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

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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

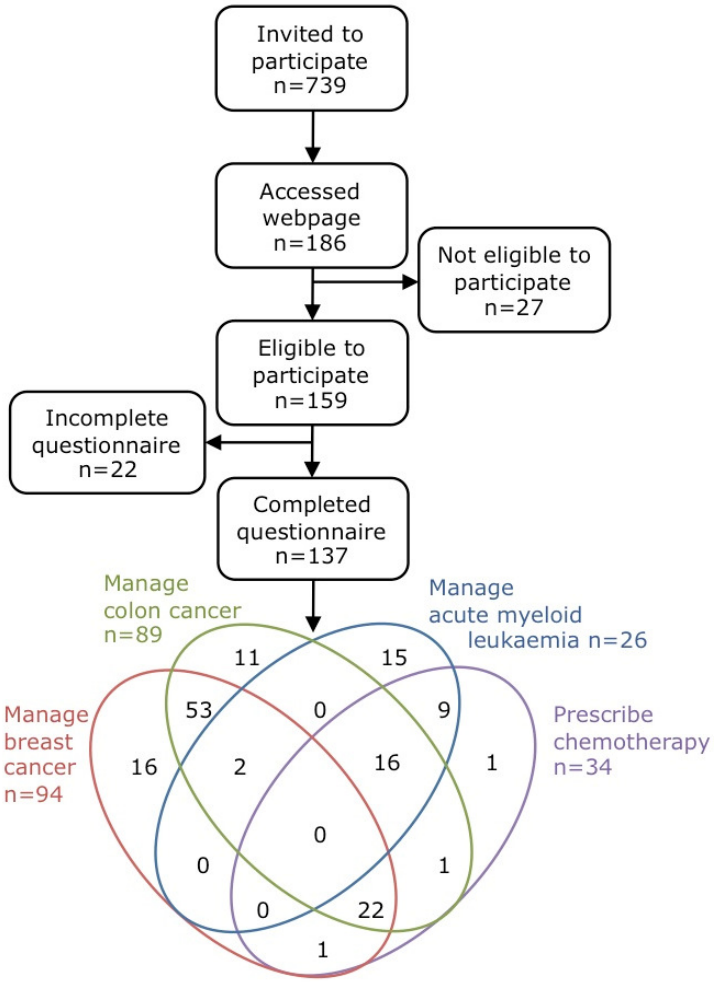

Table 2. Seniority and specialty of survey participants

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.

Competing interests: None.

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