndrome. Thus, it is important to emphasise that conventional tests for cortisol excess (1mg DST, 24hr UFC and bedtime salivary cortisol) have low specificity in obese patients with T2DM and such results need to be interpreted with caution.

Competing interests: None declared.

Author information: Elna Ellis, Endocrinology Registrar, Christchurch Hospital, Christchurch; Paul K L Chin, Clinical Pharmacology Registrar, Christchurch Hospital, Christchurch; Penelope J Hunt, Consultant Endocrinologist, Christchurch Hospital, Christchurch; Helen Lunt, Consultant Diabetologist, Christchurch Hospital, Christchurch; John G Lewis, Steroid Biochemist, Canterbury Health Laboratories, Christchurch; Steven G Soule, Consultant Endocrinologist, Christchurch Hospital, Christchurch

Correspondence: Dr Steven G Soule, Department of Endocrinology, Christchurch Hospital, Riccarton Avenue, Christchurch, New Zealand. Fax: +64 (0)3 3641159; email: steven.soule@cdhb.govt.nz

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Beyond PSA: are new prostate cancer biomarkers of potential value to New Zealand doctors?

Lance Ng, Nishi Karunasinghe, Challaraj S Benjamin, Lynnette R Ferguson

Abstract

The widespread introduction of prostate-specific antigen (PSA) screening has enhanced the early detection of prostate cancer within New Zealand. However, uncertainties associated with the test make it difficult to confidently differentiate low-risk patients from those that require a definitive diagnostic biopsy. In consequence, the decisions surrounding prostate cancer treatment become extremely difficult. A number of new tests have become available which might have the potential to complement the current PSA screens. We review a number of the best validated of these which provide data that, although currently not available in clinical practice, some of these might have considerable potential to aid diagnosis, prognosis and therapeutic decisions for men with prostate cancer in New Zealand.

Prostate cancer is the most commonly registered male cancer in New Zealand making up 25.2% of all registrations, ahead of colorectal cancer and malignant melanoma of the skin, and the third most common cancer registration for both sexes.

Prostate cancer was also the third leading cause of male cancer deaths in 2006[1]. Although recent data might be interpreted as suggesting that there has been a decline in the incidence of prostate cancer since the year 2000[2], this may be an artefact of increased uptake of prostate-specific antigen (PSA) screening at that time. With increased PSA testing comes earlier diagnosis and registration of patients, which in turn will lead to an elevation of diagnosis in *younger* age groups (giving the pre-2000 increase).

The apparent post-2000 decline is thus a result of those patients already being picked up by the test who would have otherwise been diagnosed at that time. The likely result is a paradigm shift in the age distribution of patients with diagnosed prostate cancer, and a return to a steady gradual increase in diagnosed prostate cancer patients, as seen in the pre-PSA years[2].

PSA testing—the current method of prostate cancer risk and progression assessment *a prima facie*, falls well short of the performance required of a screen in an age of evidence-based medicine, with sensitivity and specificity of PSA testing being quoted as 74–84% and 90–94% respectively[3,4] and a positive predictive value of 21.9% (when using the traditional value of PSA 4.0 ng/mL as a threshold)[5].

Use of such a test as the basis of clinical decisions for prostate cancer patients renders *active surveillance* (a programme consisting of regular PSA and DRE (digital rectal examination) testing (in addition to regular biopsy of a patient's prostatic tissue) or *watchful waiting* (where treatment has a stronger palliative element and curative treatments are foregone)[116] as the most prudent course of action when a PSA level is shown to be in the *grey zone* of 2.5 ng/mL–10 ng/mL[6].

It should be noted, however, that active surveillance and watchful waiting, despite the implication of PSA values, are primarily indicated through key parameters of biopsy results, including Gleason score, clinical grade of disease, number of cores positive upon biopsy and volume of malignant tissue in each positive core. The current dependence on an invasive test for disease prognosis is reflective of the difficulty to differentiate between indolent and aggressive neoplasms with PSA, which is, in essence, a risk-stratification tool.

Indeed, this is further underpinned when one observes the high rate of false positive (95 in 1000 men aged 55–69 years who have the PSA test) and a substantial number of false negative results (23 per 1000 men aged 55–69 who have PSA testing and then biopsy)[3]. As a result, the decisions surrounding treatment become extremely difficult if the sole basis for the decision to treat was a non-invasive test such as PSA (in practice, just as for active surveillance, the decision to treat is primarily indicated through parameters of prostate biopsy).

Patients who do not need treatment may opt to be treated and suffer unnecessary side effects. Equally, those who do need treatment may choose not to be treated, and miss the opportunity for an early intervention. It is this dilemma which epitomises the experience of both patient and practitioner in dealing with the inherent uncertainty of PSA testing. Ideally, clinicians would be able to call on an accurate and reliable non-invasive risk-stratification system, whereby patients are empowered with precise knowledge to make more fully informed decisions on their health, and equally have a clearer understanding of the risk of recurrence[8].

This review discusses novel biomarkers in prostate cancer which have the potential to be incorporated in new risk-stratification systems, and their role in delivering the diagnostic and prognostic precision currently lacking in clinical prostate cancer treatment. We note that this list is not exhaustive, but covers several that would be potentially applicable to the New Zealand clinical situation.

PSA testing: the status quo

Current policy and practice

Screens for genetic susceptibility to breast cancer (BRCA1/2 screening[114]), or for the presence of early signs of cancer in the cervix (cervical cancer screening[113]) are both well established in Aotearoa/New Zealand. However, comparable well established methods are not available for screening genetic susceptibility to prostate cancer, despite the similarity in incidences of breast (2572 registrations, 2006) and prostate (2484 registrations, 2006) cancers[2].

The lack of a well substantiated and non-invasive screening test for early prostate cancer[3] (as compared with PAP smear testing in cervical cancer) requires a more aggressive and concerted effort from policymakers, clinicians and researchers to address the uncertainties and errors manifest in the PSA test, which defines the current status of prostate screening and on a more global level, the plight of men's health, in this country.

As a reflection of where the New Zealand healthcare system stands with its current prostate screening procedures—out of the eight criteria outlined by the New Zealand

National Health Committee (NHC) screening assessment, prostate cancer screening meets *only one criterion*—that prostate cancer is a condition which is a suitable candidate for screening[3]. Indeed, PSA and direct rectal examination (DRE) are described as unsuitable tests as:

> *"neither can be described as reliable, accurate, sensitive or specific enough for screening asymptomatic men."*
> National Health Committee (2004)

However, there exists a growing body of evidence which tentatively suggests that screening for prostate cancer is not without its benefits. Specifically, criterion three outlined by the NHC—that there is an effective and accessible treatment or intervention for the condition identified through early detection[3]—would seem to be supported by data presented from the Scandinavian Prostate Cancer Group-4 trial[144] demonstrating a reduction in metastatic disease incidence (RR=0.65; p=0.006) and disease-specific death (RR=0.82; p=0.09) for clinically localised prostate cancer specimens after a 12-year follow-up period with radical prostatectomy, as compared to watchful waiting.

Additionally, data extracted from a cohort of 7578 men in Sweden, randomised to screening, demonstrated a prostate cancer-specific mortality reduction of almost 50% (RR=0.56; p=0.002) over 14 years compared to non-screened controls[145], which would provide randomised controlled trial evidence demanded by the fourth criterion stipulated by the NHC—that a screening programme is effective in reducing morbidity and mortality.

Although the inevitable risk of overdiagnosis has been acknowledged by the study authors and elsewhere[145,146], these recent developments perhaps signal that it may be pertinent to once again review the current government policy on prostate cancer screening.

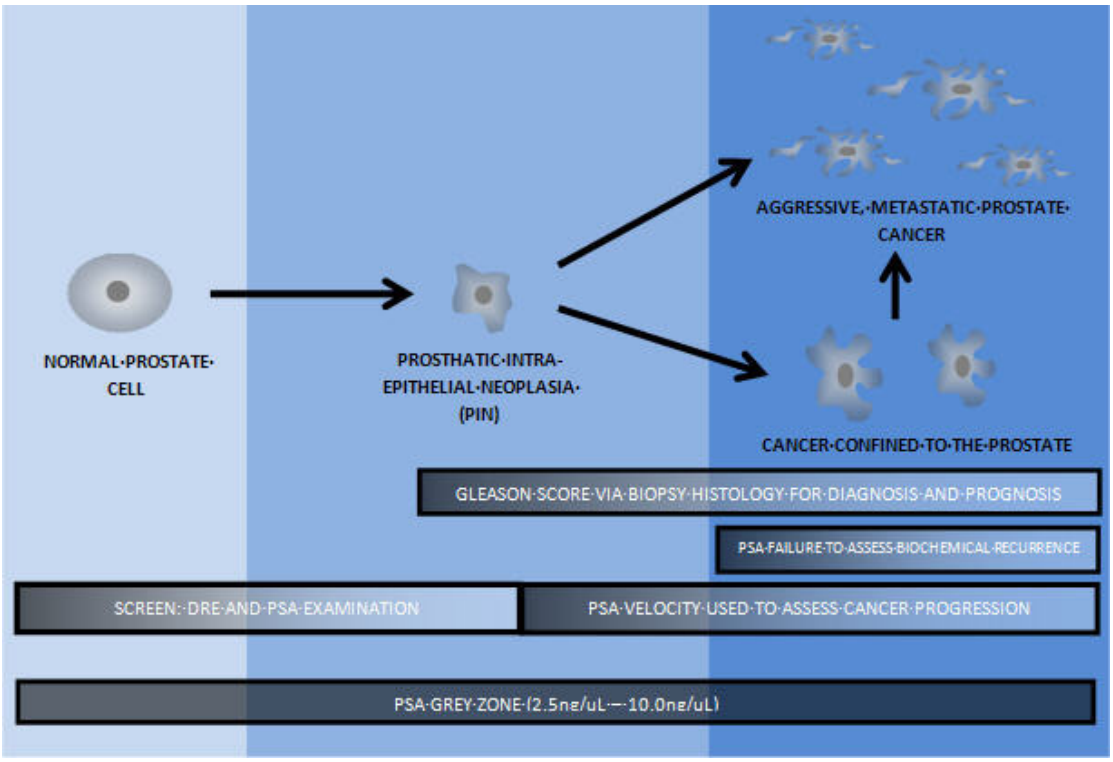
Strengths and limitations

PSA testing has demonstrable strengths. With 90% of new cases detected early enough for curative treatment[115] (where the treatments offer cure rates between 70%–90%) and changes in prostate cancer mortality ranging from 10%–39% in countries in Western Europe, North America and Australia[116] we can recognise that, although flawed, PSA is having a positive effect of the clinical treatment of prostate cancer.

In addition, when we consider that prostate cancer has a tendency to progress slower than other cancers (and even slower with androgen ablation therapy), the burden associated with the myriad of medical interventions such as radiotherapy, surgery and hospice care will often become more costly than an early, curative intervention administered on the basis of a routine PSA test[116].

Moreover, the natural course of prostate cancer means that if we were to forego PSA testing and diagnose on the appearance of symptoms, 70% of these cases will already have metastases. It must be acknowledged too, that PSA should only be seen as the initial step in prostate cancer assessment—TRUS (transrectal ultrasound) biopsy remains the gold standard in delivering diagnostic and prognostic data on prostate cancer.

Figure 1. Current use of PSA in monitoring progression, diagnosis and prognosis of disease



Note: The PSA *Grey Zone* (2.5ng/uL – 10ng/uL) [6] extends across the whole continuum of prostate cancer progression.

These recognised limitations of PSA testing have led to international initiatives towards developing and validating new biomarkers with higher sensitivity and specificity which alone, or in conjunction with current screening methods, are able to deliver more definitive results on the presence and nature of cancer in the prostate, in a fast, cost-effective and non-invasive manner.

Through the clinical application of novel biomarkers and effective implementation in the healthcare system, clinicians may aspire to deliver well informed and clear-cut decisions on the course of prostate cancer patients' treatments and prognoses, and ultimately deliver better health outcomes for men in Aotearoa/New Zealand.

Novel biomarkers: beyond PSA

As researchers delve further into the elements underlying sporadic prostate cancer, we begin to unearth increasing evidence of this being a heterogeneous disease[18]. Unlike the discovery of the Bcr-Abl gene in chronic myeloid leukaemia, it is unlikely that more research will reveal a single specific gene locus that is responsible for prostate cancer. Naturally, such a multifaceted disease demands an equally multifaceted approach to risk-stratification, screening and diagnosis.

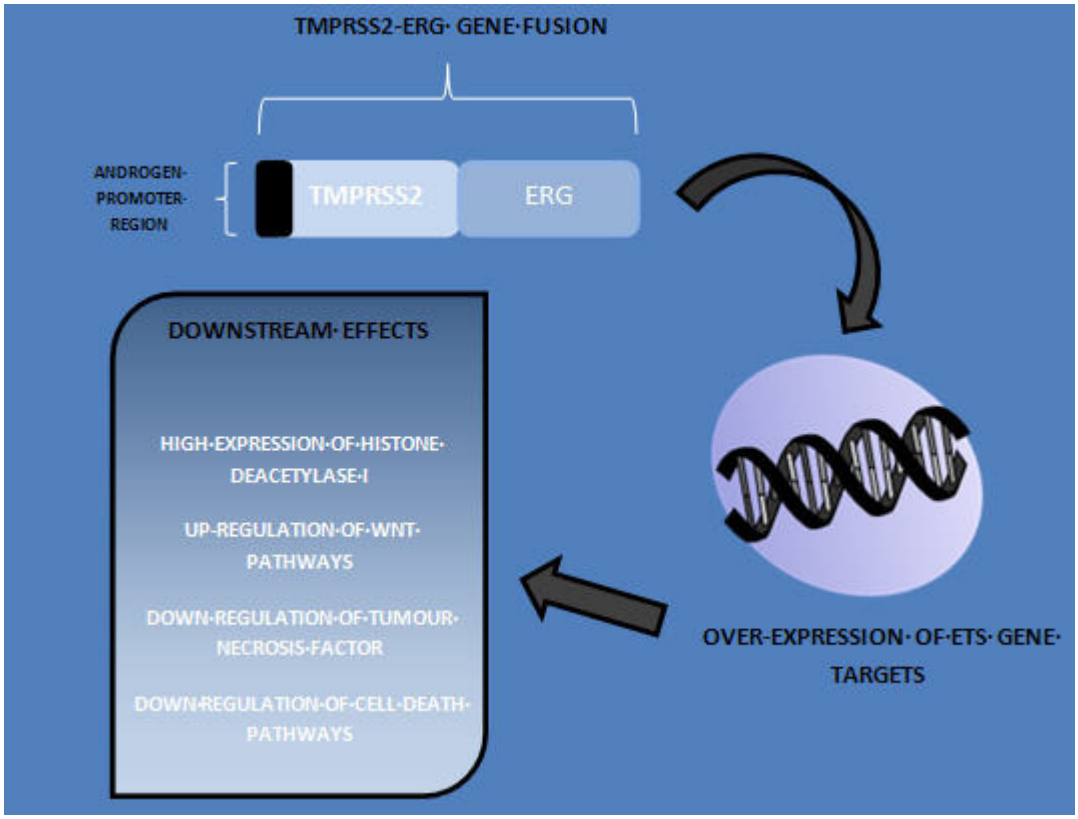
Novel biomarkers for sporadic prostate cancer have been found on many echelons of the central dogma of genetics: genetic (specifically DNA), epigenetic, transcriptomic,

proteomic and metabolomic approaches all show promise for use in clinical medicine in the future.

Genomics

TMPRSS2-ERG—This marker can be detected using RT-PCR methods, applied to urine samples from subjects whose prostate has been massaged. Discovery of this gene fusion is potentially the most significant advance in the last decade in the molecular pathology of prostate cancer.TMPRSS2 is a prostate specific gene[19,20] on chromosome 21 that codes for a transmembrane-bound serine protease[20]. The protease is predicted to react with a number of proteins on the cell surface, as well as extracellular matrix components, soluble proteins and proteins on nearby cells[21].ERG is a member of the ETS family of transcription factors which are able to activate or repress expression of genes involved in cellular proliferation, differentiation and apoptosis[22].

Figure 2. The potential significance of the TMPRSS2-ERG fusion



Note: The androgen-sensitive promoter region of the TMPRSS2 gene, through fusion to ETS family genes, could lead to androgen-driven overexpression of ETS family genes such as ERG. These in turn have been shown to cause downstream effects such as a high expression of the histone deacetylase I (HDAC I) gene, upregulation of Wnt pathways and downregulation of tumour necrosis factor and cell death pathways.[23]

Genes from the ETS family and TMPRSS2 lie nearby on chromosome 21, and hence fusions typically occur via rearrangements including deletion and translocation[24]. Cross et al[22] have suggested the possibility of certain sequences in TMPRSS2 and ERG which make some men more prone to these fusions that are seen in 49% of localised prostate cancers[22].

Furthermore, the timing of the occurrence of these fusions is particularly significant – TMPRSS2-ERG fusions have not been detected in morpohologically benign prostatic tissue but arise at a very specific point in the pathogenesis of prostate cancer, namely the high-grade prostatic intra-epithelial neoplastic stage (HGPIN) (essentially analogous to *carcinoma in situ*). In addition, in late-stage androgen receptor-negative cancers, TMPRSS2-ERG fusions were still present in the DNA but were not expressed[25], which aligns with the current understanding of the bypass mechanisms involved in androgen-independence and the fact that TMPRSS2 contains an androgen-dependent promoter region[22].

The clinical significance of these novel discoveries in the TMPRSS2-ERG fusion will be delineated more clearly as further studies are published.

In terms of prognostication, there have been groups who have looked at TMPRSS2-ERG fusions in comparison to measures such as Gleason Score, survival data and tumour recurrence. In general, TMPRSS2-ERG fusions were shown to be linked with worse prognoses[22]:

- 44% of Gleason pattern 5 contained TMPRSS2-ERG fusions compared with 7% of Gleason pattern 2 tumours[26]
- Non-fusion patients had a 90% survival at 8 years compared with 25% survival at 8 years in those identified having a particular pattern of TMPRSS2 fusion known as 2+ Edel (duplication of TMPRSS2-ERG fusion sequences and interstitial deletion of sequences 5' to ERG)[27]
- Tumours with TMPRSS2-ERG fusions had a higher recurrence rate after radical prostatectomy with an odds ratio of 7.1 (95% confidence interval 1.1-45)[28].

Despite their prostate specificity and their appearance in Prostatic Intra-epithelial Neoplasia (PIN), TMPRSS2-ERG fusions are unlikely to be suitable for screening as they have been found by Hessels et al[29] to show low sensitivity (37% in a cohort of 108). However, in the same study, the fusions were detected with a positive predictive value (PPV) of 94%[29], which suggests that it could be a useful risk-assessment tool whereby a clinician could request further biopsies in the cases where patients have a negative initial biopsy but persistently elevated PSA and positive test for the gene fusion product.

A similar pattern of *low sensitivity* but a *high positive predictive value* is seen in TMPRSS2-ERG fusions and their association with five key histological features[30]:

- Blue-tinged mucin
- Cribriform growth pattern
- Intraductal tumour spread

- Macronucleoli
- Signet-ring cell features

Ninety-three percent of cases in 253 prostate cancers with three of more of these features were TMPRSS2-ERG fusion positive (*high PPV*) but equally, 24% of TMPRSS2-ERG fusions did not show *any* of these features (*low sensitivity*) [30]. Its positive predictive value is comparable to the morphological features of HNPCC and BRCA-associated breast cancers, but the link between genotype and phenotype is not yet fully understood. Tumour morphology and association between TMPRSS2-ERG fusions thus stands as a potentially useful addition to the current armoury of diagnostic and risk-stratification methods, but further research is required in the field before we see collaboration between clinicians and histopathologic and cytogenetic services in New Zealand.

Urinary 8-hydroxydeoxyguanosine (8-OHdG)—It is widely agreed that reactive oxygen species (ROS) are direct causes of DNA damage. 8-hydroxydeoxyguanosine (8-OHdG), an oxidised nucleoside of DNA, is a frequently detected lesion where mismatch repair plays a key role[43].Upon DNA repair, 8-OHdG is excreted in the urine and thus can not only be a measure of DNA repair capacity, but *also* a biomarker for oxidative stress and potential carcinogenic initiation[44, 45].

Increased urinary DNA lesions were detected by Chiou et al[43] in both prostate and bladder cancer patients (58.5ng/mg creatinine of urinary DNA lesions in prostate cancer patients compared with 36.1ng/mg creatinine of Urinary DNA lesions in healthy patients) with a sensitivity of 31% and a specificity of 100%. Although their study population was small (and the fact that a biomarker of oxidative stress is not prostate-specific), the specificity of the test and the non-invasive nature of it suggests that with further investigation urinary 8-OHdG has potential as a biomarker which can allow for risk-stratification in those who have elevated serum PSA or a strong family history of prostate cancer.

8-OHdG is frequently detected in both non-malignant and malignant tissue. However, in non-malignant tissues extensive oxidative DNA damage drives cells to cell-cycle arrest (metabolic blockage), while in neoplastic prostate cancer cells it activates repair mechanisms favouring the escape from senescence and the expansion of DNA-damaged clones[133]. The combination of 8-OHdG in urine, measured along with cell-cycle check point evaluators such as CDKN1A, a cyclin-dependent kinase inhibitor and the product of the growth-arrested and DNA damage inducible gene Gadd45, from a parallel blood sample, may provide a greater understanding of the progression towards malignancy[134, 135].

Transcriptomics

Hepsin—Hepsin is a type II membrane associated serine protease whose structure and similarity to other serine proteases suggests that hepsin is involved in tumour growth, and hence hepsin stands as an attractive target in cancer biomarker development. Its prostate-specificity is best demonstrated through evidence of overexpression of hepsin (median 46.1-fold) in cancerous prostate tissue in 90% of prostate cancer samples (n=90)[46].

These findings have been confirmed through the work of Magee et al[47] in an analysis of 4712 genes. In the same analysis, Hepsin was found to be over-expressed in prostatic intra-epithelial neoplasia in comparison to BPH which points to a relationship between Hepsin and neoplastic transformation. In addition, one can propose that such a biomarker can aid in the prognostication of Gleason 4 and 5 tumours with the discovery of a correlation between increased Hepsin expression and higher Gleason score[46].

The major shortcoming of the use of Hepsin is the fact that it can only be detected in tissue specimens and, despite attempts to use RNA extracted from urine for quantitating hepsin[136] is not currently detectable from urine or serum samples[48]. Thus, the arrival of Hepsin as a prognostic tool for differentiation of indolent from aggressive tumours depends firmly on the discovery of novel methods of detection that will render it more accessible to clinical practice.

Prostate cancer antigen 3 ($DD3^{PCA3}$)—$DD3^{PCA3}$ is a novel, prostate-specific gene found to be up-regulated in cancerous prostate cells and over-expressed in >95% of clinical specimens[31,33]. PCA3 is more specific for prostate cancer than serum prostate-specific antigen (PSA), which is prostate-specific but not cancer-specific[41].

The proof of its prostate specificity has been shown through RT-PCR methodologies, in which PCA3 mRNA expression was low but quantifiable in benign prostatic tissue, but undetectable in normal and malignant tissue from other organs[32]. Equally, proof of over-expression of $DD3^{PCA3}$ in malignant prostate tissue with a median 66-fold up-regulation (compared to expression in benign tissue) has been demonstrated by Northern Blot analyses[31].

$DD3^{PCA3}$ has been concluded to express non-coding mRNA (defined through the presence of alternative splicing, polyadenylation, lack of an extended open reading frame and numerous stop codons) for which there is no discrete cytoplasmic protein product—despite overexpression of the mRNA transcript[31]. The function of the $DD3^{PCA3}$ gene and its non-coding mRNA transcript are currently undefined; hence, there is equally little known about the role of the $DD3^{PCA3}$ gene in pathogenesis of prostate cancer.

The magnitude of overexpression of the $DD3^{PCA3}$ gene in malignant specimens when compared to the near-negligible amounts of $DD3^{PCA3}$ expression in benign prostatic tissue confirms that the ultimate cause of the lack of a cytoplasmic protein product from PCA3 mRNA expression lies in the transcription as opposed to translation of other processing steps[31].

Although conflicting literature does exist on the subject of the $DD3^{PCA3}$ gene's clinical utility, the majority pertaining to the matter confirm that $DD3^{PCA3}$ has strong diagnostic value, particularly in differentiating early-stage prostate cancer from benign prostatic hyperplasia (BPH)[34,35,36]. PPV of 52.2% in men with PCA3 ≥100 is reported by Roobol et al 2010a and Robool et al 2010b.

This marker stands as one of the most attractive risk-stratification tools to detect early prostate cancer for a gamut of reasons:

- The $DD3^{PCA3}$ test does not require a biopsy– the mRNA is collected from urine after DRE and prostatic massage[34].
- $DD3^{PCA3}$ levels are directly reflective of tumour burden (as it is mRNA from cancer cells) and are *not* affected by prostate size, unlike PSA (which is a surrogate serum marker). This reduces the number of false positives detected in BPH cases and hence *increases* overall specificity[32].
- $DD3^{PCA3}$ mRNA expression adds the most value to current diagnostic tools at PSA values between 2.5ng/ml and 4.0ng/ml[34].
- The quantitative PCA3 score has been found to correlate to the frequency of prostate cancer-positive biopsy—thus it can act as a means to stratify patients into categories of prostate cancer risk[32].

In theory, it has all the hallmarks of a test which can deliver the much sought after specificity that is currently lacking in determining whether to biopsy or not. However, current validation studies have struggled to produce definitive results confirming $DD3^{PCA3}$ mRNA as a clinically applicable biomarker.

Five studies which look the performance of $DD3^{PCA3}$ which use ≥2.5ng/ml or ≥3.0ng/ml as PSA cut-off values gave the following values (as an average across the five studies)[37, 38,39,40,41]:

PPV:	**28.3%**
Sensitivity:	**62.6%**
Specificity:	**74.8%**
(Sample Size [average]: 303)	

Values for sensitivity have been quoted as high as 82% at 2.5ng/ml PSA cut-off[42] and for specificity. Mearini et al[34] claim 100% sensitivity (when PSA and $DD3^{PCA3}$ are combined) in a tPSA range <4ng/ml. It must also be noted that PCA3 scores and PSA cut-offs can be varied to change the specificity and sensitivity, whereby a higher PCA3/PSA cut-off will produce very high specificity (i.e. very few false positive results) but much compromised sensitivity (high number of false negative results) and vice versa with lowered cut-off values.

In addition, the means by which PCA3 is assayed for (i.e. the technology used) can also alter these results. What these values demonstrate is a classic teething issue of a novel biomarker; the lack of consistency in the type of assay used to identify the marker as well as small sample sizes hampers the production of consistent results and ultimately prevents the attainment of a definitive answer on the applicability of $DD3^{PCA3}$ as a prostate cancer biomarker.

This being said, its prostate-specificity and its potential to differentiate between indolent neoplasms and early malignant tumours ensures that further extensive

research will be conducted into the utility of DD3^{PCA3} as a biomarker aiding clinicians in early diagnosis of prostate cancer.

Epigenomics

Glutathione-S-transferase P1 (GSTP1)—From the family of Glutathione-S-transferases, GSTP1 conjugates chemically reactive electrophiles with glutathione, thus preventing DNA damage from reactive oxygen species and carcinogens which release reactive electrophilic metabolites[49]. Promoter hypermethylation of the region expressing GSTP1 has been directly linked to the loss of GSTP1 expression in prostate cancer[50,51,52]; indeed, this somatic genomic alteration is manifest in over 90% of prostate cancers—making it the most frequent epigenetic event reported in prostate cancer[51,52,53].

With respect to its role in cancer pathogenesis, GSTP1 hypermethylation and the resulting loss of expression is a process presently considered as a *promoter* of cancer (as opposed to an *initiator*), with loss of GSTP1 increasing susceptibility of DNA to oxidants and free radicals[54].

GSTP1 hypermethylation is an attractive target for more intensive investigation into its role as a prostate cancer biomarker for many reasons:

- Its role in the pathogenesis of prostate cancer has been elucidated and the mechanism is well understood.
- GSTP1 hypermethylation is not frequently observed in normal prostate tissue[50,53] (although there have been reports of GSTP1 hypermethylation in high grade prostatic intra-epithelial neoplasia).
- GSTP1 hypermethylation is less frequent in non-prostate genitourinary malignancies (e.g. renal and bladder cancer) [54].
- GSTP1 is not limited by the accessibility of sample collection; it can be identified in a range of body fluids: urine, serum, and ejaculate [54].

Although non-invasive procedures including collection of urine and ejaculate are held as the ideal means of attaining diagnostic information, there are key shortcomings with the use of these tissues. It has been shown that GSTP1 methylation levels are higher in plasma compared to urine, suggesting that prostate cancer is preferentially disseminated into the bloodstream rather than the prostatic ductal system[54].

With ejaculate, the inherent nature of such a collection procedure, particularly with older men, renders this avenue as one unlikely to see significant clinical exposure. Solutions such as prostatic massage to release cancer cells into the prostatic urethra before collection have so far delivered mixed results[48,58,59]. The difficulties faced in attaining clinically applicable detection rates through non-invasive methods remains a barrier yet to be surmounted.

Currently, the most promising results portraying GSTP1 hypermethylation have been produced from tissue samples. The use of quantitative methylation specific PCR (QMSP) in screening for GSTP1 methylation has been reported to deliver 85.5% sensitivity and 96.8% specificity (n=128)[56].

When further tests were conducted on the same set of tissue specimens to assess the capacity for differentiation between non-cancerous tissue and histologically-proven adenocarcinoma (n=21), the QMSP assay correctly diagnosed the specimens with 90.9% sensitivity and 100% specificity and 100% positive predictive value.

In addition, Harden et al[57] demonstrate a 15% increase in specificity of the gold-standard of prostate diagnosis—histopathologic assessment—through combining histopathologic assessment with QMSP for GSTP1. Furthermore, there is evidence that this method may be complemented with a measure of ENT SCTR methylation[137].

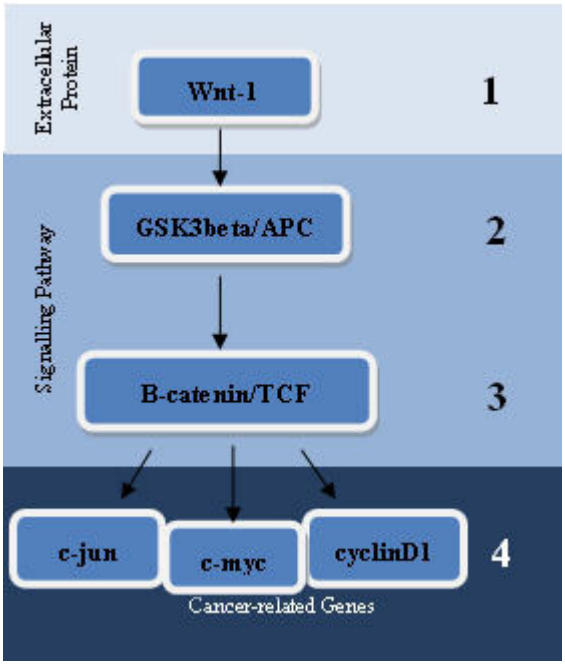
These results highlight the potential for GSTP1 hypermethylation as a means of complementing histopathological diagnosis of prostate samples and furthermore, a means of differentiating indolent and malignant neoplasms in cases where PSA levels alone are unable to discriminate[56].

Wnt signalling and methylation—Wnt signalling and its subsequent pathways are known to be crucial in mammalian and embryonic development[60, 61].

Its role in the pathogenesis of cancer can be summarised by the following diagram (modified from van der Poel HG[60]):

Figure 3. Potential involvement of the Wnt pathway in the development of malignancy. The steps portrayed are:

- **Binding of Wnt ligand to the frizzled transmembrane receptor.**
- **Decreased phosphorylation of B-catenin by GSK3-B. Therefore, stabilised B-catenin now accumulates in the nucleus.**
- **Nuclear B-catenin converts the TCF/LEF DNA binding complex from a transcriptional repressor into a transcriptional activator.**
- **Transcriptional activation of many cancer-related genes[61].**



In the case of prostate cancer, there are a handful of epigenetic changes which are thought to alter the Wnt signalling pathway:

- Hypermethylation of the APC (adenomatous polyposis coli) gene is increased 8-fold in prostate tumours relative to samples of benign prostatic hypertrophy[61]. It has been proposed that DNA hypermethylation of the APC gene, an important component of the B-catenin degradation complex, may lead to the nuclear accumulation of B-catenin and hence the activation of the Wnt signalling pathway activating various oncogenes[61].
- Equally, E-cadherin is a cell-membrane protein, which is known to both interact with B-catenin and be involved in the process of epithelial-to-mesenchymal transmission (EMT), a key step in the development of malignancy[63]. When the promoter for the E-cadherin gene is silenced by methylation, it not only promotes EMT but also the release of B-catenin away from the cell membrane and into the cytoplasmic and nuclear compartments. The presence of B-catenin in the nucleus will hence activate Wnt signalling[61,62].
- Secreted-frizzled related proteins (SFRPs) and Wnt inhibitory factor-1 (Wif-1) are antagonists for Wnt signalling. Thus, silencing of genes which express SFRPs and Wif-1 through hypermethylation will lead to aberrant Wnt signalling and cancer progression. Although silencing of genes encoding SFRPs and Wif-1 has been identified in many cancers, including colorectal, lung, and bladder cancers and lymphocytic leukaemia[64], there is insufficient evidence to definitively claim that Wnt antagonist genes play a key role in prostate cancer development.

Despite the extensive elucidation of the Wnt signalling pathway, there remain questions over its relevance to prostate cancer and whether assays for hypermethylation of any of the aforementioned genes will aid the delineation of a diagnostic landscape. However, the role of potential cancer promoters, exemplified by Wnt signalling, should be investigated further, as their presence may well be of use in risk-stratification processes in future. For example, Wnt pathway factors also promote osteoblastic lesions[138,139].

Xenobiotic metabolism and methylation—Xenobiotics (chemical compounds that are foreign to the body) have been widely studied as potential initiators for cancer. An extensively researched xenobiotic is the family of polycyclic aromatic hydrocarbons (PAHs): particularly prevalent in automobile exhausts and cigarette smoke, these compounds are known to be both toxic and carcinogenic[61].

The two cytochrome P450 enzymes responsible for initiating PAH metabolism through oxidation, CYP1A1 and CYP1B1, have been shown to be subject to alterations in expression in human prostate cancer specimens and prostate cancer cell lines through epigenetic activity[61]. In knock-down mice studies, there has been proof demonstrating that:

- Loss of CYP1A1 induction acutely *increases* sensitivity to PAH toxicity.
- Loss of CYP1B1 *protects* against PAH toxicity.

With this in mind, when observing results of experiments on prostate cancer specimens and cell lines which reveal both suppression of CYP1A1 induction and overexpression of CYP1B1 through respective hypermethylation and hypomethylation, we can ascertain that:

- A gene which protects against a carcinogen (PAH) is suppressed.
- A gene which positively mediates carcinogenic toxicity is over-expressed.

Thus, the epigenetic effects on these two genes synergise to have the combined effect of increasing sensitivity to PAH toxicity[61].Furthermore, in the context of GSTP1 promoter hypermethylation and hence GSTP1 suppression, there is not only down-regulated oxidation of PAHs but additionally, down-regulated glutathione conjugation, which ultimately renders both phases of xenobiotic metabolism adversely suppressed.

This information suggests that some prostate cancers may display acute sensitivity to PAH exposure. Such a finding has strong potential for clinical utility in New Zealand, and might be included in risk-stratification for prostate cancer given that:

- The 2006 Census shows 23.0% of all New Zealanders aged 15-64 are regular or current smokers[65] (smoking being a known behavioural exposure to high PAH levels).
- Smokers have been associated with higher prostate-cancer associated mortality in large epidemiologic studies[66] (although the strength of this association has varied between studies and meta-analyses[67, 68]).

The strong epidemiologic facet to the issue, particularly in an Aotearoa/New Zealand context with a high prevalence of regular tobacco use, demands further investigation into the epigenetic alterations to xenobiotic metabolism, in the hope of uncovering further putative biomarkers for prostate cancer.

Proteomics

α-methyl-acyl-coenzyme A-racemase (AMACR)—AMACR is an isomerase which is involved in both R-stereoisomer to S-stereoisomer conversion and peroxisomal B-oxidation of branched-chain fatty acids[69,70].It is currently in clinical use as an immunohistochemical marker for prostate cancer (autoantibodies to AMACR have been detected in serum more readily than the AMACR protein itself)[48], aiding in diagnosis of biopsy specimens, in which it delivers impressive sensitivities and specificities of over 90%[71,72].

Although androgen ablation therapy has been shown to down-regulate AMACR expression[73], it is widely agreed that AMACR is a major improvement on serum PSA testing with biopsy specimens, when differentiating between benign and malignant neoplasms[74].

The success of AMACR in biopsy specimens of prostate cancer however has not yet been reproduced in urine or serum. Rogers et al.[75] report 100% sensitivity and 58% specificity (n=26) when performing Western blot analyses on urine specimens and Zielie et al.[76] produced sensitivity and specificity values over 85% (n=21). However, this was only through use of normalised AMACR transcript levels relative to PSA

level for each prostatic secretion sample, whereby these levels were then compared to an experimentally-defined diagnostic cut-off value determined by a control group.

The small sample sizes and lack of long follow-up periods in such studies leave scope for further, larger-scale studies, to be conducted on the clinical utility of AMACR as a non-invasive biomarker. Furthermore, development of a standardised, reproducible protein-based assay. such as an ELISA (Enzyme-linked immunosorbent assay) with a standardised cut-off value for differentiating positive and negative results, would go a long way in validating such a biomarker as one able to distinguish indolent from aggressive tumours.

Human kallikrein 2 (hK2 or KLK2)—Homologous to PSA in 80% of its amino acid sequence identity, hK2 is a serine protease that is prostate-specific, with expression regulated by androgens on an androgen receptor. As a result, there is extensive immunologic cross-reaction between hK2 and PSA rendering comparisons between hK2 and PSA expression difficult. Despite the paucity of studies in the field, it has been identified that hK2 tissue expression is higher in malignant compared with benign prostate tissue—moreover, cells expressing PSA tend to be less frequent in poorly differentiated malignant tissue compared to benign tissue[49, 77, 78]. This lends hK2 prognostic capability and predictive value in monitoring the course of disease more robust than what is currently delivered through PSA testing.

hK2 is a biomarker which is limited through the variability in assay configuration and antibody specificity in particular, in addition to other atypical issues with biomarkers which include diagnostic and sampling criteria and age of samples. Furthermore, one must note that, as with PCA3/PSA ratios, the sensitivity and specificity of such a test is completely dependent on the diagnostic cut-off value chosen. One can produce a 95% sensitivity, that is *detect* 95% of all cancers, but at the same time, have a specificity of 24% (meaning 76% of men will have to undergo an unnecessary biopsy) at a given hK2/free PSA ratio[79].

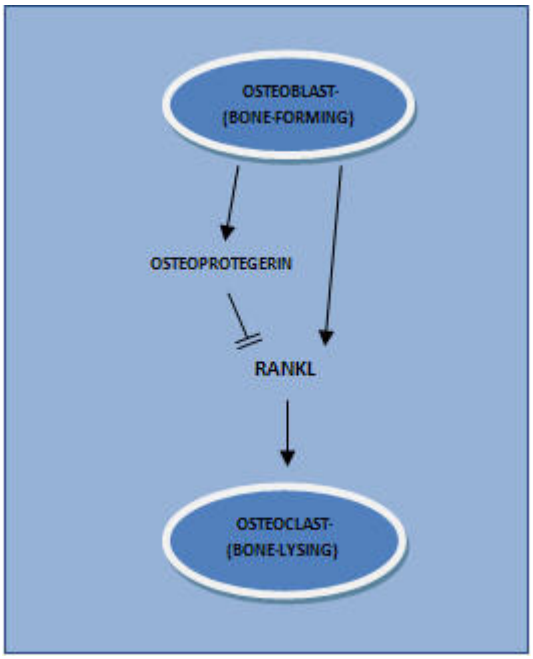
The greatest strength of this potential biomarker lies perhaps in its predictive value for biochemical recurrence in patients with PSA $\leq$ 10.0ng/mL (AUC for extra-capsular extension and seminal vesicle invasion were 0.662 and 0.719 respectively for hK2 compared with 0.654 and 0.663 respectively for tPSA). Additionally hK2 is able to maintain its prognostic value for biochemical recurrence of disease when corrected for clinical variables[80, 81]. This is clinically pertinent as hK2 performs comparatively well in the "grey zone" of PSA 2.5 – 10.0ng/ml - the area of greatest weakness of PSA testing.

Furthermore, the "grey zone" of PSA 2.5 – 10.0ng/ml is a category with burgeoning numbers of patients as a result of a drive for early diagnosis ultimately culminating in more men being diagnosed with prostate cancer whilst having a PSA level in the "grey zone". Thus, hK2 may play a synergistic role with PSA testing, to deliver more accurate prognoses for patients with low-PSA level cases of disease.

The significance of the improvement with hK2 testing in diagnostic and prognostic strength on current methods is insufficient to see it replace PSA testing outright, but rather, with further validation, provide adjuvant diagnostic and prognostic value in serum testing.

Osteoprotegerin—As prostate cancer advances, it has the ability to induce the formation of osteoblastic lesions, which in turn manifest themselves as osteosclerotic (abnormally hardened or dense bone) lesions, initially forming in the axial, but later in the appendicular skeleton[82]. Osteoprotegerin (OPG) is a cytokine produced by osteoblasts (bone-forming cells) which inhibits RANKL (also produced by osteoblasts), an activating cytokine of bone-lysing osteoclasts[82,83]:

Figure 4: A simplified schematic representation of the role of osteoprotegerin (OPG) in the inhibition of osteoclastic activity and hence formation of osteoblastic lesions



Thus, the possibility of metastatic prostate tumour cells secreting OPG and potentially causing osteoblastic changes in the architecture of bone is of interest in monitoring the progression of advanced prostate cancer cases. Moreover, bone is known to be the most common site of prostate cancer metastases[18], further underpinning the importance of OPG as a potential biomarker in advanced prostate cancer.

Indeed the data produced from current studies highlight OPG as a promising serum-based marker which, unlike PSA, is specific for detection of bone metastases:

- Serum levels of OPG were found to be significantly higher in advanced prostate cancer patients than those at other stages of prostate cancer[84, 85].
- Serum OPG identified patients with bone metastases at a sensitivity of 88% and specificity of 93%[86].
- Elevation of serum OPG not observed in bone metastases of any other malignancies[87].

Although there is much promise in the potential of OPG to provide prognostic information post-androgen ablation, one must be aware of a key caveat in the interpretation of serum OPG levels. OPG levels, although not elevated through bone metastases of other malignancies, are increased in cases of rheumatoid arthritis and vascular diseases[88, 89].

Given that these pathologies, as well as prostate cancer, generally occur in older populations, it would be appropriate to interpret serum OPG levels based on age-stratified values in a clinical setting, normalised for the presence of "background" OPG sources such as vascular disease.

With a commercial serum OPG ELISA now available[18], the progress of randomised, controlled studies of serum OPG as a marker for prostatic bone metastases now have the reproducibility required for clinically robust diagnostic and prognostic assays. Ultimately, such studies can produce further data on a biomarker which may aid clinicians in determining the course of disease for advanced, metastatic prostate cancer.

Telomerase—Telomeres are sequences of DNA which stabilize and protect the ends of chromosomes, and their maintenance is regulated by telomerases, which in turn are encoded for by the telomerase reverse transcriptase (*TERT)* gene. Loss of telomeres is associated with the processes of chronic inflammation, oxidative stress and cell division. Whether telomeric loss in such processes is causally linked to the finding that telomerase activity is expressed in at least 90% of prostate cancers[90, 91], remains to be seen.

Telomerase has been successfully detected in prostate biopsy specimens, prostatic fluid and urine[18]. However, the variability of results produced by various studies, suggests techniques such as prostatic massage, as well as the sensitivity of differing assays, plays a role, particularly with urine samples, in the qualitative analysis of telomerase in prostate cancer urinary specimens[49].

Sensitivity and specificity value ranges of 58%, 90%, 100% and 100%, 76%, 88%[92, 93, 94], respectively, are testament to the inconsistency that currently stands in relation to telomerase assays and testing.

Further evaluation of telomerase assays through multi-centre investigations with large cohort numbers is required before we can ascertain its true value in the discernment of malignancy in the prostate.

Metabolomics

The field of metabolomics is perhaps the most underexploited pathway in the search for novel cancer biomarkers. Analysis of metabolic alterations in prostate cancer may be of use in tracking the progression of malignancy. A selection of the well-studied metabolites and their relationship to prostate cancer are summarised in the table below:

Table 1. Associations of prominent metabolites with prostate cancer

Metabolite	Association with prostate cancer
Lactate	High levels in prostate cancer compared to normal prostate and BPH tissue[95, 96, 97, 98, 99, 100]. Associated with increased glucose metabolism is a characteristic feature of tumour cell metabolism[107] as glucose is converted to lactate via glycolysis[103].
Citrate	Low levels in prostate cancer compared to normal prostate and BPH tissue[95, 96, 97, 98, 99, 100]. Loss of citrate has strong correlation with tumour grade (determined through Gleason Score[105, 106])—low levels in early stage prostate cancer and absent in poorly differentiated tumours[101]. Citrate oxidation and hence lower levels of intracellular citrate occurs due to loss of ability to accumulate and hence lower levels of intracellular zinc in malignant cells[102, 103].
Choline/Creatine	Elevated in prostate cancer[95, 96, 97, 98, 99, 100]; increased levels correlate to Gleason Score[105, 106].
Polyamines	Higher levels in healthy tissues[104] compared with lower levels in prostate cancer[95, 96, 97, 98, 99, 100]. Absent in 80% of high grade tumours—thus loss of polyamine metabolites are potentially a marker for both stage and grade of prostate cancer[104].
Sarcosine	Despite considerable interest in a paper in the journal Nature reporting a potential role for sarcosine in prostate cancer, as delineated by metabolomic profiles[142], the relevance of this metabolomic marker is widely debated[140,141]. However, there may be utility in its inclusion as a component in multiplex modelling with other prostate cancer biomarkers[143].
Others	Taurine, glutamine, glutamate, and alanine have been found to be associated with malignancy, but have not correlated directly with tumour grades[103].

The elucidation of the link that exists between prostate cancer and metabolites of tumour cells continues. The early data published on the significance of the association of metabolites, particularly citrate and choline (indeed a low citrate/choline ratio is indicative of a high-grade tumour, when measured with Magnetic Resonance Spectroscopy (MRS) [104, 108]) stipulates that further studies are warranted in the quest to uncover metabolomic tests which are able to accurately map the progression of prostate cancer tumours through clinically feasible and robust biomarker assays.

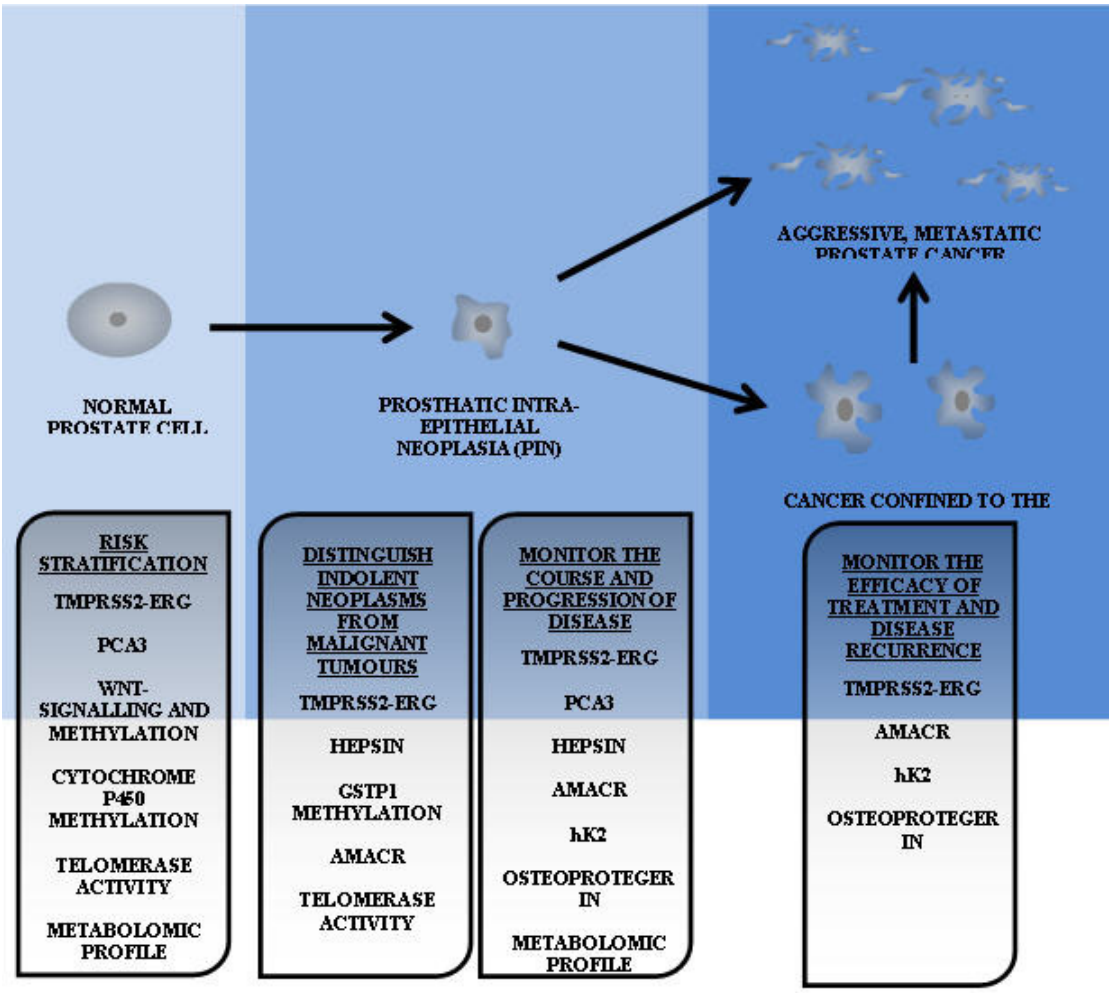
Summary of the potential clinical applications of novel prostate cancer biomarkers

Table 2. Applications of promising novel biomarkers for prostate cancer

Application	Biomarker	Specimen
Risk-stratification for prostate cancer	TMPRSS2-ERG[22]	Urine[22]
	PCA3[32]	Urine[34]
	8-OHdG[43]	Urine[43]
	Wnt-Signalling and Methylation[61]	Biopsy[61]
	Cytochrome P450 Methylation (Altered Xenobiotic Metabolism)[61]	Biopsy[61]
	Telomerase Activity[90, 91]	Urine[49]
	Metabolomic Profile[104, 108]	–
		(*In situ* Endorectal Magnetic Resonance Spectroscopy Imaging [MRSI])[98]
Distinguish indolent neoplasms from malignant tumours	TMPRSS2-ERG[22]	Urine[22]
	Hepsin[46, 47]	Biopsy[46]
	GSTP1 Methylation[50, 53, 56, 57]	Biopsy, Serum, Urine, Ejaculate[54]
	AMACR[71, 72]	Biopsy, Urine, Serum[74, 75, 76]
	Telomerase Activity[90, 91]	Urine[49]
Monitor the course and progression of disease	TMPRSS2-ERG[30]	Urine[22]
	PCA3[18]	Urine[34]
	Hepsin[46]	Biopsy[46]
	AMACR[73]	Biopsy, Urine, Serum[74, 75, 76]
	hK2[49, 77, 78]	Serum[80, 81]
	Osteoprotegerin[84, 85]	Serum[18]
	Metabolomic Profile[104]	–
		(*In situ* Endorectal Magnetic Resonance Spectroscopy Imaging [MRSI])[98]
Monitor the efficacy of treatment and disease recurrence	TMPRSS2-ERG[28]	Urine[22]
	AMACR[73]	Biopsy, Urine, Serum[74, 75, 76]
	hK2[80, 81]	Serum[80, 81]
	Osteoprotegerin[86]	Serum[18]

Adapted from Hessels et al.[18]

Figure 5. Potential application of new biomarkers in prostate cancer diagnosis and assessment of status



Implementation of novel biomarkers into clinical practice: a strategy unique to Aotearoa/New Zealand

"Research is to see what everybody else has seen, and to think what nobody else has thought." (Albert Szent-Gyorgyi, 1893–1986; 1937 Nobel Prize for Medicine)

Such an adage epitomises the ethos of biomedical research and undoubtedly encapsulates the modern approach to discovery and development of novel biomarkers in prostate cancer. However, the voyage of such scientific idealism from theory to practice will ultimately always be dictated by a plethora of guidelines and regulations as well as financial and practical limitations.

Indeed, Pepe et al[110] have delineated five phases with which researchers are able to stratify biomarkers into stages of development.

Table 3. Phases of biomarker development

Phase	Aims
Phase 1—Preclinical Exploratory Studies	Identify and prioritise potentially useful biomarkers.
Phase 2—Clinical Assay Development for Clinical Disease	Assess true positive and false positive rates in the assay. Assess the ability of the assay to differentiate specimens with and without cancer. Compare biomarker measurements in tissue specimens and non-invasive specimens. Optimise the reproducibility of the assay. Assess factors such as age, gender and ethnicity with relation to biomarker measurements. Assess correlation between biomarker measurements and the stage, grade, histology and prognosis of tumours.
Phase 3—Retrospective Longitudinal Repository Studies	Assess ability of biomarker to detect preclinical disease. Define criteria for a positive screening test. Compare multiple biomarkers and develop a combination-biomarker algorithm for screen positivity.
Phase 4—Prospective Screening Studies	Assess of the sensitivity and specificity of the biomarker-based test in a population. Assess the feasibility of implementation of such a screening programme. Assess patient compliance and the factors governing patient compliance. Assess speculatively effect of screening on costs and cancer-associated mortality. Monitor character and progression of tumours not detected by screen (the false negative results).
Phase 5—Cancer Control Studies	Estimate the reduction in burden of cancer and cancer mortality in the population resulting from biomarker. Analyse costs of screening and treatment in comparison to alternative screening methods.

Although few biomarkers will progress linearly through each phase[110], the significance of such a framework lies within the depth with which a biomarker must be analysed and rigorously assessed before the decision is made to impart sparse resources into a novel development. The lengthy wait for novel biomarkers in the clinical assessment of prostate cancer is testament to the stringency of the processes and regulations required.

What has transpired is a delicate balance between the production of biomarkers that are accurate, non-invasive, inexpensive and clinically-robust, and the demand for having such biomarkers available in the near future for clinical use, given the progressive increase in cancer burden in New Zealand over the last 15 years (due to a 7% increase in cancer incidence in males between 1996-2011 and a 20% decrease in cancer mortality in males over the same time period[111]).

The reversal of this upward trend in cancer burden in men will not only occur with the more immediate introduction of novel prostate cancer biomarkers, but also through integration of novel discoveries into primary health care. The primary healthcare system in New Zealand stands as the crucial interface between the healthcare system and the population in which many biomarkers through risk-stratification methods will potentially be able to diagnose pre-clinical prostatic disease and differentiate indolent from aggressive phenotypes, ultimately leading to potential substantial improvements in current clinical practice.

It is also important that, despite statistics portraying more New Zealand European men being diagnosed with prostate cancer it has been shown, through mortality data, that more Pacific Islands and Maori men die of the disease[126]. Whether the disease is of a fundamentally different nature in this group and requires a different approach to treatment, or whether it is being diagnosed at a later stage, may also become far clearer with more systematic use of a panel of biomarkers which may become available in future as more biomarkers become validated through evidence manifest in large-scale clinical trials.

The realisation of a comprehensive prostate cancer screening programme depends primarily on the work of researchers and their capacity to "*think like nobody else has thought*", unearthing one or many biomarkers which may provide evidence-based, compelling and definitive diagnostic and prognostic information in the field of prostate cancer, which clinicians will ultimately be able to utilise in bringing about better health outcomes for men in Aotearoa/New Zealand.

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Author information: Lance Ng, Research Student, Auckland Cancer Society Research Centre, University of Auckland; Nishi Karunasinghe; Research Technician, Auckland Cancer Society Research Centre, University of Auckland; Challaraj S Benjamin, Professor, Consultant Oncologist, Auckland Cancer Society Research Centre, University of Auckland and Department of Clinical Oncology, Auckland Hospital, Auckland; Lynnette R Ferguson; Professor, Head of Department, Nutrition, School of Medical Sciences, Auckland Cancer Society Research Centre, University of Auckland

Correspondence: Lance Ng, Research Student, Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland, New Zealand. Email: lng036@aucklanduni.ac.nz

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Reporting of adverse effects in randomised clinical trials of chiropractic manipulations: a systematic review

Edzard Ernst, Paul Posadzki

Abstract

Objective To systematically review the reporting of adverse effects in clinical trials of chiropractic manipulation.

Data sources Six databases were searched from 2000 to July 2011. Randomised clinical trials (RCTs) were considered, if they tested chiropractic manipulations against any control intervention in human patients suffering from any type of clinical condition. The selection of studies, data extraction, and validation were performed independently by two reviewers.

Results Sixty RCTs had been published. Twenty-nine RCTs did not mention adverse effects at all. Sixteen RCTs reported that no adverse effects had occurred. Complete information on incidence, severity, duration, frequency and method of reporting of adverse effects was included in only one RCT. Conflicts of interests were not mentioned by the majority of authors.

Conclusions Adverse effects are poorly reported in recent RCTs of chiropractic manipulations.

Chiropractic has been defined the "diagnosis, treatment and prevention of mechanical disorders of the musculoskeletal system and the effects of these disorders on the function on the nervous system and general health".[1] The hallmark intervention of chiropractic is spinal manipulation which is used to adjust spinal "subluxations". The founder of chiropractic believed that 95% of all diseases are caused by vertebral subluxations.[2]

Many authors have expressed doubts about the safety of spinal manipulation. A particular concern relates to vascular accidents caused by arterial dissection after upper spinal manipulation.[3,4] The main aim of this review is to examine the reporting of adverse effects of chiropractic manipulations in recent randomised clinical trials (RCTs).

Method

Literature searches were performed in July 2011 to identify adverse effects reported in randomised clinical trials (RCTs) of chiropractic manipulation. The following databases were searched (from January 2000 to July 2011): **Cochrane Library, MEDLINE, EMBASE, CINAHL, AMED, PsycINFO. Chiropractic manipulation OR chiropractic OR spinal manipulation** were employed as Medical Subject Heading (MeSH) terms or key words for our search.

The reference lists of all located articles were scanned for further relevant literature. Additionally, relevant published book chapters and our own extensive files were hand-searched for further articles. No language barriers were imposed.

Exclusion criteria were trials by osteopaths, physiotherapists and medical practitioners, or trials by chiropractors not testing chiropractic manipulation. Data were extracted according to pre-defined criteria (Table 1 and 2) by both authors. Discrepant opinions were settled through discussion.

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http://journal.nzma.org.nz/journal/125-1353/5143/content.pdf))

Results

Sixty RCTs met our eligibility criteria.[5–64] Twenty-nine RCTs (48%) did not report information regarding AEs[6,9,13–20,26,29,32,36,40,41,45–49,53,56,60,62,64] and 31 RCTs (52%) did. Of those 31 RCTs, 16 (51.6%) reported that no adverse effect of chiropractic manipulations occurred during the study.[5,9,18,20,21,23,24,26,30,38,42–44,59,60,63] Eight of the 31 RCTs mentioning AEs described the method of establishing AEs: interview,[31,33] questionnaire,[23] questionnaire and telephone interview,[38] self-reports,[39] diary,[61] standardised form,[8] and notes.[9] Eleven RCTs mentioned the severity of AEs.[7,8,17,19,27,29,31,33,34,46,51] Four RCTs reported the duration of AEs.[27,29,34,51] One RCT reported the frequency of AEs.[38] One RCT (1.6%) reported complete information on AEs, i.e. method of reporting, severity, duration and frequency.[38]

The source of funding was provided in 47 RCTs (78.4%%)[5–10,12,14,15,17–22,24–29,31–37,40–46,51,52,54–60,62–64] and in 13 RCTs (21.6%) this information was missing [11,13,16,23,30,38,39,47–50,53,61] Conflicts of interest were declared in 17 RCTs (28.3%)[7,24,27,29–31,37,40,41,43,45,57–60,63,64] and in 43 RCTs (71.7%) this information was missing[5–12,16–20,22–51]

Table 3 summarises the findings related to AEs as a function of source of funding, conflict of interest and affiliation to chiropractic institutions. Sizable proportions (55.8%) of RCTs without a declaration of interest also failed to mention AEs. The method of reporting AEs was not mentioned in large proportions of RCTs without a statement of conflict of interest (86%) or with affiliations to chiropractic institutions (91.8%).

The severity of AEs was not reported in 83.7% of RCTs without declarations of conflict of interest, and in 81% with affiliations to chiropractic institutions. The duration of AEs was not reported in 95.3% of RCTs without declarations of conflict of interest, and in 91.8% of RCTs with affiliations to chiropractic institutions. The frequency of AEs was not reported in 95.3% of RCTs without declarations of conflict of interest and in 100% with affiliations to chiropractic institutions.

Discussion

A remarkably low number of RCTs of chiropractic manipulation was published during the last decade: 60 RCTs compared to nearly 300 000 RCTs that emerged in the conventional healthcare during the same period.[65] The reasons for this paucity of RCTs might be complex and could involve a shortage of funding and a general lack of insight by chiropractors into the necessity of submitting their therapeutic claims to scientific tests.[66]

Forty eight per cent of RCTs reviewed here fail to mention AEs and sizable proportions of those which do mention AEs provide no information as to how AEs were recorded, their severity, duration or frequency (Table 2). For instance, of the 31 RCTs reporting AEs, only 8 (25.8%) mentioned the method of reporting, 11 (35.4%) the severity, 4 (12.9%) the duration, one (3.2%) the frequency of AEs. Further analyses (Table 3) seem to suggest that not declaring conflicts of interest and being

affiliated to chiropractic institutions might be risk factors for incomplete reporting of AEs.

Guidelines of reporting or designing RCTs strongly emphasise that details on AEs are an ethical imperative in clinical research.[e.g.67] Our review seems to indicate that, in chiropractic research, this imperative is frequently ignored. Similarly, the source of funding and any conflicts of interest should be declared in publications of RCTs.[67]

Our review shows that, in chiropractic research, this is frequently not the case. Our analyses also suggest that being affiliated to a chiropractic institution, arguably a conflict of interest in itself,[68] is associated with poor reporting of AEs. Twelve of the RCTs were funded by the US National Center for Complementary and Alternative Medicine,[10,11,19,20-22,25,32-35] and 19 by chiropractic organisations.[13,17,18,22,32,33,35–38,45–47,51,56–60] Of those funded by chiropractors, 6 (31%) failed to report AEs.[64 13,17,22,51,60] Forty-three (71.7%) RCTs failed to report conflicts of interest. Similar deficits in ethical standards have also been noted in other areas of alternative medicine research.[69]

Several hundred severe complications after upper spinal manipulations have been reported.[e.g.70,71] The estimates as to the incidence of these complications vary hugely.[72] The opinion of most chiropractors that such complications are extreme rarities is partly based on the fact that clinical trials of chiropractic manipulation fail to demonstrate the existence of such events. Our review shows that authors of such RCTs frequently neglect to mention AEs. Thus the lack of trial evidence for severe complications could well be due to the failure of triallists to report AEs.

Our review also points to an overt contradiction regarding the incidence of mild to moderate AEs. Sixteen of the 31 RCTs mentioning AEs stated that no AEs occurred and the RCTs which did report AEs provided incidence figures between 1.4%[21] and 50% [61] Numerous prospective studies specifically designed to investigate AEs of chiropractic manipulation agree that about 50% of patients experience mild to moderate AEs after such treatments.[72] Method of monitoring AEs in RCTs strongly influences their incidence.[73,74] Thus lack of rigorous methods for assessing AEs might have generated spuriously low incidence figures in RCTs.

In conclusion, this review shows that AEs are poorly reported or not mentioned at all in RCTs of chiropractic manipulations. Further concerns relate to the prevalent failure to report conflicts of interest or sources of funding.

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Author information: Paul Posadzki, Honorary University Fellow; Edzard Ernst, Director; Complementary Medicine, Peninsula Medical School, Universities of Exeter & Plymouth, Exeter, UK

Correspondence: Paul Posadzki, Complementary Medicine, Peninsula Medical School, Universities of Exeter & Plymouth, Veysey Building, Salmon Pool Line, Exeter, EX2 4SG, UK. Email: Paul.Posadzki@pcmd.ac.uk

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Hepatocellular carcinoma during pregnancy: case report and review of the literature

Peter Russell, Pandanaboyana Sanjay, Ilse Dirkzwager, Kai Chau, Peter Johnston

Abstract

Hepatocellular carcinoma (HCC) during pregnancy is very rare with poor prognosis. We report a case of a HCC in a 33-year-old, pregnant female with an otherwise normal liver and no risk factors, diagnosed by routine prenatal ultrasound scan and elevated alpha-feto protein levels. She underwent a synchronous caesarean section and liver resection at 30 weeks of gestation with good perioperative outcome and no recurrent disease at 1-year follow-up. This case report discusses the clinical presentations, diagnostic and therapeutic strategies and literature review of this rare presentation.

Hepatocellular carcinoma (HCC) has a distribution that typically follows the prevalence of the hepatitis B and C viruses. As a consequence a third of cases are found in China and another third in the rest of Asia.[1]

In New Zealand, rates of HCC for Māori and Pacific people were 7.3 and 18.0 times that for other ethnicities.[2] HCC in pregnancy is extremely rare, especially if viral hepatitis negative.

We present a case of HCC diagnosed in pregnancy in a young New Zealand Māori woman in an otherwise normal liver. This case highlights the difficulty in diagnosis preoperatively, and timing of surgery in the presence of a viable fetus.

Case report

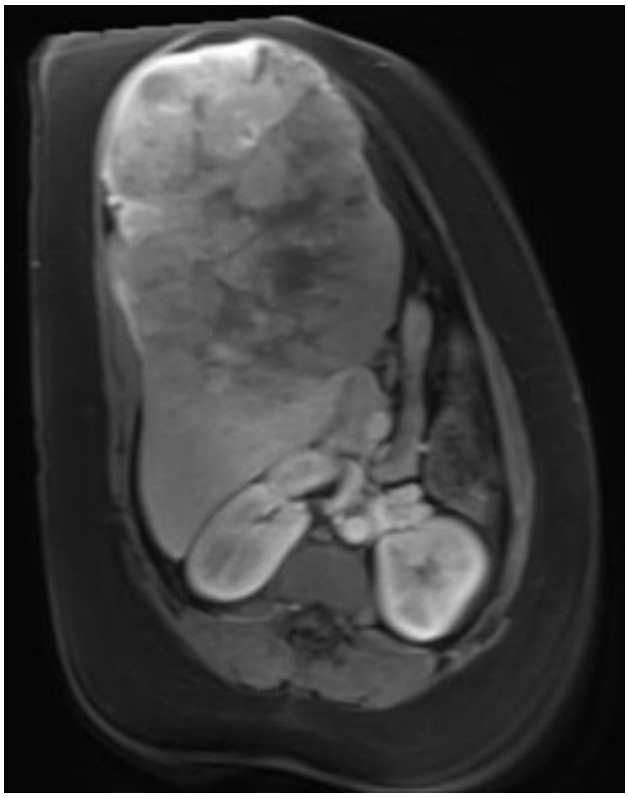
A 33-year-old, gravida eight para four, Māori woman, had a liver mass detected on routine prenatal ultrasound scan at 20 weeks gestation. Her alpha feto protein level was 295 and hepatitis screen was negative. She had no history of oral contraceptive (OCP) use.

She underwent an MRI scan (Figure 1) which showed a large (24 cm) lobulated, heterogenous mass centred in segments IVB and V with areas of restricted diffusion, and heterogenous enhancement including areas of arterial phase enhancement which showed washout on the venous phases and areas of delayed enhancement.

Given the clinical setting and MRI appearances, the lesion was thought most likely to represent a liver cell adenoma (LCA) or HCC. Biopsy was deemed to be inappropriate as it was unlikely to yield a definite diagnosis and carried an undue risk of rupture.

The patient was admitted at 30 weeks gestation for lower segment caesarean section and simultaneous resection of the hepatic mass. Laparotomy revealed a large, lobulated liver tumour from segments IV, V and VI (Figure 2). The lesion was successfully resected with good haemostasis and no bile leak.

Figure 1. Portal venous phase post contrast T1 fat saturated (VIBE) image showing liver mass. The patient was scanned on her side which explains the contour of her abdomen



Macroscopically, the tumour had a thick pseudocapsule, it measured 290 × 180 × 140 mm and weighed 3.7 kg (Figure 2). Microscopic examination showed a poorly differentiated HCC (Fig. 3). There were sheets or trabeculae of tumour cells with fibrovascular stroma, focal haemorrhage and necrosis.

The tumour cells had clear, foamy to eosinophilic cytoplasm. Some had bizarre multilobated nuclei, and mitotic figures were frequently seen. There was vascular space invasion, but the resection margins were clear. Immunohistochemically the tumour cells were moderately positive for HepPar1, and showed a canalicular staining pattern for CD10. The uninvolved liver showed no evidence of cirrhosis, chronic hepatitis, or other underlying abnormalities.

Figure 2. Intraoperative image of resected hepatic tumour

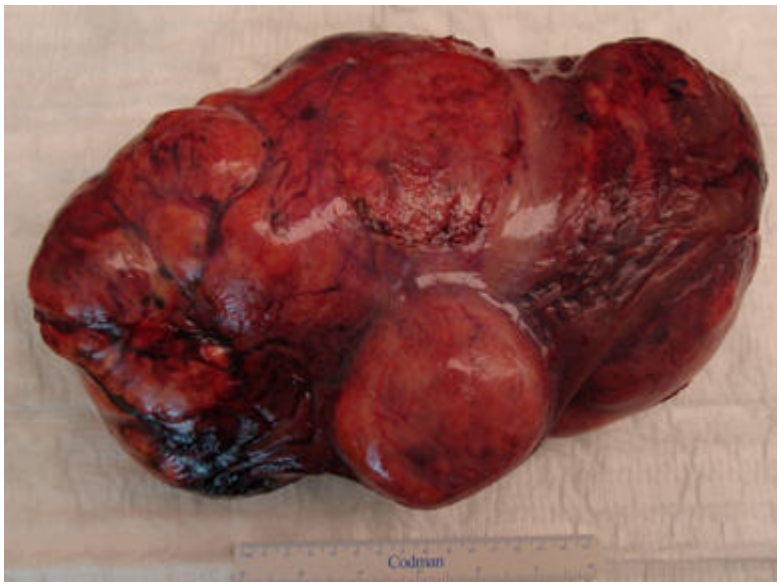
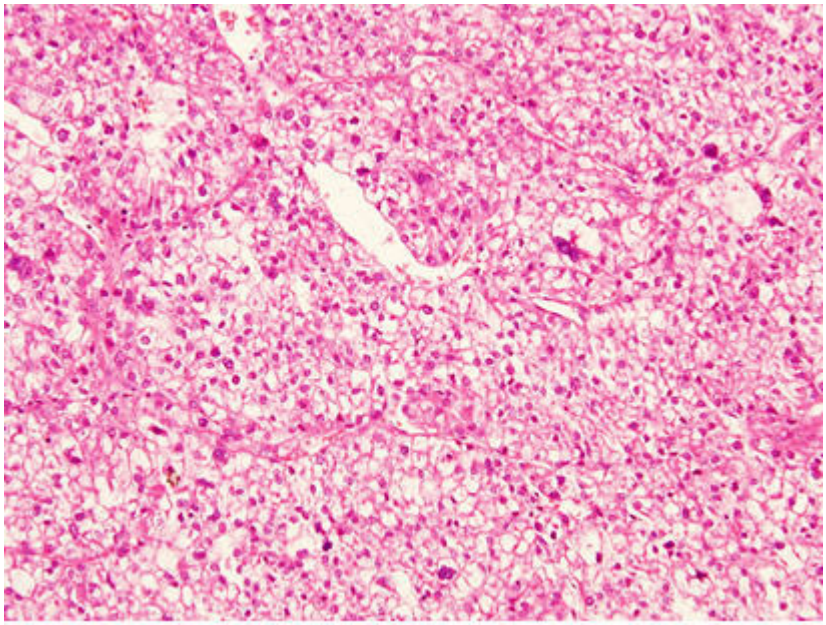


Figure 3. Microscopic examination showing features consistent with poorly differentiated hepatocellular carcinoma (details in text)



Postoperatively the patient had a CT chest and abdomen which showed no residual HCC. There was no indication for further chemotherapy or radiotherapy. There was no evidence of recurrent disease at 1-year follow up.

Discussion

Hepatocellular carcinoma is uncommon in pregnancy. This is partly because cirrhosis, which predisposes to HCC, is associated with infertility. However, oral contraceptives, early menarche, late menopause and increasing parity have all been shown to contribute a small risk to HCC development, suggesting oestrogens play an important role. There are also several case reports of LCA transformation into HCC years after cessation of OCP use.[3]

With the scarcity of cases it is difficult to quantify the effects and risks of pregnancy, specifically rupture, accelerated growth and a poorer prognosis. However, worse outcomes in pregnant women with HCC were noted in the literature. One review quoted only three of 29 patients surviving 12 months or more and live infants being delivered in only 57% of cases.[4] Another case study followed an HCC over time and noted acceleration of growth during the pregnancy.[5]

A 2011 retrospective review of all 47 case studies worldwide of HCC in pregnancy showed poor but improving survival rates over time (median survivals of the groups before and during/after 1995 were 18 and 25.5 months, respectively).[6] Improving survival is due to both earlier diagnosis and surgical intervention.[6] This need for early imaging and resection poses an obvious challenge in pregnancy.

Management has traditionally focused on termination due to the adverse effects of pregnancy on the tumour, followed by resection. This is often undesirable, such as the present case, where a diagnosis was not made until 20 weeks gestation.

Resection is undoubtedly the gold standard of management if possible. However this must be weighed with risks to the fetus of early delivery. Unfortunately there are no clear guidelines on timing of resection due to the rarity of the condition and patient variables. Adjunctive measures such as steroids for fetal lung maturation are recommended to allow earlier delivery.

We report on an interesting and rare case of a hepatocellular carcinoma in a young, pregnant female with an otherwise normal liver. This case highlights the difficulty in making a diagnosis based solely on imaging. Even in a patient with no known risk factors, early resection remains the gold standard for management if it is unclear whether the mass is an HCC or LCA.

Timing of delivery and resection must be balanced between fetal maturation and increasing risks of rupture and tumour development and taken on an individual basis.

Author information: Peter Russell, House Officer; Pandanaboyana Sanjay, HPB Fellow; Peter Johnston, HPB Surgeon, Department of General Surgery; Ilse Dirkzwager, Radiologist, Department of Radiology; Kai Chau, Pathologist, Department of Pathology; Auckland City Hospital, Auckland

Correspondence: Dr Sanjay Pandanaboyana, Fellow in Hepatobiliary Surgery, Auckland City Hospital, Private Bag 92 024, Auckland 1142, New Zealand. Email: sanjay.pandanaboyana@nhs.net

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THE NEW ZEALAND MEDICAL JOURNAL
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"Valve in valve" percutaneous aortic valve implantation for severe mixed bioprosthetic aortic valve disease

Frederic De Vroey, Malcolm Legget, John Ormiston, Mark Webster, James Stewart

Abstract

Transcatheter aortic valve implantation (TAVI) is an effective treatment for patients with severe aortic stenosis at high risk for surgical valve replacement. We present a case of successful, off-label transfemoral valve-in-valve implantation of the self-expandable Medtronic-CoreValve prosthesis in an inoperable elderly patient with structural deterioration of an existing bioprosthesis in the aortic position. This case illustrates that TAVI for a deteriorated aortic bioprosthesis is feasible in a patient who was not suitable for reoperation.

Transcatheter aortic valve implantation (TAVI) is an effective treatment for patients with severe aortic stenosis at high risk for surgical valve replacement.

We present a case of successful, off-label transfemoral valve-in-valve implantation of the self-expandable Medtronic-CoreValve prosthesis in an inoperable elderly patient with structural deterioration of an existing bioprosthesis in the aortic position.

Case report:

A 76-year-old woman, with a past history of bicuspid aortic valve and rheumatic fever, had undergone aortic valve replacement, with a size 21 Carpentier Edwards Perimount porcine pericardial bioprosthesis, 8 years previously, for severe aortic stenosis. At operation, friability of the aorta had been noted. In addition, the patient had smoking-related severe chronic obstructive pulmonary disease (COPD), requiring intermittent systemic steroid therapy.

She had become progressively more breathless over the previous 12 months. Findings on clinical examination were consistent with severe mixed aortic valve disease, and left ventricular failure. There was elevation of N-terminal-brain natriuretic peptide (NT-ProBNP) at 145 pmol/L (normal <35), suggesting a significant cardiac contribution to her symptoms.

Serial echocardiography had demonstrated gradual degeneration of the porcine aortic valve prosthesis and, at presentation, there was severe prosthetic valve stenosis (mean gradient of 24 mmHg, peak velocity of 3.1 m/sec, peak to peak gradient 30 mmHg, calculated valve area of 0.8 cm^2), and, by standard Doppler echocardiographic criteria, moderate aortic regurgitation due to prolapse of one cusp. Left ventricular function had deteriorated with a reduction in echocardiography-derived ejection fraction from 53% to 38% over the previous 6 months.

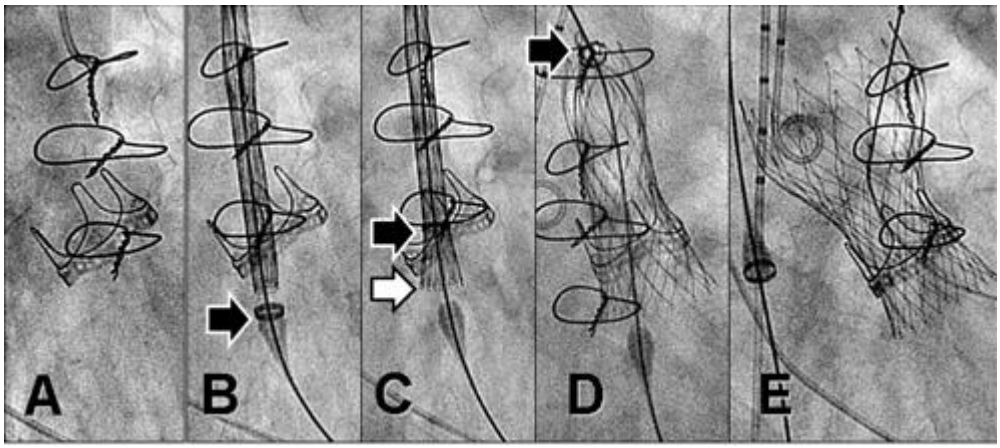
Given the patient's severe COPD, fragile aorta, and small aortic annulus, the risk of repeat aortic valve replacement was felt to be prohibitive. The logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) for perioperative mortality was 31% and STS (Society of Thoracic Surgeons mortality risk) score was 40%. A

multidisciplinary committee recommended TAVI. Coronary and peripheral angiography showed trivial coronary disease, an ascending aortic diameter of 42 mm and suitable iliac and femoral arteries for a transfemoral approach.

Percutaneous aortic valve replacement was performed under general anaesthesia, using a size 26 mm CoreValve ReValving system (Medtronic-CoreValve, Irvine CA). This prosthesis consists of a self-expanding nitinol frame with valve leaflets fashioned from porcine pericardial tissue, delivered through a 18 F deployment catheter.

Delivery and deployment of the CoreValve were uncomplicated (Figure 1) with an immediate reduction in the peak to peak gradient from 30 to 0 mmHg and trivial (Grade 1) aortic regurgitation. Echocardiography 3 days later showed normal function of the percutaneous aortic valve, with a calculated valve area of 1.3 cm^2 and an improvement in left ventricular ejection fraction to 53%. She remains well at 18 months with significantly reduced dyspnoea and no need for a permanent pacemaker.

Figure 1. Shown in A is a frame from a cine angiogram showing the Carpentier Edwards Perimount bovine pericardial aortic bioprosthesis, In B, the sheathed CoreValve percutaneous valve prosthesis lies across the degerated surgical prosthesis with a black arrow indicating the marker on the distal end of the sheath. In C, the sheath (black arrow) has been partially withdrawn allowing the nitinol frame to expand partially (White arrow). In D the sheath has been largely withdrawn but is still attached to the CoreValve nitinol frame (black arrow). In E, the CoreValve is fully released and expanded.



Discussion:

The need for redo surgery due to structural valve deterioration is approximately 10% at 10 years,[1] depending on valve type and population studied. Given the large number of tissue valves that have been implanted over the last 20 years, there will be an increasing number of elderly patients with multiple co-morbidities and bioprosthetic aortic valve deterioration. Percutaneous aortic valve replacement will likely become an attractive therapeutic option in this population.[2,3]

The ability to treat deteriorating prosthetic aortic tissue valves percutaneously, may alter valve selection, especially in patients between the ages of 60–70 years, in whom there is often a clinical dilemma as to the optimal prosthesis, balancing valve durability against the need for long-term anticoagulation.[4]

Percutaneous implantation of an aortic valve for degenerated bioprostheses may be safer than repeat surgical aortic valve replacement for native calcific aortic stenosis. First, precise percutaneous valve positioning is facilitated by the radio-opacity of the bioprosthetic frame.

Second, previous surgical removal of the native heavily calcified valve lessen the risk of underexpansion of the TAVI prosthesis and subsequent paravalvular aortic leak, and reduces the risk of valve material displacement covering a coronary ostium or inducing conduction disorder. Similarly, there may be a role for balloon expandable valve implantation from the transvenous or transapical routes for deteriorated mitral valve bioprostheses.[5]

This case illustrates that TAVI for a deteriorated aortic bioprosthesis is feasible in a patient who was not suitable for reoperation. Long term studies are required before firm recommendations can be made regarding the optimal treatment in this difficult patient group.

Author information: Frederic De Vroey (Cardiologist)[1]; Malcolm Legget, (Cardiologist) [2,3]; John Ormiston, (Cardiologist)[2,3]; Mark Webster, (Director of Interventional Cardiology)[1,3]; James Stewart (Director Cardiology Department)[1,2,3]

1. Green Lane Cardiovascular Department, Auckland City Hospital, Auckland
2. Auckland Heart Group
3. Mercy Angiography, Mercy Hospital, Epsom, Auckland

Correspondence: Dr Frederic De Vroey, Cardiology Department, Green Lane Cardiovascular Service, Auckland City Hospital, Park Road 1023 Grafton, Auckland, New Zealand. Email: fredericd@adhb.govt.nz

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Septic cavernous sinus thrombosis

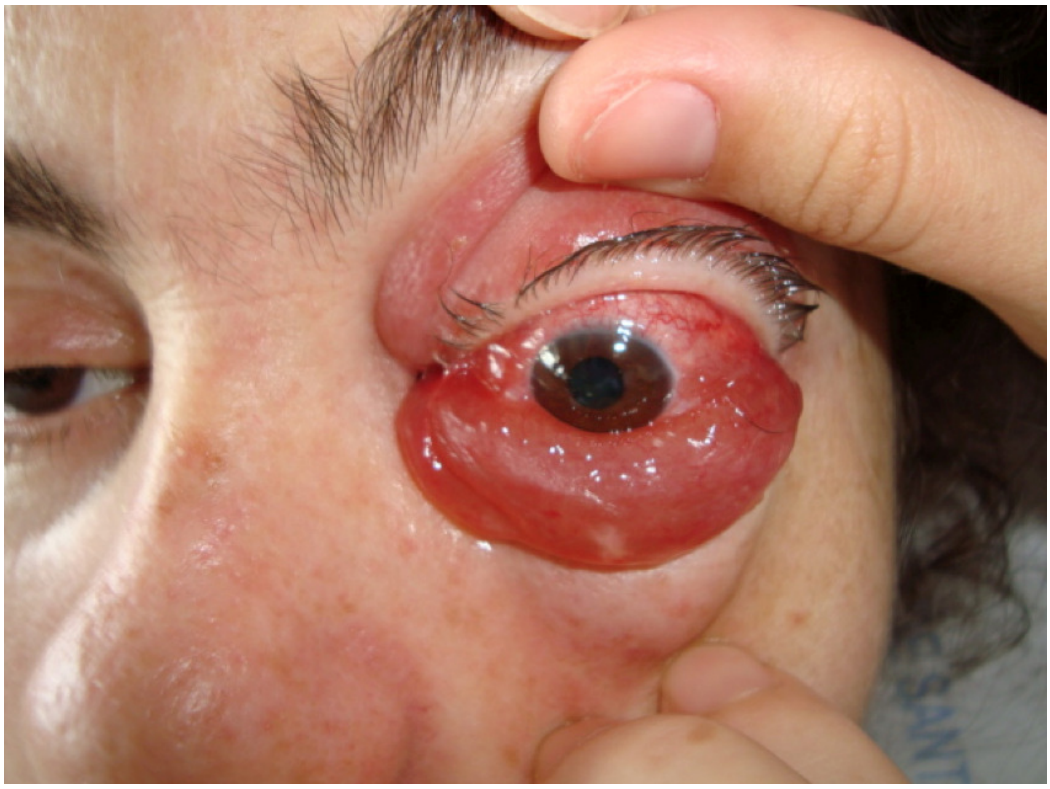
Giordano R T Alves, Letícia M F Machado, Daniela O Teixeira, Carlos Jesus P Haygert

Clinical

A 42-year-old woman presented complaining of frontal headache, postnasal dripping, recurrent vespertine fever and left eye pain for 15 days. Physical examination revealed mild signs of sinusitis, associated with a left lower eritematous palpebral oedema, which initially suggested periorbital cellulitis. She was admitted for proper evaluation and clinical management.

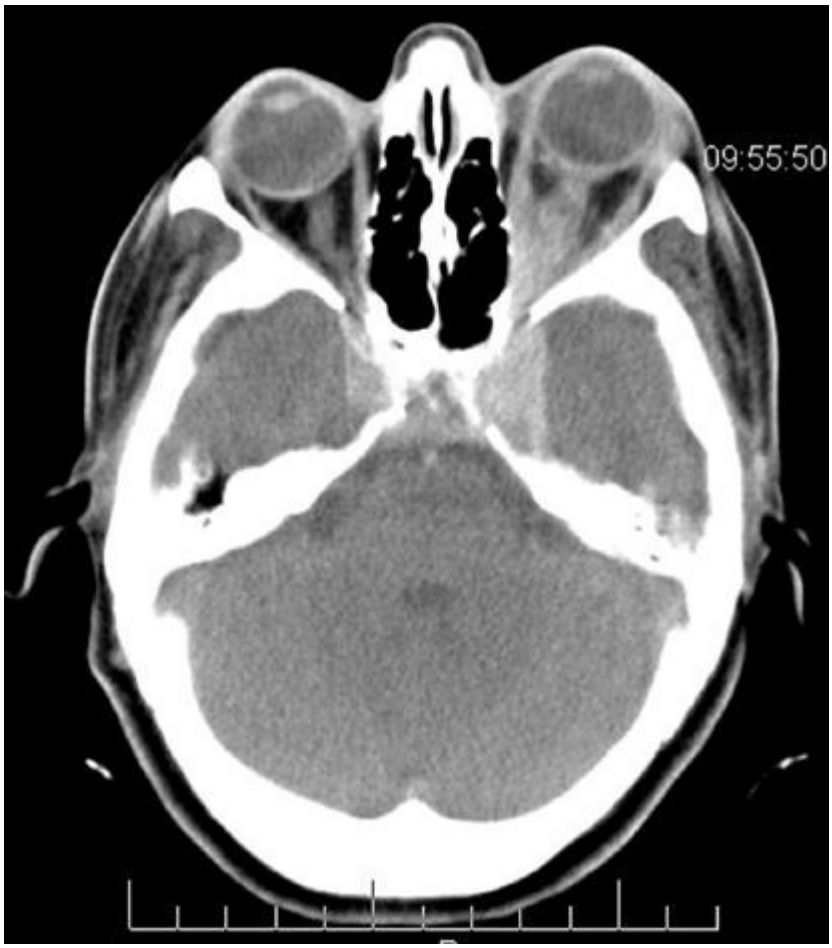
Laboratory analysis, including haemogram and coagulation tests were both normal. Nevertheless, oral cephalexin therapy was initiated to empirically treat periorbitary cellulitis. On the third day following admission, the pain has worsened, and the patient presented left-eye ptosis, proptosis and chemosis (Figure 1). On behalf of this clinical scenario, the diagnosis of septic cavernous sinus thrombosis (SCST) was promptly considered.

Figure 1. Photograph showing extensive chemosis associated with periorbital oedema. A patient with this clinical presentation should always be suspected for having cavernous sinus thrombosis



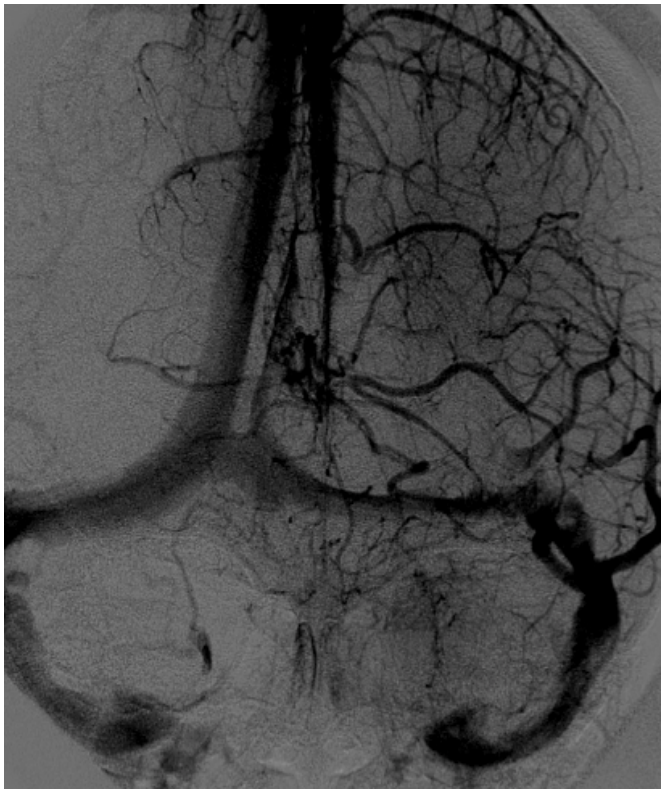
Computed tomography (CT) of the head confirmed the presence of left-eye proptosis, and revealed diffuse thickening of the neurovascular optical tract and orbitary muscles (Figure 2).

Figure 2. Computed tomography (CT) scan of the head showing significant thickening of the neurovascular tract and orbitary muscles of the left eye



Moreover, angiography showed bilateral interruption of contrast flow inside the cavernous sinus (Figure 3), corroborating the diagnosis of cavernous sinus thrombosis (CST).

Figure 3. Angiography revealing bilateral flow interruption (bottom of the image), demonstrating bilateral thrombosis of the cavernous venous sinus



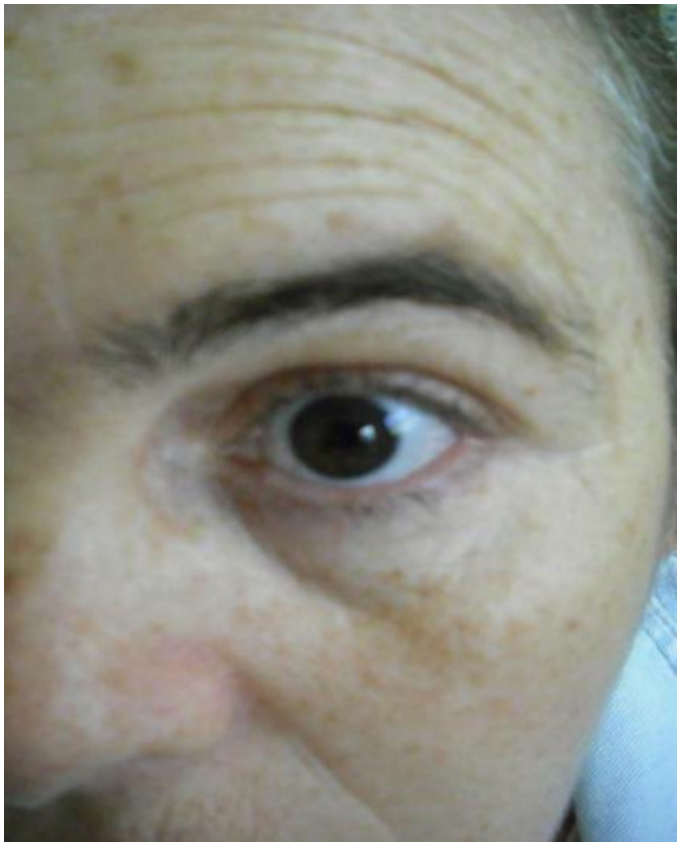
The patient was treated with broad-spectrum antibiotics, corticosteroids and heparin, and was discharged asymptomatic within 5 weeks (Figure 4).

Discussion

Septic cavernous sinus thrombosis (SCST) is a quite rare but life-threatening condition, which mortality used to reach 100% before the antibiotic era.[1] The order symptoms appear depends on the primary site of infection;[2] however, fever, ptosis, chemosis, proptosis and cranial nerves palsies are very frequent.[1,3] In this case, no signs of dental infection or sinusitis were radiologically confirmed, but symptoms` cronology had suggested primary external infection.

In association with clinical parameters, imaging modalities currently play a diagnostic role, especially angiography and magnetic resonance (MR), which was not performed in this case due to institutional issues. In such situations, thin-section CT (3 mm or less)[4] demonstrates to be useful, even though it may not provide early diagnosis and great anatomical detailing as MR does.

Figure 4. Photograph of the patient after 5 weeks of treatment, showing almost complete resolution of initial presentation



Therapy mainly consists in broad-spectrum endovenous antibiotics and corticosteroids, associated or not with anticoagulant drugs.[5] The duration of treatment is variable, and will respect individual basis. Although, mortality rates are still high, ranging from 15% to 30%. Therefore, recognizing and treating SCST as soon as possible demonstrates to be the most effective action to decrease mortality and prevent subsequent sequelae.

Author information: Giordano R T Alves, Clinical Medicine Department; Letícia M F Machado, Division of Vascular Medicine; Daniela O Teixeira, Interventional Radiology Division; Carlos Jesus P Haygert, Radiology Division; University Hospital of Santa Maria, Brazil

Correspondence: Giordano R T Alves, Department of Clinical Medicine, Federal University of Santa Maria, Roraima Avenue, 1000. Zip Code: 97105-900. Santa Maria, Rio Grande do Sul, Brazil. Email: grtalves@gmail.com

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Deposit on the skin in critical care: can it be a clue to diagnosis?

A 42-year-old male patient presented with sudden onset high rise of temperature with altered sensorium. On examination the patient was obtunded, having tachycardia (pulse 110/minute) and positive meningeal signs. Laboratory evaluation showed high leukocyte count, raised erythrocyte sedimentation rate (ESR), normal electrolyte and altered renal profile (blood urea nitrogen 32.84 µmol/L and creatinine 707.2 µmol/L), and eGFR of 7 mL/min/1.73 m^2 (according to 'modification of diet for renal disease' formula).

On the fourth day of admission the patient developed white powder-like material all over his body—predominantly on the face, trunk and upper extremity (see Figure 1). The patient was diagnosed to be a case of septicaemia with acute renal failure (due to septic acute tubular necrosis) with deposition of uremic frost on the skin. The patient died on the sixth day despite receiving one session of haemodialysis.

Figure 1. Photograph of the patient showing white powder-like deposition over the face, front of neck, trunk and upper extremity

Uremic frost was first described by Hirschsprung in 1865 and is believed to result from evaporation of sweat that contains high levels of urea and other nitrogenous waste products. These waste products crystallize on the skin, most commonly on the face.[1]

Author information: Manish Saha, Resident; Tarkeswar Aich, Resident; Chiranjib Das, Resident; Mainak Mukhopadhyay, Resident; Kartick Patar, Resident; Department of Medicine, Nil Ratan Sircar Medical College and Hospital, Kolkata, India

Correspondence: Manish Saha, 1/A East Talbagan Road, P.O. Nona Chandanpukur, Barrackpore, Kolkata – 700122, India. Email: drmanishsaha@gmail.com

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Comparing Finland with New Zealand: lessons from Finland for controlling infectious diseases

There has recently been public and media discourse comparing Finland with New Zealand (in both countries). This discussion was triggered by comments in the New Zealand Parliament, and has not always been well informed by facts. Nevertheless, country comparisons can provide learning opportunities and hence we continue the comparison in the domain of infectious diseases. This domain is a particularly relevant one for New Zealand, given evidence for increasing rates of serious infectious diseases in this county over time.[1]

Methods—We examined infectious diseases related data detailed on the World Health Organization (WHO) website for the two countries for the three most recent years available (2008–2010).[2] This data source was selected as it contains an internationally agreed set of indicators and complete data from both countries.

Results and Discussion—The results indicate more favourable indicators for health service activities to control infectious diseases for Finland (4/6 indicators) vs. one being more favourable for New Zealand (Table 1). In terms of infectious disease burdens, the indicators also tended to favour Finland (8/17) compared to New Zealand (1/17) (Table 1). Furthermore, this comparison using WHO indicators ignores those infectious diseases for which New Zealand has particularly serious problems: skin infections,[3] rheumatic fever,[4] meningococcal disease,[5] and campylobacteriosis.[6]

Many reasons for these differences in infectious diseases burden between Finland and New Zealand are plausible. There is the fact that Finland is wealthier, spends more per capita on health, and has more physicians per capita.[2] Other reasons could relate to better levels of education in Finland (for all indicators[7]), lower levels of socioeconomic inequality (for all versions of the Gini index[8]), and probably better housing quality. Indeed, Finland has "good" housing conditions along with other long-standing northern EU member states.[9] Nevertheless, comparisons with New Zealand on housing are difficult in the absence of systematic data gathering through a regular, comprehensive national housing survey.

As shown in Table 1, the lower levels of immunisation coverage are also likely to be relevant (though this is an area that the New Zealand Government is actively addressing as one of its six health priorities[10]). In addition, to the credit of Finland, the tabulated data do not convey that measles, mumps and rubella have all been regarded as eliminated in this country since the mid-1990s (albeit with occasional imported cases).[11] Some other European countries may have also achieved measles elimination e.g., there were zero cases of measles in a total of eight such countries in 2010.[12] Furthermore, Finland has introduced routine rotavirus vaccination for children[13] (in 2009), while New Zealand has not.

In summary, the control of infectious diseases is clearly a domain where Finland leads New Zealand and where there is scope for New Zealand health sector leaders and politicians across the political spectrum to learn lessons from such countries.

Table 1. Comparison between Finland and New Zealand in infectious disease related health service activity and outcome measures (WHO data for 2010 unless otherwise indicated, bolded data shows the better result from a health perspective, except where this is not statistically significant)*

Indicator used by WHO	Finland	New Zealand
Health service activities (infectious diseases [IDs])		
Measles (MCV) immunization coverage among 1-year-olds (%)	**98**	91
Diphtheria tetanus toxoid and pertussis (DTP3) immunization coverage among 1-year-olds (%)	**99**	93
Hib (Hib3) immunization coverage among 1-year-olds (%)	**98**	89
Polio (Pol3) immunization coverage among 1-year-olds (%) [2009 data]	**99**	93
Case detection rate for all forms of tuberculosis	87 [77 – 99]	90 [79 –100]
Smear-positive tuberculosis treatment-success rate (%) [2009 data]	68	**76**
Population using improved drinking-water sources (%) [2008 data]	100	100
Health outcomes (IDs)		
Distribution of years of life lost by broader causes (%) – Communicable diseases [2008 data]	**3**	5
Age-standardised mortality rate by cause (per 100 000 population) – Communicable [2008 data]	**11**	15
Distribution of causes of death among children aged <5 years (%) – Pneumonia [2008 data]	**2**	5
Distribution of causes of death among children aged <5 years (%) – Diarrhoea [2008 data]	0	0
Distribution of causes of death among children aged <5 years (%) – Measles [2008 data]	0	0
Distribution of causes of death among children aged <5 years (%) – HIV/AIDS [2008 data]	0	0
Incidence of tuberculosis (per 100 000 population per year)	6.70 [5.90 – 7.60]	7.60 [6.60 – 8.70]
Prevalence of tuberculosis (per 100 000 population)	8.5 [1.9 – 15]	9.3 [2.9 – 16]
Deaths due to tuberculosis among HIV-negative people (per 100 000 population)	0.67 [0.62 – 0.72]	**0.17 [0.15 – 0.21]**
Prevalence of HIV among adults aged 15 to 49 (%) [2009 data]	0.1 [0.1 – 0.1]	0.1 [0.1 – 0.1]
Measles - number of reported cases (N)	**5**	43
Rubella (N)	**0**	2
Congenital Rubella Syndrome (N) [2009 data]	0	0
Mumps (N)	**4**	14
Diphtheria (N)	0	0
Pertussis (N)	**336**	462
Reported cases of tuberculosis (N) (DOTS) [2008 data]	**104****	101

* Ignoring tropical infectious diseases e.g., malaria, Japanese encephalitis, yellow fever.

** Better than NZ when considered as a crude annual population rate since Finland has a larger population (5.33 million vs 4.27 million for New Zealand in 2009).

Nick Wilson*, Philippa Howden-Chapman, Michael G Baker
Department of Public Health, University of Otago, Wellington

* Email: nick.wilson@otago.ac.nz

Competing interests: Competing interests: The authors declare no competing interests.

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Crimes Amendment Act (3) 2011

Changes to the Crimes Act 1961 ("the Act") came into effect on 19 March 2012. The changes are intended to protect children and vulnerable adults from assault, neglect and ill-treatment by creating liability for not only those people who are actively involved in the mistreatment, but also those who have frequent contact with the child or vulnerable adult and fail to take reasonable steps to protect them from mistreatment by others in certain circumstances.[1]

The changes should be viewed as a reminder that health providers have a broad responsibility in the face of known risk to children or vulnerable adults.

A newly amended s 151 of the Act holds that:

Everyone who has actual care or charge of a person who is a vulnerable adult and who is unable to provide himself or herself with necessaries is under a legal duty:

(a) to provide that person with necessaries; and

(b) to take reasonable steps to protect that person from injury.

A vulnerable adult is defined as "a person unable, by reason of detention, age, sickness, mental impairment or any other cause to withdraw himself or herself from the care or charge of another person".[2]

Section 151 of the Act is likely to apply to family members, hospital staff, community nursing staff, rest homes and mental health providers, who have actual care or charge of a vulnerable adult. Criminal liability could now attach to improper discharge planning for example, if it led to a vulnerable adult being injured as a result. However criminal responsibility only arises if the omission or neglect is a *major departure* from the standard of care expected of a reasonable person to whom that legal duty applies in those circumstances.[3]

Section 152 of the Act now places a duty on parents or a person in place of a parent "who has actual care or charge of a child" under the age of 18 years to provide necessaries and to take reasonable steps to protect the child from injury. The significant changes are the introduction of a duty to take reasonable steps to protect from injury, the extension of the duty to children under 18 years, and the addition of the words "who has actual care or charge of a child" (which could arguably extend the group of people who could be liable for failing to protect children).

An amended section 195 also extends the offence of cruelty to a child to a new offence of cruelty to a vulnerable adult. This section could apply to a health provider who intentionally engages in conduct or omits to discharge or perform any legal duty that then causes suffering, injury or adverse effects to health or mental disorder, and which is a major departure from expected standards.

There is also a new section 195A, which creates a new offence of failing to protect a child or vulnerable adult who is at risk of death or grievous bodily harm or sexual assault as a consequence of an act or omission of a duty of care by another. This

section requires a person who knows about the risk of violent or sexual offending or gross negligence, to bring the matter to the attention of the police or a person of authority if the person is:

- A member of the same household or a staff member of a hospital, institution or residence where the child or vulnerable adult resides; and
- Has frequent contact with the child or vulnerable adult; and
- Has knowledge of the risk.

Whilst it is unclear how broadly or restrictively this section will be interpreted it could have an impact on health providers who have frequent contact with children or vulnerable adults. They now face potential criminally liability in some circumstances if they fail to take reasonable steps to protect a victim when they know there is risk of death, grievous bodily harm or sexual assault.

What does this all mean in a practical sense?

Health care workers must take steps to protect vulnerable adults where there is knowledge of a risk that the patient is being discharged into a violent or unsafe environment. Applications for personal orders can be made to the Family Court or concerns reported to the Police. Failure to take these steps could potentially impose liability under section 151 or 195. Before disclosing information about a patient to a third party however, it may be appropriate to seek medico-legal advice. In the case of a vulnerable child the appropriate step would be to report concerns to the Child Youth and Family Service

Health providers take steps to protect their patients by informing relevant authorities usually because they feel it is their ethical obligation to do so. The Crimes Act amendments now also clearly make it their legal duty to do so.

Hiranthi Abeygoonesekera
Chief Legal Counsel
Capital & Coast District Health Board

Dr Brendon Gray
Head of Medical Services (New Zealand)
Medical Protection Society

Margaret Barnett-Davidson
Lawyer
New Zealand Nurses Organisation

Footnotes:

1. Crimes Amendment Bill (No 2) 2011 (284-2) (select committee report) at 1.
2. Crimes Act 1961, s 2.
3. Crimes Act 1961, s 150A.

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Chronic arthropathy management in haemophilia: assessing the impact of a new model of care

Healthcare costs are rising and are recognised as being unsustainable at the current rate of expenditure in New Zealand. Cost is a major consideration in the management of haemophilia, a lifelong bleeding disorder, predominantly due to the expensive factor replacement therapy required for patients with severe disease.

The challenge for clinicians managing high-cost chronic conditions such as haemophilia is to show leadership by innovation and a preparedness to do things differently with the aim of achieving the best value for money without compromising quality of care.

With this objective in mind the Auckland DHB Regional Haemophilia Centre introduced a modified multidisciplinary treatment approach for adult patients with severe haemophilia in 2009. It is recognised that more than 85% of all bleeding episodes are within the peripheral musculoskeletal system with the overwhelming majority occurring within knees, ankles and elbows (1). As few as four bleeds into a single joint prior to epiphyseal fusion can mediate an irreversible cycle of joint destruction with long-term haemophilic arthropathy when primary prophylaxis, the current standard of care, is not used (2, 3).

Many of our adult patients were unable to be treated with primary prophylactic factor replacement during their younger years and therefore have significant arthritic joint disease. Most however find it impossible to differentiate between bleeding-associated joint pain and pain secondary to the underlying arthropathy when joint symptoms occur and usually default to managing the symptoms with expensive factor concentrate replacement therapy. This is relatively ineffective if the pain is due to arthritis and therefore inappropriately costly for the healthcare system. The goal of our modified management approach was to optimise the use of factor replacement by ensuring an early correct diagnosis of the precise cause of joint pain and providing the correct intervention.

We selected our highest-user adult patients, including both those receiving ‘secondary’ prophylaxis and ‘on demand’ treatment regimens. All patients had a past medical history of recurrent joint bleeds and significant haemophilic arthropathy involving at least one joint.

Updated studies of the factor peak level and half-life were performed to ensure that each dose (based on body weight) and the weekly dosing regimen resulted in an adequate duration of response. Overweight patients were also educated about weight reduction to potentially reduce both the required dose size and the impact of excess weight on their joints. All patients within the cohort were encouraged to report suspected ‘bleeds’ as soon as they occurred and a rapid assessment pathway introduced enabling immediate or early assessment with the goal being within 24 hours of the symptoms being reported.

Product usage was closely monitored when symptoms were due to an acute bleed but arthritic symptoms were managed aggressively with effective analgesia using the funded Cox-II inhibitor Meloxicam and physiotherapy. A low impact, low resistance exercise-based rehabilitation programme was provided under the supervision of our senior haemophilia physiotherapy practitioner to improve muscle strength, proprioception and biomechanics with a focus on reducing the load on arthritic joints, improving aerobic capacity and emphasising the importance of continued weight control.

An audit of the service was undertaken. The analysis included the 29 highest users of factor VIII/ IX (excluding inhibitor patients) in the wider Auckland region for 2009/10 financial year compared to product orders for the same individuals in the 2010/11 year. In the 2009/10 financial year these 29 patients had total product orders of 5,312,500iu (international units) at a cost of approximately NZ$1 per unit.

In the following 2010/11 financial year these same patients recorded total product orders of 4,295,000iu, a year-on-year reduction of 19%. Over the same period, data collected independently of this audit revealed that orders for the most commonly used FVIII concentrates (used by 80% of patients in the region) had fallen from an average of 400,000iu/ month to 245,000iu/ month, a 39% reduction consistent with the findings from the audited patient group.

A patient satisfaction audit was developed. Twenty two patients were asked to complete the questionnaire and return it by post. A 68% response rate was achieved. Patients either agreed or strongly agreed to each of the nine question fields which assessed their perception of the knowledge of their condition by the clinical team, interdisciplinary communication within the team, direct access to the specialist nurse or physiotherapy care, a timely response to all patient queries and overall usefulness of the service. Crucially all respondents either agreed or strongly agreed that the service had improved over the preceding 12 months, indicating that they did not perceive the changed model of care to be a purely cost-saving exercise.

In summary, this revised treatment approach resulted in a 19% reduction in year-on-year product orders for the audit population corresponding to an indicative saving in excess of one million dollars. The approach was multifaceted but in essence was directed towards early diagnosis of pain not attributable to a joint bleed and reducing the likelihood that factor concentrate is used inappropriately for a prolonged period for an incorrect indication. This meant a change for patients who had become used to relatively independent home therapy management afforded by the more widespread availability and ease of use of high specific activity recombinant factor concentrates.

The patient satisfaction audit during the same period confirmed patient acceptance and a positive perception of the closer supervision of product use. Cost saving was achieved without compromising patient outcome.

Ian d'Young
Physiotherapy Practitioner and National Clinical Lead for Haemophilia Physiotherapy
Auckland District Health Board
iand@adhb.govt.nz

Dr Laura Young
Consultant Haematologist
Department of Haematology, Auckland District Health Board

Mary Brasser
Nurse Specialist
Auckland DHB Haemophilia Centre, Auckland District Health Board

Dr Paul Ockelford
Consultant Haematologist
Department of Haematology, Auckland District Health Board

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Acute yellow atrophy of the liver

Excerpt from article written by G. Bruton Sweet, M.B., and published in NZMJ 1911 May:11(42):141–142.

Acute Yellow Atrophy must be ranked among the rarest of diseases. According to Hunter, it is seldom met with in the largest hospital practice. Out of 25,700 cases admitted during nine years into the London Fever Hospital at a time when a brown tongue and delirium constituted a sure passport to admission, Murchison only met with one case.

Although observed as early as the year 1616, Best in 1903 estimated that the total number of records d cases did not exceed 500 in number. Rare as this disease is in adult life—the great bulk of cases on record are in female adults between the age of 20 and 40 years—it is still more uncommon in children, although no age is exempt. Of 343 cases collected by English and Continental authorities, only 21 were in children under the age of 10. In America some years ago Heyes collected 17 cases, including one of his own, the youngest being only three months old.

The disease in children presents the same symptoms and runs the same course as in adult life. At the onset, it cannot be distinguished from simple catarrhal jaundice. Icterus, nausea or vomiting, general malaise, with some enlargement of the liver and clay-coloured stools present a group of symptoms commonly associated with this mild disorder. After a period of from one to eight weeks from the onset, however, grave signs appear—extreme restlessness, delirium, and widely dilated pupils point to some severe cerebral disturbance ; vomiting becomes persistent, and the vomit often becomes black or coffee ground in appearance.

Examination of the abdomen shows all extraordinary diminution or even entire absence of the usual liver dullness, and a microscopical examination of the urine in a certain percentage of cases reveals crystals of leucin or tyrosin or both. In the great majority of cases the patient rapidly loses ground, becomes comatose, and the disease has a fatal termination; only very few apparently authentic cases having been recorded of ultimate complete recovery.

Recently a case of this disease was observed by me in the Auckland Hospital, and the symptoms during life and the morbid condition of the liver and other organs discovered at the autopsy were typical of acute yellow atrophy.

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Consensus statement from the Health of the Health Professional Conference, November 2011

Susan J Hawken, Peter Huggard, Patrick Alley, Angela Clark, Fiona Moir

Abstract

This article presents a consensus statement that arose from the views of participants that attended the multidisciplinary conference "The Health of the Health Professional", in Auckland in November 2011. A healthy workforce is the key to improving the health of all New Zealanders. Yet health practitioners' health is of concern, and despite the evidence of real problems little has been done to constructively and systematically address these issues. This consensus statement provides some potential ways to move forward.

In this article we briefly cite examples of some issues affecting the health of New Zealand practitioners, before moving on to present a summary of the key messages from the recent multidisciplinary international conference, "The Health of the Health Professional" (HOHP).

Internationally, conferences focusing on the health of the health workforce are driven and informed by concerning statistics regarding the health of health professionals at all levels, from students to experienced clinicians.

Even at the point of student selection, there is evidence indicating that some may well already be at a higher risk of developing mental ill-health compared to their peers.[1] Certain personality traits are a risk factor for mental ill-health, for instance conscientiousness,[2,3] and maladaptive perfectionism.[4] These same traits may also be seen as 'desirable' characteristics for future health professionals. Being a student in one of the health professions, may contribute to ill-health, now or in the future.[5,6]

There are many stressors alongside the workload, which contribute to this picture.[7,8] For instance, financial stress in nursing students has been shown to be a predictor of both mental and physical health problems.[9] Medical students at the University of Auckland report lower depression and anxiety scores and are more satisfied with life compared to students from other disciplines (nursing, health science and architecture).[10]

This is one of the few New Zealand studies which compares the mental health characteristics of medical students to other student groups. However it has also been reported that Asian medical students have lower satisfaction with social relationships compared with their non- Asian peers.[11] In a qualitative study it was found that students felt clinicians would view them 'as weak' if they took time off when unwell.[12]

The health of the health professional may also be affected by their help-seeking behaviour. It is well documented that students and staff perceive a variety of barriers to asking for help,[13] often founded on fears of lack of confidentiality, and further

influenced by habits such as self-prescribing or informal consultations with colleagues and peers.[14,15]

In terms of the medical profession the recent Consensus Statement defining aspirations as to *The Role of the Doctor in New Zealand* highlighted the importance of doctors maintaining their own health as well as being advocates for a health-promoting workplace for all staff: "Doctors accept responsibility to positively influence the culture and environment in which they work…exhibiting behaviours that are nurturing, supportive and respectful and which enable individuals and teams to flourish and enjoy their work…"[16]

The prevalence of health issues in the New Zealand health workforce is of concern. Up to 10% of doctors across disciplines display psychological symptoms[17–19] and there are similar trends reported in nurses and audiologists.[20,21] One overseas study, which followed up doctors regularly in the 10 years following graduation, found that they had a lower life satisfaction than other people the same age.[22]

In New Zealand there is minimal research comparing the health of health professionals with others the same age and of the same socioeconomic bracket in the general population. However one study examining suicide rates reports that nurses and female pharmacists are at higher risk of suicide than other occupational groups including doctors.[23]

Whilst more research needs to be done to document the prevalence of illness in the New Zealand health workforce, it is clear that there is a problem. Issues of stress, burnout, staff retention and low morale persist, upheld by anecdotes and research.[8,24]

A disempowered workforce can languish in a state of learned helplessness which affects staff recruitment and retention.[25,26] There is nothing to be lost and perhaps much to be gained by proactively taking steps towards change. Some of this has started to happen. There has been inter-professional leadership in the form of Health Workforce New Zealand, set up in 2009 to provide co-ordination and development of the health workforce. Although some direction may need to be provided at an institutional/system level, there may be other smaller changes which can be accomplished by an individual.

Change to enable a move towards a more supportive culture has been called for,[24,27] but in an era in which staff may feel undervalued it may be difficult to instigate. However research has shown that even establishing simple habits like eating regularly can make a difference to personal and professional practice.[28]

In summary, the HOHP conference reached the conclusion that the status quo is not acceptable because an unhealthy health practitioner workforce impacts on the effectiveness of the health workforce and on patient outcomes.[29,30] The conference participants made a commitment to focus on some solutions and take action as outlined in Table 1.

Table 1. Recommended solutions and actions to improve the health of the New Zealand health workforce

LEVEL	SOLUTIONS
At all levels	
	Establish one organisational framework or overseeing body for the health of health professional in New Zealand
	Convene an annual multidisciplinary conference
	Start a compassion revolution by joining Hearts in Health Care www.heartsinhealthcare.com
	Adopt a strength-based approach
	Encourage improvement in collaboration and communication
	Advocate for HOHP at a political and professional level
	Advocate for de-stigmatisation and normalising of HOHP
	Address the frequent negative dialogue by reframing issues positively
	Establish programmes for early intervention and prevention
	Assist in career matching - the process of finding a role that makes the most of a person's innate strengths
	Develop a culture of trust between health professionals and society and facilitate reasonable expectations
	Develop a code of health rights or charter for health professionals and students
Individual	
	Encourage self-empowerment and personal responsibility for change
	Role model 'wellness' in the community
	Develop and implement a personal health toolkit: e.g. self-care contract as part of performance appraisal, own general practitioner, undertake supervision or mentoring, participate in Balint groups, retreat weekends and other groups
Organisational	
	Support managers to understand, embrace and act on HOHP
	Develop a constructive cultural approach to managing errors
	Encourage debate about what sort of leadership is needed and then implement effective leadership training programmes
	Develop more support for practitioners at all transition points e.g. new managers, new graduates, new specialties, retirement
	Develop organisational support for practitioner well-being
	Introduce funding for supervision in work time
	Implement healthy workplace practices for all
Educational	
	Support continuing research e.g. neurosciences, qualitative approaches
	Develop and implement HOHP into health practitioner education
	Encourage sharing of curriculum internationally and showcasing what works
	Encourage a culture of support in students

It is important to acknowledge that we need to address these issues at all levels—from the individual through to all levels of health organisations, primary through tertiary, and in educational institutions. By collating the evidence, learning from colleagues, sharing ideas and research, we will initiate a dialogue which reaches across disciplines and countries, and is a call to action.

Competing interests: None declared.

Author information: Susan J Hawken, Senior Lecturer, Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland; Peter Huggard, Director, Goodfellow Unit, Department of General Practice and Primary

Health Care, Faculty of Medical and Health Sciences, University of Auckland; Patrick Alley, Director of Clinical Training, North Shore Hospital, Waitemata District Health Board, Auckland; Angela Clark, Professional Nursing Advisor, NZ Nurses Organisation, Auckland; Fiona Moir, Senior Lecturer, Department of General Practice and Primary Health Care, Faculty of Medical and Health Sciences, University of Auckland

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Correspondence: Dr Susan J Hawken, Senior Lecturer, Department of Psychological Medicine, Faculty of Medical and Health Sciences**,** University of Auckland**,** Private Bag 92019, Auckland 1142, New Zealand. Fax +64 9 373 7013; email s.hawken@auckland.ac.nz

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Should people over 65 be screened for atrial fibrillation?

Atrial fibrillation is a significant risk factor in the aetiology of strokes. It can be effectively treated with drugs such as warfarin, but evidence indicates that up to half of patients who could benefit from treatment are not receiving it. This issue was addressed by UK stroke specialists at a 2-day consensus conference organised by the Royal College of Physicians of Edinburgh.

The conclusion reached by conference members was—"Screening for AF (atrial fibrillation) in people of 65 or older satisfies the UK National Screening Committee criteria for a screening programme and such a national screening programme should be undertaken in the UK." The consensus noted that the most cost-effective screening method would be opportunistic pulse-checking of people over 65 by GPs, followed by electrocardiogram examination for those with an irregular pulse. When such patients were detected, the consensus recommended treatment with warfarin rather than low-dose aspirin which has proved to be ineffective.

BMJ 2012:344:e1644.

Do differences in blood pressure between arms matter?

This paper is based on the premise that different arm blood pressures of 10 mmHg or more may predict widespread vascular disease. The researchers included 20 reports in their meta-analysis. They note that a 15 mmHg or more difference was associated with peripheral vascular disease in 9 cohorts, pre-existing cerebrovascular mortality in 5 cohorts and increased cardiovascular mortality in 4 cohorts. A difference of 10 mmHg or more was associated with peripheral vascular disease in 5 studies.

They advocate blood pressure reading in both arms and further vascular assessment in those with such findings. An editorial writer concurs but points out that ideally the blood pressure readings should be simultaneous as sequential pressure reading doubles the prevalence of difference.

Lancet 2012;379:905–14 and 872–3.

Oral laquinimod for multiple sclerosis

Preclinical studies have shown that laquinimod reduces inflammatory cell infiltrates in the central nervous system, decreases demylination, and prevents axonal loss. This report concerns a randomised double-blind trial conducted in 24 countries, involving 1106 patients with relapsing–remitting multiple sclerosis. They were randomly assigned in a 1:1 ratio to receive oral laquinimod at a dose of 0.6 mg once daily or placebo for 24 months. The primary end-point was the annualised relapse rate during the 24-month period.

Those patients assigned to laquinimod 0.6 mg daily did better than those receiving placebo. They had a modest reduction in relapse rate ($p=0.002$), a reduction in disability progression ($p=0.01$) and less new or enlarging lesions noted on their gadolinium MRI images ($p<0.001$). There were no significant adverse events noted.

N Engl J Med:366:1000–9.

Antihypertensive drugs and risk of gout

Hypertension is a common comorbidity of gout, affecting up to 74% of patients with gout. Some antihypertensives drugs are associated with elevation of serum uric acid and therefore may increase the risk of gout. On the other hand, calcium channel blockers and losartan are known to lower serum uric acid levels and so possibly lower the risk of gout. This nested case–control study from a large UK general practise database investigated this matter. They report the relative risk of incident gout associated with the use of various antihypertensive drugs. The relative risk for diuretics was 2.36, β-blockers 1.48, calcium channel blockers 0.87, ACE inhibitors 1.24, losartan 0.81, and non-losartan angiotensin-2 receptor blockers 1.29.

So calcium channel blockers and losartan might be the best treatment for the hypertensive patient with gout or hyperuricaemia.

BMJ 2012:344:d8190.

Smoking cessation post-discharge following nicotine replacement therapy use during an inpatient admission

This study involved 123 smokers who elected to stop smoking during their hospital admission. All were given supportive management and the choice of 2 nicotine replacement therapies (NRT)—a nicotine patch or an inhaler formulation.

37 elected to use the inhaler, 50 the patch, and 36 no NRT. At 12 months continuous abstinence rates were 38%, 38%, and 25% respectively. All adverse effects were mild and transient and no subjects withdrew from their treatment as a result of toxicity. The cessation rates achieved were similar to those reported in the community setting.

The researchers recommend that such cessation policies should be used in hospitals generally. The predominant cost would be the employment of a dedicated professional.

Internal Medicine Journal 2012;42:154–9.

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Roy Frederick Hough

BSc 1942, MBChB 1951, FRCPA 1966 (21 October 1920 – 24 November 2011)

Roy Hough was born in Christchurch and attended Christchurch Boys High School. On leaving school he worked in the Meteorological Service and then studied Science at Victoria University, majoring in Physics, and graduating BSc in 1942. He served in the Navy in Radar during the war.

After his wartime service he studied medicine at Otago University Medical School, in the same year as George Hitchcock, and graduated MBChB in 1951.

He worked as a House Surgeon and Pathology Registrar at Christchurch Hospital and was then appointed as a Junior Specialist in Anatomical Pathology.

He was admitted to Membership of the Royal College of Pathologists of Australia (as it then was) in 1966. A few years later that was changed to Fellowship and later again to Australasia.

In 1963, Roy was seconded to Princess Margaret Hospital and subsequently was appointed there as Pathologist in charge, doing the anatomic pathology and running the cytology service, as well as overseeing the other pathology departments

In 1972 he was appointed to Green Lane Hospital which was a General Hospital with major Cardiothoracic and ENT surgical units. He took sabbatical leave to study in Chicago, San Diego and the Walter Reed Hospital Washington. He continued to work at Green Lane Hospital until his retirement in 1985. The following two years he worked in a private laboratory in Singapore, followed by several shorter locums in Dunedin and Townsville.

Roy was a quiet, conscientious, methodical, thoroughly competent and meticulous pathologist, much appreciated by the surgeons with whom he worked. He was steady and reliable in his diagnoses, was very supportive to registrars and taught a good practical approach to histopathology and a few useful histopathology “tricks”.

Roy was very pleasant to work with, well disposed to all and liked by all including medical colleagues, scientific laboratory staff and registrars. Never impatient with interruptions, Roy was always gentle, helpful and patient. He had a “low key” approach, was helpful without being “pushy”, was not given to excesses of any kind, and was not known ever to raise his voice in anger.

Within the department he had a calming influence, always taking a cautious approach when others tended to be more vocal or impetuous. His wry sense of humour was evident to those with whom he worked and there was often a twinkle in his eye when he was correcting some junior pathology registrar. He didn't waste time in small talk but had a very good general knowledge.

In his spare time, Roy was a keen sailor. In 1977 he was due long service leave and took delivery of a 9.2 metre yacht hull and decks, and finished off the boat including plumbing, wiring and interior teak woodwork making a wonderful job of it. The family spent many happy times sailing in it on weekends and holidays. His other outdoor pursuits included tramping and skiing. He enjoyed gardening, reading and travel.

Roy was a member of the New Zealand Medical Association for 50 years, and was also a member of Probus, Forest and Bird Society, and U3A.

In 1958 he married Jenny Maitland and is survived by her and their three children: David, a radiologist at the Mayo Clinic; Nicola a qualified Food Technologist in Auckland; and Nigel, who is a vet in the UK.

Roy died on 24 November 2011 after a long illness. He will be remembered as one of our profession's true gentlemen.

Mary Miller, retired histopathologist (Algies Bay), wrote this obituary, in conjunction with other colleagues of Roy.

THE NEW ZEALAND MEDICAL JOURNAL
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Heart Foundation: 2012 Douglas Senior Fellowship in Heart Health (Prevention)

THE AWARD

Heart Foundation Senior Fellowships have been awarded since 1983 to support New Zealand graduates who have trained as cardiologists or scientists working in the field of cardiovascular research. This Senior Fellowship will be awarded in the area of preventive heart health research to work in association with the newly established Chair in Heart Health, in the University of Auckland. The Fellowship is tenable for 3 years.

CONDITIONS

Candidates must possess an appropriate postgraduate degree or diploma and may undertake work for a higher degree such as a PhD or MD. The Fellowship must be taken up within 12 months of the award. Other conditions applying to the Senior Fellowship and other Heart Foundation awards are outlined in the publication, “A Guide to Applicants for Research and Other Grants”.

SALARY AND ALLOWANCES

The initial salary level will be determined by the Scientific Advisory Group in conjunction with the Host Institution according to the qualifications and seniority of the Fellow and will normally maintain parity with appropriate rates paid by Universities and the Health Research Council.

The Foundation may provide an initial Grant-in-Aid of up to $1,500 to enable research work to commence. In subsequent years, Senior Fellows may apply for working expenses not exceeding $1,000 annually with no single item to exceed $500.

Further research funding will require an application for project grant funds from the Foundation. Funding for conference expenses must be applied for separately.

FORMAT FOR APPLICATIONS

Applicants should follow the format outlined in the revised “A Guide to Applicants for Research and Other Grants" which is available on http://www.heartfoundation.org.nz

Applications should be sent to:

Professor Norman Sharpe
Medical Director
The National Heart Foundation
P O Box 17160
Greenlane 1546
AUCKLAND

Closing date for the Senior Fellowship award is **1 June 2012**

THE NEW ZEALAND MEDICAL JOURNAL
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Clinical Cardiology Fellowship in Inherited Heart Disease

An opportunity for trainees in either cardiology or paediatric cardiology to specialise in all aspects of inherited heart disease investigation and management. Based in Auckland City, Starship and Greenlane hospitals, there will be clinical supervision from adult and paediatric cardiology as well as clinical and molecular genetics. Specific exposure will be given to cardiac genetic clinics and the investigation of sudden unexpected death in the young. Research in this area will be actively encouraged and supported with appropriate time allocation for this. Continued exposure and training in other relevant cardiology areas will be arranged according to the trainee's preference (eg arrhythmia, imaging).

Senior clinical supervisor will be Associate Professor Jonathan Skinner. Secondary supervisor will depend on desired subspecialty area in cardiology or paediatric cardiology.

This Fellowship will be tenable for 2 years.

An application form for a Fellowship is available on our website www.heartfoundation.org.nz or from

Helen Stewart
Heart Foundation
PO Box 17160
Greenlane
AUCKLAND 1546

Ph: (09) 571 9191
Fax: (09) 571 9190
Email: HelenS@heartfoundation.org.nz

Applications close **1 June 2012**

THE NEW ZEALAND MEDICAL JOURNAL
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Heart Foundation: 2012 Grant Applications

PROJECT GRANTS

Project Grant applications will be considered at the July 2012 meeting of the Scientific Advisory Group. The closing date is: 1 March 2012.

FELLOWSHIPS AND SCHOLARSHIPS

Applications for Overseas Training and Research Fellowships, Research Fellowships and Postgraduate Scholarships will also be considered in July 2012. The closing date is: 1 June 2012.

Two further Fellowships are available for 2012. These are:

- The Douglas Senior Fellowship in Heart Health (Prevention)

  Applications for the Douglas Senior Fellowship will be considered at the July 2012 meeting. The closing date is: 1 June 2012.

  (Refer to separate advertisement)

- A Clinical Cardiology Training Fellowship in Inherited Heart Disease

  Applications for this Fellowship will be considered at the July 2012 meeting. The closing date is: 1 June 2012.

  (Refer to separate advertisement)

LIMITED BUDGET GRANTS

Small Project Grants

Applications for small project grants will be considered at the July and November meetings with the closing dates being: 1 June and 1 October 2012.

Grants-In-Aid

Applications for grants-in-aid will be considered at the July and November meetings with the closing dates being: 1 June and 1 October 2012.

Travel Grants

Applications for travel grants will be considered at the July and November meetings with the closing dates being: 1 June and 1 October 2012.

The scoring criteria for Travel Grants is available on the Heart Foundation website under Research/2011 Grant Advertisement. **NB Retrospective funding of travel will not be considered. Note the granting dates.***

***SCIENTIFIC GRANTING DATES**

- Thursday 26 July
- Tuesday 1 November

PRIORITIES FOR RESEARCH

Applications are particularly encouraged in areas that align with National Heart Foundation strategic priority objectives.

CRITERIA FOR ASSESSING RESEARCH PROPOSALS

Each research proposal will be assessed on:

- Importance to the Heart Foundation
- Scientific merit
- Design and methods
- Project achievability, expertise & track record of research team.

CV TEMPLATE

Applicants are encouraged to use the CV template available on the Grant Advertisement on the Heart Foundation website

FORMAT FOR APPLICATIONS

Applicants should follow the format outlined in the revised “A Guide to Applicants for Research and Other Grants" which is available on http://www.heartfoundation.org.nz

Applications should be sent to:

Professor Norman Sharpe
Medical Director
The National Heart Foundation
PO Box 17160
Greenlane
AUCKLAND 1546

NB: When the closing date falls on a weekend or a public holiday, the closing date will be the first working day following this day.