Time for healthy investment

The state of quality improvement and patient safety teaching in health professional education in New Zealand

The outcomes of patients returned to general practitioner after being declined hip and knee replacement

Health data research in New Zealand: updating the ethical governance framework

Waikato District Health Board: a trustworthy custodian of New Zealand's future doctors?
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The state of quality improvement and patient safety teaching in health professional education in New Zealand
Gillian Robb, Susan Wells, Iwona Stolarek, Gillian Bohm

This study investigated the teaching of healthcare quality and safety in all institutions providing training for medicine, nursing, midwifery, dentistry, pharmacy, physiotherapy, dietetics and 11 other allied health professions in New Zealand. Interviews were undertaken with 43 people who led the teaching programmes. Evidence-based practice, patient-centred care and teamwork and communication were well embedded in programmes, while leadership, systems thinking and the role of IT were less explicitly included. Patient safety teaching was focused mainly around incident reporting, and to a lesser extent learning from adverse events. Except for two institutions, specific application of improvement science was absent from pre-registration curricula. Improvement science is relatively new for healthcare, but as an applied science, it offers a robust approach to addressing real life problems in real life situations. Healthcare training needs to address the identified gaps so that new graduates will be able to improve the quality and safety of healthcare.

The outcomes of patients returned to general practitioner after being declined hip and knee replacement
Toni Anitelea, Ella Iosua, Ayaaz Ebramjee, David Gwynne-Jones

Three hundred and seventy-four (31%) of patients listed for total hip or knee replacement in Dunedin were returned to their GP over the two-year period 2013–15 due to lack of capacity to meet the four-month target for surgery. At a minimum follow-up of 12 months, 122 (33%) remain in the community without further contact. One hundred and ninety-four (52%) had qualified for public surgery and 22 (6%) had gone privately. Thirty-six (10%) had been referred and failed to qualify a second time. The average wait for surgery was 14.6 months from their initial clinic appointment. The delay results in waste, added costs to the patient, healthcare system and society, and may reduce the benefit of surgery.

Deceased donor kidney transplantation in New Zealand: use and audit of a survival prediction tool
Frances Dowen, Nicholas Cross, Philip Clayton, Helen Pilmore

In New Zealand, those with renal failure who require kidney transplantation are assessed using a system that predicts five-year survival. In order to join the waiting list for a kidney transplant from a deceased donor, guidelines state that patients should have a greater than 80% chance of surviving five years. This paper shows that those listed in New Zealand have an average of 89.4% chance of surviving five years and that the system used to calculate this is used universally and accurately throughout the country.

Gene expression profiling of breast tumours from New Zealand patients
Anita Muthukaruppan, Annette Lasham, Cherie Blenkiron, Kathryn J Woad, Michael A Black, Nicholas Knowlton, Nicole McCarthy, Michael P Findlay, Cristin G Print, Andrew N Shelling

Genomic profiles, which are reflective of tumour biology, showed no clear difference between breast tumours from New Zealand patients and those from an international breast cancer cohort. This suggests that other factors may contribute to the high and increasing breast cancer incidence in New Zealand compared to international populations. Our findings also suggest that as breast tumours from New Zealand women exhibit similar features to international cohorts, and were found to share multiple clinical associations, genomic tests should have the same relevance to clinical practice in New Zealand as they do overseas.
Is cardiomegaly on chest radiograph representative of true cardiomegaly: a cross-sectional observational study comparing cardiac size on chest radiograph to that on echocardiography

Jane McKee, Katherine Ferrier

A chest x-ray (CXR) is a common tool used in medicine. When a chest x-ray is interpreted, comment is often made of the heart size, the term ‘cardiomegaly’ being used to indicate the person has an enlarged heart. This study looked at the heart size on CXR in patients who had suffered a heart attack compared to echocardiography, which is often considered to be the “gold standard” in measuring a person’s heart. The study showed that cardiomegaly on CXR was indicative of true cardiomegaly only 56% of the time, thereby concluding that, in our sample population, a diagnosis of ‘cardiomegaly’ cannot be made purely based on CXR findings.

Health data research in New Zealand: updating the ethical governance framework

Angela Ballantyne, Rochelle Style

Demand for health data for secondary research is increasing, both in New Zealand and worldwide. To support the ethical governance of patients’ data, we argue in favour of the establishment of: (1) a specialist Health and Disability Ethics Committee (HDEC) to review applications for secondary-use data research; (2) a public registry of approved secondary-use research projects (similar to a clinical trials registry); and (3) detailed guidelines for the review and approval of secondary-use data research. We present an ethical framework based on the values of public interest, trust and transparency to justify these innovations.
As the term of the new coalition government begins, the New Zealand Medical Association (NZMA) urges all parties to invest in the health of New Zealanders.

Last month’s release of the NZMA’s ‘Health as an Investment’ position statement1 makes this simple point: spending on health is a positive investment in the health, well-being and productivity of New Zealanders and our economy. Ultimately, health money saves money in many sectors.

Many health professionals are baffled by the frequent casting of public healthcare as a “cost” to government. This framing has to change. Health spending does not drain the economy. Instead, better health lifts the lives of individuals and their families/whānau, and grows our economy.

The NZMA statement describes the many benefits of health spending—both direct financial and indirect, where:

• Better health is associated with increased labour supply and productivity.2
• Despite known measurement issues,3 health has been shown comprehensively to be a major contributor to economic growth.3,4
• Analysis of recent spending by government sectors in multiple countries in the European Union strongly suggests considerable economic gains from government spending on health and education—with (in the short term at least) a return on investment near $5 for each $1 of government spending on health.5

Our health system requires high levels of resources to meet the needs of individuals, family/whānau and the population. The NZMA statement also strongly supports an investment approach to health, as articulated in the New Zealand Health Strategy.6 This approach takes the long view, which accounts for full long-term costs,7,8 including life cycles; we have all been young, and we will all die.

Beyond the NZMA statement, and beyond looking for potential efficiency gains,9 we need evidence-informed10,11 discourse and funding choices within, and across, sectors.12–14 How we value long-time horizons, and take a consistent approach across government sectors, matters. So for starters, if balancing upfront costs with enduring benefits, the discounting of non-budgetary costs and benefits for time15 when using cost-effectiveness analyses should be at a social discount rate with a long-term rate of return that is riskless (ie, risk-free),16–21 not risk-adjusted.22 In short, using a lower discount rate than was used and promoted years ago. (Meanwhile, evidence-informed public policy has to balance robust evidence with social values,10 where value from other complexities6,23 (eg, clinical severity24) is not necessarily captured, measured or condensed in simple benefit-to-cost ratios.9,21)
Similarly, consistency across government sectors means treating like with like. How we value the gains from treatment or programmes or big projects can lead into how much we are prepared to spend. Thus, the same valuations of lives should apply to the health sector as to other government sectors, when helping determine funding. The NZMA calculates, for example, that the imputed values of lives saved for major strategic roading decisions in New Zealand have been 15 to 19 times that of some health investments historically (see supplementary information).

Back to the NZMA statement, addressing the social determinants of health such as education, housing and poverty is crucial. Inequity in health is fiscal failure as well as moral failure, because health equity improves economic performance. It makes sense to invest in health by investing to improve health equity. Acting decisively to reduce health inequities benefits both our economy and wider society.

We don’t, and won’t, necessarily get best health outcomes by investing in the latest (sometimes very expensive) health technologies or programmes. Instead, an evidence-informed approach is likely to get better outcomes from both continuing with public health actions that have good value—and from improving access to, and uptake of, much currently-funded universal healthcare of value, so that everyone who needs care can and does get it. These outcomes are more likely when we better understand and address fundamental inequities in underlying social determinants.

Finally, investing in health equity helps the health system. The increasing costs of healthcare are partly driven by increasing treatment costs for conditions largely preventable by focusing on the social determinants of health—the conditions in which people are born, grow, live, work and age, their education, employment, access to healthcare, food security, housing, income, leisure, in homes, communities, towns, or cities—and their chances of leading a flourishing life. Addressing the social determinants of health not only achieves better health equity, but is crucial to the financial sustainability of the health system.

Most of the social determinants of health lie outside the health sector, so this requires inter-sectoral and whole-of-government approaches. Action on the social determinants of health must be a major focus for both the health sector, wider government and society.

In short, investing in New Zealanders’ health grows our economy—and fundamentally, isn’t better health and wellbeing the purpose of any economy?

Note: The NZMA published last month its position statement on Health as an Investment. The statement has been endorsed by the Association of Salaried Medical Specialists (ASMS) and the New Zealand College of Public Health Medicine (NZCPHM). The NZMA is grateful for their support.

Competing interests:
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REFERENCES:
18. Metcalfe S, Brougham M, Moodie P, Grocott R. PHARMAC responds to Richard Milne on discount-


Rationing access to deceased donor kidney transplantation: New Zealand charts her own course

Stephen Munn

Until a little over 60 years ago, kidney failure was a death sentence. Dialysis and transplantation have changed that sequitur irrevocably, but not without the creation of additional dilemmas. Dialysis is an effective means of prolonging life in such patients but it is not cheap. Access to dialysis varies enormously around the globe and even in highly developed countries there is controversy about thresholds for access based on resource utilisation and cost utility. But at least these discussions about dialysis can be had in health economic terms. The controversies that surround access to kidney transplantation and the allocation of deceased donor kidneys to those deemed eligible are further complicated by the fact that money is not the currency that is limited. Rather there is an extreme imbalance between the number of kidneys available and the number of potential recipients that might benefit. And, because almost any patient with kidney failure that could make it through an operation would obtain a greater number of quality-adjusted life years from a transplant when compared with dialysis, there is an underlying expectation that, from an equity perspective, all patients meeting such minimal criteria ought to be placed on the waiting list for a deceased donor kidney if they so desire.

Such a ‘right’ to access the waiting list has created scenarios, especially in the US, whereby patients with limited life expectancy even up to the age of 90 have been transplanted often with kidneys from donors that are far younger. Indeed, in the US, access to the waiting list is so easy that there are more than 100,000 patients on it with a further 36,000 added each year and only 26,000 coming off (17,000 transplanted and 9,000 having died or been delisted because of deterioration each year). The simple truth is that many listed patients will never receive a transplant and not all transplanted patients, especially those over the age of 65, will live long enough to optimise the utility of the transplanted organ. There has been much work done in the US on the distributive side of the deceased donor kidney transplant algorithm, and this may well improve the utility of donated kidneys but it does nothing for the fundamental discrepancy between supply and demand.

Transplantation is perhaps one of a number of the exceptions to John Maynard Keynes’ demand-side economics. The continuing increase in the demand for deceased donor kidneys is unlikely to ever be met (outside of success with xenotransplants from a plentiful source) and one potential means of solving the problem is, as unpalatable as it might be, to reduce demand. Professor Donald Berwick, Past-President Obama’s nominee to be Administrator of the Centers for Medicaid and Medicare and nicknamed “Obama’s Rationing Man” by the Republicans once said: “The decision is not whether or not we will ration care. The decision will be whether we ration care with our eyes open”. Here in New Zealand there has been an effort to bring patient eligibility criteria into clear focus so they are visible to all. This has not been without controversy but, as the authors of the article entitled “Deceased donor kidney transplantation in New Zealand: use and audit of a
survival prediction tool” point out in this edition of the Journal; it has been implemented in a pragmatic, reproducible and accurate manner. The goal was to achieve the 80% five-year post-transplant survival stipulated by the Transplantation Society of Australia and New Zealand7 and it is heartening to know that both predicted and actual post-transplant survivals exceed this threshold in those that are listed and transplanted8. What is less clear is why the average scores of those that are declined listing (79.8%) are so high, with more than half of these having scores above the 80% threshold. We are simply told that such patients “had a significant comorbidity precluding transplantation”. These comorbidities thereby trump the predicted survival score, making the latter necessary but not sufficient to obtain a coveted place on the list. It might be useful for the authors, as representatives of the kidney transplant professional community, to make plain the kinds of pre-existing conditions, outside of those encompassed by the scoring tool, that make for either poor patient outcomes or poor utility of transplanted kidneys.

The application of the survival prediction tool to the deceased donor kidney transplant waiting list in New Zealand is a world first. Once again, like Hilary, Rutherford, Munroe, Hamilton and, more recently, Emirates Team New Zealand before them, the pragmatic New Zealand transplant community has seen fit to chart its own course rather than follow international dictums or trends. Such a reasoned approach to waiting list access is at once both fair and practical even though it is clearly rationing. Hearty congratulations are in order!


Competing interests: Nil.

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REFERENCES:
The state of quality improvement and patient safety teaching in health professional education in New Zealand
Gillian Robb, Susan Wells, Iwona Stolarek, Gillian Bohm

ABSTRACT

AIM: To investigate how quality and patient safety domains are being taught in the pre-registration curricula of health profession education programmes in New Zealand.

METHODS: All tertiary institutions providing training for medicine, nursing, midwifery, dentistry, pharmacy, physiotherapy, dietetics and 11 other allied health professions in New Zealand were contacted and a person with relevant curriculum knowledge was invited to participate.

Interviews were conducted using a semi-structured interview guide to explore nine quality and safety domains; improvement science, patient safety, quality and safety culture, evidence-based practice, patient-centred care, teamwork and communication, leadership for change, systems thinking and use of information technology (IT). Transcribed data were extracted and categorised by discipline and domain. Two researchers independently identified and categorised themes within each domain, using a general inductive approach.

RESULTS: Forty-nine institutions were contacted and 43 (88%) people were interviewed. The inclusion and extent of quality and safety teaching was variable. Evidence-based practice, patient-centred care and teamwork and communication were the strongest domains and well embedded in programmes, while leadership, systems thinking and the role of IT were less explicitly included. Except for two institutions, improvement science was absent from pre-registration curricula. Patient safety teaching was focused mainly around incident reporting, and to a lesser extent learning from adverse events. Although a ‘no blame’ culture was articulated as important, the theme of individual accountability was still apparent. While participants agreed that all domains were important, the main barriers to incorporating improvement science and patient safety concepts into existing programmes included an ‘already stretched curriculum’ and having faculty with limited expertise in these areas.

CONCLUSIONS: Although the building blocks for improving the quality and safety of healthcare are present, this national study of multiple health professional pre-registration education programmes has identified teaching gaps in patient safety and improvement science methods and tools. Failure to address these gaps will compromise the ability of new graduates to successfully implement and sustain improvements.

There is now a general consensus that widespread system change for improving the quality and safety of healthcare will not be a reality unless health professionals make improvement ‘an intrinsic part of everyone’s job, every day, in all parts of the system’.1

This idea was founded by reports from the Institute of Medicine (IOM), which highlighted the poor quality of healthcare,2 called for a radical redesign of the healthcare system3 and led to the third IOM report, Health Professions Education: A Bridge to Quality.4 The latter developed strategies for restructuring teaching and learning activities, and identified five high-level core competencies essential for improving the quality and safety of healthcare that applied across all health professions: provide
patient-centred care, work in interdisciplinary teams, employ evidence-based practice, apply improvement science and utilise information technology (IT). These were then adapted for nursing, who added a sixth core competency, ‘patient safety’. The World Health Organization subsequently developed comprehensive curriculum guides in patient safety both for medicine and multi-professional groups.

Improvement science has its roots in industrial quality improvement methods, but is relatively new for healthcare. As an applied science, improvement science offers a robust and pragmatic approach to addressing real life problems, in real life situations and in real time, utilising simple frameworks for change that are underpinned by a strong focus on measurement, sampling, qualitative and quantitative data collection and iterative tests of change using Plan-Do-Study-Act (PDSA) cycles. It has been advocated that mastery of the theory and methods of improvement science should be regarded as a core competency for all health professionals if we are to effect the necessary system changes. Its value as a way of keeping pace with change has also been recognised in both engineering and education.

Building healthcare workforce capability in improvement science is a challenge. The field is broad and is subject to multiple interpretations and approaches. Many practitioners lack the confidence and capability to effectively engage in change in their workplace. Rather than intrinsic to everyday work, this has resulted in pockets of improvement, poor sustainability and beliefs that improving quality is a ‘project’ (and someone else’s responsibility) or that it is simply techniques such as PDSA cycles.

A considerable amount of work has been undertaken internationally to develop and implement frameworks to build capability in quality improvement science and patient safety across the healthcare sector. In New Zealand, the Health Quality & Safety Commission (the Commission) has identified building sector capability in quality and patient safety as one of its strategic priorities. As part of this mandate, the Commission has developed a framework for quality and safety capability for the New Zealand healthcare workforce. This framework provides a common understanding of what healthcare workers and consumers are expected to ‘know and do’ with respect to quality and safety domains across all levels of the health system. These expectations apply also to new graduates, implying the required knowledge and skills should be addressed as part of the pre-registration education and training. There are concerns that pre-registration education for the health professions has not kept pace, and that institutes of higher learning have been slow to adapt and prepare students to become critical thinkers, problem solvers and lifelong learners.

Whether New Zealand tertiary institutions providing health professional education are teaching quality and safety knowledge and skills is unknown. The aim of this study was to identify how quality improvement and patient safety domains are being taught in the pre-registration curricula of health professional training.

Methods

Sampling frame

We identified all tertiary education institutions (university and technical institutes) in New Zealand that provided health professional education in 18 disciplines (Table 1).

Table 1: Included health professional disciplines.

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<th>Tertiary education institutions</th>
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<td>Medical radiation technology</td>
<td>Podiatry</td>
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<td>Medicine</td>
<td>Speech language</td>
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Study instrument

A semi-structured interview guide was developed to solicit participant information.
Interview questions were constructed to explore nine domains (Table 2), which were identified and adapted from the Institute of Medicine core competencies,\(^4\) the Quality & Safety Education for Nurses framework\(^5\) and the recently developed New Zealand Health Quality and Safety Commission's Knowledge to Action Framework.\(^15\)

**Study participants**

Each eligible institution was contacted and invited to identify the appropriate course coordinator/s or curriculum leader/s who would be willing to participate in this study. After receiving consent, a time for an interview was scheduled and participants were sent information describing the Commission’s interest in this area, outlining the purpose of the study and describing the quality and safety domains of interest.

The semi-structured interview schedule was piloted with two sites. The first site was used to check the logic and clarity of the questions. The second site was used to pilot test the questions. Minor changes were made based on the feedback. Information from the pilot test site was included as part of the analysis. To maintain consistency, at the time of the interview, participants were given a brief description of each domain according to the definitions (Table 2), and then asked to what extent each domain was included in the curriculum, how it was included and at what stage of the programme.

Their views were also sought about their perceived importance of including quality and safety knowledge and skills in their pre-registration programme, and what the associated barriers and challenges were. One researcher (GR) conducted the interviews, which were digitally recorded and then transcribed. Interviewee consent was given verbally and each was informed about the confidentiality of their responses.

**Research team**

At the time of the study, three of the four members of the research team were employees of the Commission (GR, GB, IS) and one (SW) was contracted to the Commission for a one-year period. Two (GR, SW) also held teaching and research positions within the University of Auckland and were involved in teaching quality improvement in the undergraduate medical programme as well as within the Masters in Health Leadership program. Three of the four members of the research team (GB, IS and GR) had been involved in the development of the Commission’s Knowledge to Action Framework. The researchers had no formal relationships with participants prior to the study being undertaken. The Commission’s interest in the study was identified in the background information sent out to participants before the interview, and the interviewer’s role was made clear to participants at the time of the interview.

**Table 2: Quality and safety domains.**

<table>
<thead>
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<th>Domain</th>
<th>Description</th>
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<tr>
<td>1. Improvement science</td>
<td>Use improvement science methods and tools to analyse and define gaps in the quality of care, monitor the quality and reliability processes and outcomes of care, and design, test and implement changes to continuously improve the safety and quality of care.</td>
</tr>
<tr>
<td>2. Patient safety</td>
<td>Use a human factors and systems-based approach to understand and respond to adverse events and inform the design of safer and more reliable safety systems.</td>
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<tr>
<td>3. Quality and safety culture</td>
<td>A culture where reporting and learning are the norm in the context of mutual respect and transparency.</td>
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<td>4. Evidence-based practice</td>
<td>Able to locate and critically appraise evidence to identify bias and determine validity. Integrate best research with clinical expertise and patient preferences and values to achieve optimal outcomes for patients.</td>
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<tr>
<td>5. Patient-centred care</td>
<td>Empowering patients/consumers and their families/whānau to interact with healthcare providers to achieve outcomes consistent with their preferences, needs and values.</td>
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<tr>
<td>6. Teamwork and communication</td>
<td>Collaborating effectively with others across professional, organisational and cultural boundaries to achieve shared quality and safety goals and ensure care is continuous and reliable.</td>
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<td>7. Leadership for change</td>
<td>Doing what is right and setting examples for others.</td>
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<td>8. Systems thinking</td>
<td>Appreciating healthcare as a complex and dynamic adaptive collection of interrelated and interdependent components with a common purpose or aim.</td>
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<tr>
<td>9. Using information technology (IT)</td>
<td>Using information technology to manage knowledge, mitigate error and support decision-making.</td>
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Analysis

Given the assurance that anonymity would be preserved, it was established a priori that data would be aggregated by domain across all disciplines. For each interview, data were extracted and categorised by discipline and domain question using an excel spreadsheet. Responses were then collated by domain. For each domain, two researchers (GR and SW) independently interpreted the data and identified themes using a general inductive approach as well as selecting and categorising quotes. Discrepancies were discussed and further reflections drawn from the remaining research team members to reach a consensus. Although the interviews were semi-structured and responses variable, attempts were made to determine the frequency of responses where possible. Potentially identifying information was masked to protect the participants and their institutions. No attempt was made to specifically compare responses between professions.

Participants were not asked to provide feedback on the transcribed interviews.

Ethics approval

A Health and Disability Ethics Committee ethics approval was sought but not required for this study.

Results

Forty-nine tertiary education institutions were contacted and 43 people (88%) representing the 18 eligible disciplines agreed to participate (Table 3). Two declined and three did not respond to our invitations after at least three attempts. Most disciplines have one or two teaching institutions in New Zealand, whereas 15 providers (mainly technical institutes) provided undergraduate nursing tuition. Two interviewees stated that their institution provided discipline-specific education and training for a second institution.

Interviews were conducted by phone (36/43; 84%) and face to face (7/43; 16%).

Table 3: Responses by discipline and type of institution.

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<tr>
<td>Dietetics</td>
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<td>Medical imaging</td>
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<td>Medical laboratory science</td>
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<td>Medical radiation technology</td>
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<td>Medicine</td>
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<tr>
<td>Midwifery</td>
<td>4</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Nursing</td>
<td>14</td>
<td>3</td>
<td>12</td>
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<tr>
<td>Occupational therapy</td>
<td>2</td>
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<tr>
<td>Optometry and optical dispensing</td>
<td>1</td>
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<td>Osteopathy</td>
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<td>Pharmacy</td>
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<td>Physiotherapy</td>
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<td>Podiatry</td>
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<td>1</td>
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<tr>
<td>Speech language</td>
<td>2</td>
<td>2</td>
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</tbody>
</table>
They were recorded and field notes taken. The length of interview ranged from 25 minutes to 50 minutes and only the participants and the interviewer were present at the time of the interview. In some cases, more than one person from the educational institution participated in the interview. Data saturation was achieved by approaching all institutions and the high response rate.

Of the 43 that were interviewed, the majority were either programme or academic leaders or heads of school (Table 4).

**Table 4:** Institutional roles of interviewees.

<table>
<thead>
<tr>
<th>Position</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head of School, Head of Discipline</td>
<td>12 (28%)</td>
</tr>
<tr>
<td>Dean/Associate Dean/Deputy Dean</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Program Lead; Course Director; Clinical Director; Team Manager</td>
<td>21 (49%)</td>
</tr>
<tr>
<td>Senior teaching role</td>
<td>6 (14%)</td>
</tr>
</tbody>
</table>

Coverage in teaching curricula are summarised below by the nine domains (Table 2), followed by participant perspectives and challenges of including quality and safety into pre-registration curricula.

**Improvement science**

In pre-registration health professional education there was a major gap in curricula relating to the inclusion of the core concepts of improvement science. With the exception of two institutions, specific teaching of quality improvement science methods, tools and skills was absent, such as using a framework for improvement, sampling and measurement strategies, diagnostic tools and methods to understand the full extent of the problem or the uses of tools such as run or control charts to describe system performance over time and evaluate success and sustainability of improvements.

The concept of testing change ideas using iterative PDSA cycles was only mentioned by two educators from separate disciplines.

Most participants understood the concept of improving quality, but had limited knowledge of the specific application of improvement science. It was interpreted as being addressed through the concepts of evidence-based practice, audit and quality assurance systems.

“one of the things we do—we have clinical practice tutorials and we talk about best practice requirements.”

“often included in an audit—eg, documentation around vital signs/falls risk assessment—the student in the ward reviews six charts—amazing learning from this.”

Improving the quality of care was recognised as important and students had opportunities to address perceived deficiencies in the quality of care as part of their learning. This was, however, carried out more in a research context, with the focus on identifying evidence or policy practice gaps, and then identifying solutions.

“a group went into a dementia care unit and recognised there was no suitable outdoor area for them—so did some focus groups and a literature review and went back with a proposal and how they could go about doing it.”

A systematic approach to identifying and analysing problems, testing change ideas and using data to monitor change over time was not evident.

**Patient safety**

While patient safety was an important priority for most professional groups, approaches to teaching and learning about safety were mixed.

There was one example of a two-day inter-professional experiential workshop on patient safety at one university. This was underpinned by a systems approach that addressed concepts of human error and human factors and involved students working in multidisciplinary teams using vignettes of patient harm to learn about the root cause analysis methodology.

This depth of approach was not evident across other institutions or disciplines. Curricula mostly emphasised incident reporting per se rather than the potential for learning, although for some higher-risk professions (eg, midwifery) there was a stronger emphasis on learning from adverse events.

“so they are always looking at unpacking—so whenever there is an adverse outcome or near miss, that also goes through an audit process—what happened, why, what contributed to it... and be open to what you could learn.”
In contrast, safety wasn’t a focus at all for some allied health disciplines that didn’t consider themselves ‘high risk’.

“reporting not a big deal… incidents are few and far between. We are fairly low risk.”

Patient safety was otherwise interpreted and included in the curriculum in the context of other categories; the Code of Patient Rights\(^1\) (11 interviewees), cultural safety (three interviewees), occupational health and safety risks and hazards (nine interviewees), legislative requirements, protocols and policies to meet competency and accreditation requirements (15 interviewees) and how to keep personally safe (five interviewees).

**Quality and safety culture**

An overall understanding of a ‘just culture’, the components of such a culture and how this could be measured was lacking. There was however a general awareness of the concept of a ‘no blame’ approach, but the learning aspect was most often focused around the individual and their accountability.

“we don’t mention the word ‘blaming the individual’—so when incidents happen or we use scenarios, we always talk to students about how this links to the competency-based practice and how this fits within the legislation.”

A considerable number of educators (eight interviewees) reported student difficulties in speaking up during clinical placements where there were hierarchies and power imbalances.

“suggestions can be met with defensive responses so students tend not to offer comments.”

Concern was expressed about the mismatch between what is taught with regard to an open safety culture, which supports speaking up about safety concerns, the ‘pushback’ students experience in the clinical setting during a placement, and the implications of this for future clinical practice.

**Evidence-based practice**

Evidence-based practice is a strong focus across all programmes and appears to be well integrated into programmes for all 18 disciplines.

Approaches to teaching and learning ranged from formal teaching to the topic being ‘threaded’ throughout the course. By graduation, students were expected to be able to do a literature review, use the literature effectively in assignments and in some cases, as part of their reflective journals when critiquing their practice.

“they can access the literature and do critical appraisal—there are a couple of times in the programme where they learn this and have key assignment during the programme where they review and critique the literature.”

**Patient-centred care**

Patient-centred care was consistently included and well embedded in all programmes. This was reported as underpinning most aspects of education, and was represented by ideas around informed consent, presenting and discussing evidence-based options with patients and taking account of their preferences and values as part of a shared decision-making approach.

“patient-centred care is very much the bedrock of how we set up the curriculum.”

Cultural competency, cultural safety and Māori models of health were commonly emphasised in nursing.

“we introduce frameworks for care—patient centred, Māori concepts, Pasifika concepts of holistic care.”

Even where there was limited patient exposure in the training, there was an awareness of concepts such as health literacy, cultural competency, ethics, informed consent and patient rights. However, ideas around the involvement of consumers/patients at governance levels and as partners in the co-design of services were rarely reported.

**Teamwork and communication**

Teamwork and communication featured consistently across all programmes with formal teaching around the concepts of teamwork dynamics and change management. There was a strong emphasis on communication skills as a necessary element of effective teamwork.

“focus early on communication skills so they can work effectively in teams… we teach them how to negotiate safely within the team.”

Simulation training in teams was also a reasonably common theme—either within their own discipline or where possible with other disciplines. This was more established in some programmes than others.
“We do simulation training with them—and we look at it in terms of understanding peoples' roles and the importance of inter-professional engagement.”

Where there wasn’t dedicated teaching around the dynamics of teamwork and communication, students had opportunities to participate in team activities within their own discipline by working on group assignments or projects. Interviewees also mentioned that students gain relevant experience during their clinical placements where they had opportunities to work within a team and attend multidisciplinary hospital seminars.

Inter-professional education emerged during discussions about teamwork and was viewed very positively, even though for some the logistics of organising inter-professional learning events was a major barrier.

Examples of interdisciplinary teamwork involved students working together on a community project and a particularly unique example was a one-month rural immersion project where students ‘lived, worked and played’ together. Where inter-professional learning wasn’t already happening, there was an awareness of its importance as the way of the future.

“There are limited direct interactions [with other professional groups]... but we are hoping that is going to change as we see it is an important area.”

Leadership

The concept of leadership was mostly frequently discussed in the context of teamwork, communication and advocacy for patients. Formal teaching on leadership styles, change theory and models were addressed in only a few disciplines towards the end of the education programmes and mostly in association with professional practice papers.

In nursing, leadership was interpreted with reference to competencies around ‘supervision, delegation and direction’ where registered nurses have responsibilities for enrolled nurses.

“in the leadership and management paper we talk about directing and delegating—how do you give orders/communicate with others and how do you provide direction for care... how do you delegate and who is responsible once you delegate.”

Where a discipline had more of a public health role, there was some focused work around leadership models and styles. Others described it as ‘embedded in their values’.

Systems thinking

Systems thinking is a difficult concept to define and a relatively new idea for healthcare. It wasn’t explicitly included in any undergraduate programme, but most felt that students appreciated the complexities of the healthcare system and recognised the need for coordinated and integrated care across inter-dependent services.

“intuitively, people know they are working in a very complex system—we often teach them silos but because students cross silos all the time, they see where things fall in the gaps.”

Knowledge of the New Zealand health system, funding streams and structural and contextual factors that impact on health was mentioned as part of an awareness of ‘systems’.

Using information technology

Using and understanding of information technology as an important enabler of integrated care, patient safety, patient engagement or measuring and monitoring system performance was not addressed to any great extent in any curricula.

Responses referred to the ability of students to manage information technology in general, including the need to access library databases to find relevant information, access course material offered in online modules, keep electronic portfolios for assessment purposes, utilise electronic patient management systems while in clinical placements and the responsible use of social media. For the disciplines that were highly dependent on technology, this was seen as an important component, but was specifically focused around their area of work (eg, radiology).

A novel use of computer-based learning using virtual simulation and avatars as the basis for some learning was described by one nursing programme:

“we always have our eye on the future here... we anticipate the possibility that simulation might be conceived as part of clinical experience... quality simulation is also a good way to learn.”
Perspectives and challenges

There was general agreement that improving quality and safety in healthcare in the pre-registration curricula for health professionals was important. Challenges incorporating this teaching could be categorised into key themes; how to include more material in their already stretched curricula; having expert faculty with relevant education and experience; the tension around having to meet registration competency requirements; together with the complexities of providing students with relevant practical experience in clinical settings.

“(sic there is) challenging complexity of bringing together all of the different pieces people believe that people working in healthcare should have—how do you do that in training programmes—how do you bring together the range of requirements in 3,600 hours and adapt frequently to meet changing demand?”

“None [of our staff] have specific education in quality and safety.”

“space in the curriculum is constrained around core aspects that professional organisations mandate that we have to cover.”

One of the specific challenges mentioned was the disconnect between what was taught, what students subsequently experience in their clinical placement and their role as future health professionals.

“we can do so much but it is also about the culture they go into. We need more collaboration with the healthcare industry to create the change.”

Finally, it was apparent that educators on the whole were aware of the changing healthcare landscape and the need for new models of teaching such as inter-professional education as well as the need for students to acquire a relevant skillset to function in an increasingly complex healthcare system.

“Training in isolation is not as effective... if we want real change, has to be done interdisciplinary.”

“It is our expectation that students will get out there and change the culture of the environment for the future—we talk about them being cultural agents of change. We want movers and shakers.”

Discussion

In this qualitative study, we investigated how quality and safety domains are being taught in the curricula of health professional pre-registration education in New Zealand. Interviews were conducted with key personnel from 43 tertiary institutions representing 18 health professional disciplines, including medicine, nursing, midwifery, dentistry, pharmacy, physiotherapy, dietetics and 11 other allied health professions.

Most curricula were described as being integrated, meaning that rather than being taught in isolation, topics were integrated both vertically and horizontally throughout the course. It was difficult therefore to quantify the extent to which any one of the domains was included in the curriculum. The insights gained however were valuable in getting a sense of the state of quality improvement and patient safety teaching and learning across New Zealand pre-registration health professional education and training programs.

There was considerable variation in how each of the domains was addressed by education providers. However, the importance of improving the quality and safety of healthcare was recognised by all and the building blocks for the delivery of safe and effective care were certainly evident. Evidence-based practice, patient-centred care and teamwork and communication were the strongest domains and well embedded in programmes, while leadership styles, change theory, systems thinking and the role of IT to support measurement, learning from data, integration of care and patient engagement were less explicitly included.

Patient safety was acknowledged as being an important priority, but some key aspects relating to the safe delivery of care, for example human factors and an appreciation of system factors, were not consistently addressed. Patient safety was focused mainly around incident reporting, and to a lesser extent learning from adverse events. Although a ‘no blame’ culture was articulated as important, the emphasis except in a few institutions tended to be on reporting in a context of accountability rather than on learning in the context of a just culture.
In contrast to other domains, the core principles of improvement science to enable students to improve the quality and safety of services using a systematic and scientific approach were largely absent (except for two institutions) from pre-registration curricula and there was a lack of familiarity with improvement science theory, methods and tools among those interviewed. Approaches to improving quality and safety appeared to be mainly addressed in a research context where students drew on the evidence to identify gaps and implement solutions. While this approach is valid in some contexts, in complex settings, there is a need for a different approach and skillset. While participants were receptive to considering ways in which improvement science might be incorporated into their curricula, there were significant challenges raised: an already stretched curricula, meeting registration competency requirements and the limitations with respect to accessing expert faculty with relevant education and experience.

Participants were very aware of the changing healthcare landscape and the need for new approaches to education and training to better prepare students for complex work environments. The importance of inter-professional education was recognised as was the need for students to develop lifelong learning skills that would enable them to adapt and respond to changing demands. While a number of programmes are already taking steps in these directions, some find the logistics of providing relevant inter-professional clinical experience a barrier. Furthermore, concerns about the disconnect between what is taught and what students sometimes experience in the clinical setting suggest the need for better collaboration across educational and healthcare settings.

The main strength of this study is the inclusion of the multiple healthcare disciplines and encompassing whole-of-country tertiary health curricula of these professions. There was a high response rate, allowing valuable insights and establishing a baseline for the current undergraduate educational status quo.

Bias is a known limitation of qualitative studies and we attempted to address this by having two researchers review the transcriptions independently and having a process to address any disagreements. A further limitation was that by using only one source of information for each of the programmes, we may have an incomplete understanding of curricula content reflecting only the knowledge of the interviewee rather than the entire teaching faculty. Requesting documentation about the curricula may have better informed the discussions, however, the purpose of the study was to gain some insight into the current state of quality improvement science teaching in health professional education in New Zealand, rather than undertaking a comprehensive stocktake.

To our knowledge this is the first study investigating pre-registration quality and safety education in New Zealand. Internationally, a number of studies have investigated the quality and safety content in health professional curricula. Of these, four were systematic reviews, two focusing solely on the patient safety content, one investigating both the patient safety and quality improvement content and the other on the quality improvement content alone. Although most studies have concentrated on medical and nursing programmes, we identified one study investigating how pre-registration students from medicine, nursing, physiotherapy and pharmacy learned about ‘keeping patients safe’. We were unable to identify any papers that included as wide a range of health professionals as our study.

The literature describes multiple methods to establish the quality and safety content of professional curricula, including surveys of faculty and students, interviews with faculty students and health service managers, focus groups with faculty and students, case studies of selected programmes, analyses of curriculum documentation, analysis of curriculum guidelines, and course materials and gap analysis. In general, the findings from our study are similar to these studies, which also found deficiencies with respect to the inclusion of quality improvement and patient safety in the curricula of health professional education programmes. Quality improvement content has been described as fragmented or woven across multiple courses within a programme rather than being an explicit focus in the
curriculum.\textsuperscript{30} Patient safety was described in one paper as being “not visible as a curricular theme”.\textsuperscript{31} A further study identified discrepancies between faculty, student and practitioner views with respect to the adequacy of pre-registration education in quality and safety and the ability of faculty to teach this content.\textsuperscript{29} Indeed, faculty misunderstanding of concepts such as informatics and inter-disciplinary teams have been reported to lead to student confusion.\textsuperscript{28} Other barriers and challenges have been reported that are similar to our key findings. Specifically, few faculty have the necessary knowledge of safety science and improvement methods, the lack of regulation as a driver for the inclusion of patient safety and improvement science in the curricula and the influence of the practice settings in which students learn.\textsuperscript{32,37,38}

This study adds information about the baseline of improvement science and patient safety teaching and learning in New Zealand pre-registration education and training programmes for health professionals. However, the findings from our study and the literature raise questions about how best to include improvement science knowledge, methods and tools into curricula. Whether it is included as a specific focus or woven throughout the curricula, or a combination of both, it must be included in such a way that improvement becomes an intrinsic part of health professionals’ work, rather than an ‘add on’ to their profession-specific content knowledge.

One approach to re-orientate quality and safety education for health professional students is to foster much greater collaboration across professional training bodies, for curricula to be shared and to be supported by academics, healthcare educators and improvement science specialists. This has already been reported in Wales where universities, the Institute for Healthcare (IHI) Open School clinical teachers and local healthcare organisations collaborated.\textsuperscript{39} The latter provided opportunities for student participation in actual improvement campaign learning events. This not only helped bridge theory-practice gaps, it provided opportunities for educators to meet and discuss how to incorporate quality improvement into their curricula.\textsuperscript{39} Furthermore, engaging clinicians as well in these discussions has the potential to address the disconnect between what students are taught and what they sometimes experience in their clinical placements.

In New Zealand, examples were shared that described inter-professional learning experiences both within the educational institutions as well as in the field. These could be augmented further. For example, one study has described a novel approach to raising awareness of safety hazards among medical students and residents through a simulated ‘safety room of horrors’ where students were asked to identify as many common hospital-based patient safety hazards as possible within a timed period. While students were able to identify many of the hazards, they missed important patient safety priorities such as pressure injury and catheter-related risks, medication reconciliation and chart base errors.\textsuperscript{40} These types of educational interventions could also provide opportunities for teaching and learning improvement science methods. This could be supported by access to online learning modules, and facilitated by the growing number of healthcare practitioners with expertise in improvement science.

**Conclusion**

An aspirational goal for New Zealand health training organisations is that all health professional graduates in New Zealand enter the workforce as lifelong learners where improvement is an intrinsic part of their everyday work. Although the building blocks for improving the quality and safety of healthcare are present, there is a need to augment knowledge and skills in improvement science and patient safety to keep pace with the needs of rapidly changing healthcare environments.

How best to achieve this is a question for health educators, improvements science specialists and clinicians to work on together, informed by pedagogical approaches suitable to the teaching of improvement science,\textsuperscript{12,41} and utilising the Knowledge to Action Framework as a resource.\textsuperscript{15} Collaboration with other disciplines grappling with similar issues would be also be invaluable, for example education and engineering.\textsuperscript{10,42}
Competing interests:
Gillian Robb reports involvement in undergraduate medical and postgraduate education of quality in healthcare for approximately ten years at the University of Auckland.
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The outcomes of patients returned to general practitioner after being declined hip and knee replacement

Toni Anitelea, Ella Iosua, Ayaaz Ebramjee, David Gwynne-Jones

ABSTRACT

AIM: To determine the outcome of patients waitlisted for hip and knee replacement surgery who were returned to GP due to resource constraints.

METHODS: Prospectively gathered data of all patients returned to GP was analysed, including demographics, clinical prioritisation scores and patient-reported scores. Subsequent outcome was collected from departmental records and the National Joint Registry.

RESULTS: Between November 2013 and December 2015, 374 patients were returned to GP care. At minimum 12-month follow-up, 215 (57.5%) had undergone or had certainty for surgery, 36 patients (9.6%) had been re-referred and again declined surgery and 123 (32.9%) remained in GP care. The factors influencing the likelihood of a patient subsequently qualifying for surgery were need for hip rather than knee replacement, time from initial FSA and initial NZOA score. The mean waiting time for those patients who underwent publicly-funded surgery was 14.7 months.

CONCLUSION: Returning patients to GP delays treatment rather than reducing the need for surgery. This delay results in waste, added costs to the patient, healthcare system and society, and may reduce the benefit of surgery. There needs to be a significant increase in capacity to meet this demand.
procedures in the private sector. Preliminary research findings suggest that at least 25% of patients returned to GP are re-referred soon after being declined.1,4

The primary aim of this study was to determine the outcome of the return to GP group at minimum 12-month follow up after their initial orthopaedic outpatient appointment. Secondary outcome measures were to determine predictors of re-referral and the time from initial clinic appointment until surgery if subsequently undertaken.

Methods

In November 2013 we commenced a system whereby all patients waitlisted for hip or knee replacement by an orthopaedic surgeon at a first specialist assessment (FSA) were independently scored by a single prioritisation nurse using the New Zealand Orthopaedic Association hip and knee priority scoring tool (NZOA score).3 Details of the tool and process have been previously described.3,4 The threshold score was set at 71 points (0 best to 100 worst) based on the expected capacity of the orthopaedic service. Any patients who scored above the threshold would be given certainty for surgery with an expectation that the surgery would be completed within four months. If a patient scored below the threshold score they could be given a clinical over-ride by their surgeon, or were returned to GP for ongoing care. A decision had been made that no patients were to be classed as active review. The NZOA score has been compared with patient-reported outcome scores and found to be an effective tool, though patients just below the threshold score may not have a clinically important difference from those above threshold.3

Pre-operative patient-reported outcome scores (Oxford Hip or Knee Score (OHS, OKS)7 and a Reduced Western Ontario and McMaster Osteoarthritis Index (WOMAC) score (RWS))8,9 were collected prospectively as part of the prioritisation process. The Oxford score has 12 questions and is scored 0 to 48 where 0 is worst, The RWS has 5 pain and 7 function questions and is scored 0 to 48 where 48 is worst.

The cohort of patients returned to GP between November 2013 and December 2015 was identified via a record kept prospectively by the prioritisation nurse. Their subsequent outcome was determined from this database with further information, including gender and ethnicity collected from Southern District Health Board’s (SDHB) patient record software and clinical notes. There was a minimum 12-month follow-up period after the date of their FSA. Patient details were cross referenced with the New Zealand Joint Registry, which has 98% compliance in New Zealand to check whether TJR was performed in other hospitals.1

The outcomes of these patients were categorised to one of four categories: remain with GP, below threshold, private or surgery. Patients classified as remain with GP were those that had been declined surgery and had not been re-referred by their GP for reassessment. Those classified as below threshold were those that had been re-referred but still did not meet the threshold for elective surgery and were again returned to GP. The private group were those who had been declined through the public system, and self-funded surgery in the private sector. Patients classified as surgery were those that had received publicly-funded surgery after being returned to their GP.

The wait times of the surgery group from their initial FSA to eventual certainty decision, and from FSA to surgery, were collected. Comparisons were made between the first and second year of the study period, and between hips and knees.

Statistical analysis was performed with the help of a biostatistician. Associations of sex and age with the outcome group were assessed using the chi-square test for independence and Analysis of Variance (ANOVA) respectively. ANOVA was also used to investigate associations between the outcome group and each of the NZOA, OHS or OKS score and WOMAC scores. Chi square tests were used to compare outcomes between sub-groups.

Ethics approval was obtained from the University of Otago Ethics committee (Health).

Results

During the period covered by this study, 374 patients were returned to GP after being waitlisted for THR or TKR and scored by the prioritisation nurse. Demographic details are given in Table 1. The mean age across
all groups was 67.5 years with patients requiring THR on average almost four years younger than those requiring TKR. The mean time from FSA to the time of this review was 24.2 months (12 to 37 months). The same number of patients (187) had been returned in each of the two years of the study. During the same period, 832 primary elective hip and knee replacements were performed at our institution.

Table 1: Demographic details of the 374 patients returned to general practitioner (GP).

<table>
<thead>
<tr>
<th>Number</th>
<th>Age (sd)</th>
<th>Gender</th>
<th>Joint</th>
<th>Scores at initial FSA</th>
<th>Duration of follow up from initial FSA (mean, range, months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>374</td>
<td>67.5 (10)</td>
<td>Male (45.7%)</td>
<td>Hip</td>
<td>63.1 (6.5)</td>
<td>24.2 (12–37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female (54.3%)</td>
<td>Knee</td>
<td>14.5 (5.5)</td>
<td></td>
</tr>
</tbody>
</table>

Patients in the surgery group had follow-up of 26.4 months compared to 20.7 months in the remain with GP group. Patients seen in year 1 were more likely to have certainty for surgery (121/187, 64.7%) than those in year 2 (102/187, 35%) (chi square 24.7, p<0.0001). Conversely, significantly more patients remained in GP care from year 2 (86 of 187 (46%) compared with year 1 (36 of 187, 19.3%) chi square 30.4, p<0.0001). There was no significant association between sex and patient final outcome (p=0.31) nor age and patient final outcome (p=0.77).

The surgery group had the highest mean initial NZOA score, as well as the worst mean Oxford and reduced WOMAC (RWS) scores. There was a significant association between mean patient NZOA score and

Over half of the sample had received or were awaiting surgery across either public or private sectors. One hundred and ninety-four patients (51.9%) had undergone or were awaiting public elective surgery with 22 patients (5.9%) electing to self-fund private surgery (Table 2).

Patients awaiting hip replacement were significantly more likely than those awaiting knee replacement to have subsequently qualified for public surgery [100 of 156 (64%) vs 94 of 218 (43%) (Chi square 19.7, p<0.0001)]. Conversely, knees were more likely than hips to remain in GP care without re-referral: [87 of 218 (39.9%) vs 35 of 156 (22.2%) chi square 12.6, p<0.0001)]. An equal number of hips and knees had their surgery in the private sector (Table 2).

Table 2: Outcomes of patients initially returned to general practitioner (GP) at minimum 12-month follow up.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All patients (%</th>
<th>Hips</th>
<th>Knees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remain with GP</td>
<td>122 (32.6%)</td>
<td>35 (22%)</td>
<td>87 (39.9%)</td>
</tr>
<tr>
<td>Below threshold</td>
<td>36 (9.6%)</td>
<td>10 (7%)</td>
<td>26 (12%)</td>
</tr>
<tr>
<td>Private</td>
<td>22 (5.9%)</td>
<td>11 (7%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>194 (51.9%)</td>
<td>100 (64%)</td>
<td>94 (43%)</td>
</tr>
<tr>
<td>Total</td>
<td>374</td>
<td>156</td>
<td>218</td>
</tr>
</tbody>
</table>

FSA; First specialist assessment, NZOA; New Zealand Orthopaedic Association hip and knee prioritisation score, OHS; Oxford hip score, OKS; Oxford knee score, RWS; Reduced WOMAC score.

Of the 374 patients, 122 (32.6%) remained in the community without any further contact. A further 36 (9.6%) patients had been re-referred by their GP to see the specialist for another clinical assessment and had again failed to meet the financial threshold for elective surgery. Two patients had died: one in each of the above groups.
patient final outcome (p<0.01). Any association between patient outcome and mean Oxford (p=0.10) or RWS (p=0.08) did not reach significance (Table 3).

Table 3: Scores at time of initial first specialist assessment (FSA).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NZOA mean (sd)</th>
<th>RWS/48 (sd)</th>
<th>OHS, OKS/48 (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remain with GP</td>
<td>61.8 (6.4)</td>
<td>30.4 (7.3)</td>
<td>15.1 (5.6)</td>
</tr>
<tr>
<td>Below threshold</td>
<td>60.4 (9.2)</td>
<td>29.6 (8.1)</td>
<td>15.1 (5.3)</td>
</tr>
<tr>
<td>Private surgery</td>
<td>62.4 (8.2)</td>
<td>30.6 (8.8)</td>
<td>14.4 (7.4)</td>
</tr>
<tr>
<td>Surgery</td>
<td>64.2 (5.8)</td>
<td>32.4 (6.6)</td>
<td>13.4 (4.9)</td>
</tr>
</tbody>
</table>

NZOA; New Zealand Orthopaedic Association hip and knee prioritisation score, OHS; Oxford hip score, OKS; Oxford knee score, RWS; Reduced WOMAC score.

Of the 115 patients with an initial NZOA score of 70 points (a common score just below the threshold), 76 (66%) subsequently gained certainty compared with 88 of 201 (44%) with a lower score (chi square 14.6, p<0.0001).

The mean waiting time from initial FSA to certainty date was 11 months (sd 6.6, median 10 months) (range 1–30 months). The mean time from FSA to surgery was 14.7 months (sd 6.9, median 14) (range 4–33 months). Thirteen people had received certainty but were yet to undergo the proposed surgery. The mean time from the certainty decision to surgery was 3.7 months (sd 3.3, range 1–23 months) (Figure 1).

Discussion

In this study over a two year period, 374 patients who were recommended TJR by their surgeon were declined for surgery due to capacity constraints in the public health system and therefore returned to GP care. This equates to approximately 31% of patients waitlisted for surgery and has not changed from our previous paper.³ This is supposed to give patients certainty and allow them to make choices. These are essentially limited to: wait until they deteriorate, go private or request reassessment. Only 22 (5.9% of all patients returned) elected to self-fund in the private sector, which reflects the demographic of this population with few patients having the funds for a private operation. Those who can afford to self-fund tend to bypass the public system altogether. Two hundred and thirty (61.5%) were re-referred during the study period of which 194 (51.9% of all returns) went on to receive surgery and 36 (9.6%) again failed to meet the financial threshold.
for elective surgery. Only a third (122, 32.6%) remained in the community without any further referral.

The factors that had the greatest influence on the likelihood of a patient subsequently qualifying for surgery were initial NZOA score, hip rather than knee disease and the length of time from initial FSA. This is not surprising and reflects the natural history of these conditions, which is to slowly deteriorate. Patients with hip osteoarthritis are typically more disabled than those with knee osteoarthritis and less likely to respond to non-operative interventions.3,10 The surgery group had the worst patient-reported scores (OHS,OKS and RWS) at initial assessment but the trend did not reach statistical significance. The patient-reported scores of the patients (OHS 14.0, OKS 14.5, RWS 31.2) are a level similar to those who had received surgery between 2006 and 2010 in our institution4 and worse than the average scores reported in the literature for primary hip and knee replacement in other centres in New Zealand or overseas.11–20 However, during the period of the study the mean scores of patients undergoing surgery in our institution were OHS 9.9, OKS 10.6 and RWS 34.8.4 This demonstrates that those patients returned to GP were a slightly less severe group than those qualifying for surgery, confirming that the prioritisation was robust.

Prior to this study we had used active review (AR) widely with 162 patients waiting for TJR on AR in August 2012.5 Patients remained within the system and could be assessed by use of experienced nurses and patient-reported questionnaires. This created an increasing amount of work for the service and their visibility was a potential embarrassment for DHB management, the Ministry of Health and politicians. It was decided when we commenced nurse prioritisation that active review was no longer to be used. As two-thirds of patients scoring 70 points subsequently qualified for surgery the continued use of AR would have been justified and it would have avoided the additional delay, costs and administration of re-referral from a GP. The majority of patients (63%) in the surgery group got certainty for surgery within 12 months of initial FSA. Most of these patients will have waited until their initial decline decision, waited and paid for a further GP appointment and potentially waited 4–6 months for a further FSA.

The demand for TJR is increasing in New Zealand and around the world.21,22 However, between 2007 and 2013 there was there was no increase in the rate of publicly funded elective primary hip and knee replacement in New Zealand although the total numbers of joint replacements increased.2 The demand for TJR in our area appears to be higher than the New Zealand average but the problems we are seeing are not unique.3–6

The reduction of the Ministry of Health’s target from six months to four months does little to facilitate patient care.4 While those accepted onto the waitlist will get their surgery sooner, it does not increase the numbers of procedures done. Because failure to meet the target may be associated with financial penalties to the DHB, the unintended consequence is that more patients are being returned to GP purely to meet the target.6,21,23 They do not show up on waiting lists so are invisible.

In this study the mean time from certainty to surgery was 3.7 months. However, the real wait time for those patients initially returned to GP who ended up qualifying for public surgery was 14.7 months. The remaining patients are still waiting at an average of 21 months following FSA. Waiting for surgery has an adverse effect on outcomes. Studies have consistently shown that worse pre-operative scores are associated with poorer post-operative results, though the improvement in score may be greater.7,11,16,17 Waiting longer than six months can cause a 50% decrease in the odds of achieving a better than expected functional outcome compared with those who waited less than six months.24 It is not clear if this is happening in our practice as we have no comparable controls. Following introduction of an enhanced recovery programme, our post-operative Oxford hip scores compared to the New Zealand average are worse (38.8 vs 40.4) but the OKS is a little better (39.8 vs 37.5) despite poor pre-operative scores (11.1).1,25

Total hip replacement and total knee replacement are two of the most cost-effective procedures in orthopaedic surgery.11,15 By returning patients back to

ARTICLE
the care of their GP rather than operating, there is a substantial and avoidable loss of quality-adjusted life years. There may be increased medical costs for non-operative treatment and its complications, such as gastro-intestinal bleeds from non-steroidal anti-inflammatory use, and increased in-patient costs due to increased complexity of surgery, length of stay and risk of complications. In addition there are personal costs to the patient and societal costs, which are harder to quantify.

Rolfson et al estimated the cost of waiting for hip replacement in Sweden as US$7,666 per patient per year. Fielden et al calculated the mean cost was NZ$1,030 (US$688) per person per month waiting (2005 figures). Societal costs made up over 70% of this even in those who were not in paid employment. If we extrapolate these figures (but still using 2005 values and exchange rates) to our cohort then the additional cost of waiting more than six months for surgery in those who were initially returned but who subsequently underwent publicly funded surgery was NZ$1.6 million (US$1.1 million). The cost of those still waiting is a further NZ$2.6 million (US$1.7 million). Index-linking would increase these figures by 26% to NZ$2 million and NZ$3.25 million. As the current costing for an uncomplicated publicly funded hip or knee replacement is approximately $16,000 using WIESNZ15 cost-weights, this could have funded an additional 328 joint replacements at 2015 values.

A limitation of this study is that it is not clear what has happened to the third of patients who remain in primary care without re-referral or surgery. The natural history of the condition is a slow deterioration. They may have given up, modified their expectations or developed inter-current medical problems that preclude surgery. Only two patients had died. Further research would be helpful in this area but was outside the initial scope of this project. We had hoped to look at outcomes among Māori and Pacific patients. However, only three of the 374 were of Pacific ethnicity, and six were Māori, meaning ethnic specific analyses were not possible. We have previously shown higher rates of publicly funded TJR provision in Māori than New Zealand European and slightly lower rates in Pacific people. It appears that Māori and Pacific people are not over-represented in the return to GP group. Finally, the NZOA hip and knee prioritisation score used in this study has recently been superseded by a new generic score that includes a patient impact on life score. Patients with hip and knee OA will now be scored directly against patients with other orthopaedic conditions. This is likely to have an effect on the numbers and mix of patients returned to GP.

Conclusion

In our district and across New Zealand, the demand for TJR has increased, there has not been a corresponding increase in service provision and the target time allowed by the Ministry of Health for surgery has decreased. This has resulted in many patients being declined surgery despite reaching the clinical threshold for joint replacement. Those qualifying for surgery are more severely affected than in past years. Returning patients to GP delays treatment rather than reducing the need for surgery. Over half of patients returned to GP care in order to meet the four-month target will end up qualifying for surgery with a mean waiting time of 14.7 months from initial FSA. This delay results in waste, added costs to the patient, healthcare system and society and may reduce the benefit of surgery. Only 5.9% of patients returned to GP elected to pay for private surgery. Less than a third of patients remain in primary care without further referral or surgery. Further work is required to determine the fate of this group. There needs to be a significant increase in capacity in our district to meet this demand.
Competing interests:
Ms Toni Anitelea received a Pacific Summer Studentship Scholarship from the Health Research Council for this study.

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REFERENCES:


Deceased donor kidney transplantation in New Zealand: use and audit of a survival prediction tool

Frances Dowen, Nicholas Cross, Philip Clayton, Helen Pilmore

**ABSTRACT**

**AIMS:** New Zealand follows the guideline that only patients with projected five-year survival of 80% are listed for deceased donor kidney transplantation. An algorithm derived from US data estimates survival after transplantation, however, this may not be as applicable to the New Zealand population. We review use of the US derived algorithm in New Zealand. We assessed accuracy of scores calculated by referring units and audited whether the system is applied in New Zealand.

**METHODS:** Data on 422 patients assessed for transplantation was entered into the algorithm to calculate a projected survival score. Scores were generated by an independent investigator and compared with those calculated by local units. Scores and demographics of listed and not-listed patients were also compared.

**RESULTS:** Three hundred and twenty-five of 420 (77%) patients assessed were accepted onto the New Zealand transplant list. Mean estimated five-year survival in listed patients was 89.4% compared to 79.8% in those not accepted (p<0.0001). Listed patients were younger and less likely to have coronary artery disease (CAD). There was no significant difference in scores calculated by the independent assessor and referring centres (p=0.185).

**CONCLUSION:** The algorithm is universally and accurately used. Future studies are required to determine the validity of the system in New Zealand patients.

Kidney transplantation is the treatment of choice for most patients with ESKD. Mortality is significantly reduced in transplant recipients compared to those patients who are listed for transplantation but remain on dialysis in all patient sub-populations examined. In New Zealand, and internationally, the number of patients listed for kidney transplantation significantly exceeds the number of kidneys available from deceased donors and waiting times have increased substantially over the last decade.

The Transplantation Society of Australia and New Zealand (TSANZ) recommends that patients listed for deceased donor kidney transplantation should have an estimated five-year survival of 80%. In order to assist transplant teams in New Zealand to make this estimation, all patients being considered for listing have had their five-year probability of survival following deceased donor kidney transplantation estimated using a multivariable equation developed based on the outcome of 169,393 patients transplanted in the US between 1995 and 2006. The current listing criteria for deceased donor renal transplantation is to accept patients with a projected survival threshold of 70% using the US algorithm assuming they are in all other respects suitable for kidney transplantation. A cut off of 70% is used to account for a confidence interval around the estimated score, the lack of complexity of predictive factors in the calculator (eg, a patient with severe triple vessel coronary artery disease will have the same score for that factor as a patient with single vessel disease) and the potential demographic differences between the US and New Zealand populations.
The use of this predictive algorithm commenced on 1 February 2013 and since that date all patients considered for kidney transplant listing are scored using this tool. Patients are scored at the date which they are first considered by the transplant team for listing. The score forms part of the assessment for deceased donor transplant listing and does not replace the multidisciplinary team (MDT) assessment. Patients with adequate scores may not necessarily be listed if deemed unsuitable by the MDT. Equally, those patients with scores below 70% can be reviewed by the National Renal Transplant Committee if they are felt to be suitable. Patients on deceased donor waiting list are rescored at least bi-annually or when they develop new comorbidities that may affect the risk score. Patients on the waiting list whose probability of survival at five years falls below 70% due to new comorbidity or advancing age are removed from the waiting list.

We aimed to assess the use of the survival score algorithm by comparing calculated scores in a prospective cohort of patients, discussed for deceased donor transplantation listing in two of the three transplant units in New Zealand, between 1 June 2015 and 30 April 2016. We audited the decisions to list patients scored using the algorithm and compared scores calculated at the time of listing by the individual units with scores calculated by an independent researcher.

**Methods**

Ethical approval for the study was undertaken through the New Zealand Ministry of Health Ethics Committee (Approval 15/CEN/1).

**Data collection and statistical analysis**

Patients who were assessed and discussed for deceased donor renal transplant listing by the transplant groups in Auckland and Christchurch, New Zealand between 1 June 2015 and 30 April 2016 were included. Four hundred and twenty-two patients were identified and information prospectively collected. All patients had the following information collected: date of birth, gender, date of first renal replacement therapy (RRT), date listed, date discussed by transplant team (used in calculator as a surrogate for transplant date), albumin, BMI, cause of chronic kidney disease (CKD), COPD or chronic lung disease, non-ambulatory, chronic heart failure, diabetes, insulin, coronary artery disease, peripheral vascular disease, cerebrovascular disease, hypertension, smoker (at start of RRT), employment status, ethnicity and peak PRA. Employment included voluntary work and active home responsibilities. Smokers were considered to be ex-smokers after a three-month cessation period. Smoking status was recorded at the start of RRT as ANZDATA records this information upon entry to the registry, which equates to the point of commencing RRT. Information was collected from the electronic record system and from patients’ transplant assessment notes. The variables of albumin and BMI were taken from the time of listing (or time of discussion if not yet listed), as this was the most reliable point that data could be extracted from records. Some patients were being discussed for the first time during the period of data collection, while others had been previously discussed and their cases were being reviewed to ensure suitability to remain listed or review reasons for not listing previously. Components of the score are listed in Table 1.

Patients under the age of 18 or those undergoing assessment for multiple organ transplantation were excluded.

Scores calculated by the transplant units were compared to those calculated by the independent (unallied) researcher. Where there was a discrepancy between scores of >5%, they were re-calculated by the researcher. If the discrepancy remained then the individual data entry points were reviewed by the senior supervising nephrologist to ensure the correct data was entered.

Statistical analysis was undertaken using Systat 9.0. Mean and median scores were calculated separately for patients who were listed and not listed for kidney transplantation. A Students T test comparing mean and median scores and ages between those listed and not listed was applied. A comparison of demographics of listed vs not listed patients was undertaken using an ANOVA. A p value of <0.05 was considered
significant. A correlation coefficient between the scores calculated by the independent investigator and the listing units was also applied, with a c score of >0.7 considered to be a strong correlation.

### Results

#### Participant characteristics

The prospective cohort of those considered for renal transplant listing comprised of 420 people, as complete data was unavailable on two patients. Three hundred and twenty-five (77%) of these patients were accepted for listing. Demographic data for the whole cohort is listed in Table 2, alongside demographic comparators for those listed vs not listed. Patients who were listed for transplantation were younger and less likely to have coronary artery disease than those not listed.

#### Listing eligibility and transplant scoring

All patients assessed for transplantation had the US algorithm calculated at the time of formal assessment for transplantation. Of the 325 patients listed for deceased donor transplantation, scores calculated by the local units ranged from 68–98.8% while the scores ranged from 46.6–99.3% when calculated by the independent investigator. The mean and median scores for those listed and not listed are shown in Table 3. Overall, there was no significant difference between the mean scores calculated by the local units and those calculated by an independent investigator for listed (p=0.185) or unlisted patients (p=0.558). Local scores were available for 204 of the listed patients and 42 of the unlisted patients.

There was a significant difference in both mean and median scores between those listed and those not listed both when analysing scores calculated by the local units and by the independent investigator for listed (p=0.185) or unlisted patients (p=0.558). Local scores were available for 204 of the listed patients and 42 of the unlisted patients.

When scores were calculated by the assessing unit, 27 (8%) of listed patients scored 70–80% and one patient scored <70%. The patient scoring <70%, when the score was calculated locally, also scored <70% when calculated by the independent investigator, and went through an arbitration process in order to be listed.

Of the patients that were discussed and not listed, the locally calculated score ranged from 52–97.3%. When calculated by the independent investigator, 24 patients in this cohort (25%) had a score of <70% and were primarily assessed as not suitable
Table 2: Demographic data including comparators between listed and not listed patients.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Median (interquartile range) or number of patients (%)</th>
<th>Listed</th>
<th>Not listed</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53 (45–61)</td>
<td>51</td>
<td>57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>257 (61%)</td>
<td>198 (61%)</td>
<td>59 (62%)</td>
<td>0.869</td>
</tr>
<tr>
<td>Female</td>
<td>163 (39%)</td>
<td>127 (39%)</td>
<td>36 (37%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>150 (36%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Māori</td>
<td>125 (30%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacific</td>
<td>78 (19%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>60 (14%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>145 (35%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>129 (31%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>28 (7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>19 (5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>78 (19%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-dialysis</td>
<td>99 (24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>170 (40%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>99 (24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home haemodialysis</td>
<td>52 (12%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>37 (34–40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>165 (39%)</td>
<td>123 (38%)</td>
<td>42 (43%)</td>
<td>0.335</td>
</tr>
<tr>
<td>Insulin</td>
<td>109 (26%)</td>
<td>79 (24%)</td>
<td>30 (31%)</td>
<td>0.192</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>69 (16%)</td>
<td>41 (13%)</td>
<td>28 (29%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>29 (24–33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>213 (51%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>233 (55%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>71 (17%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>116 (28%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accepted for listing</td>
<td>325 (77%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to list from commencing RRT (months)</td>
<td>21 (8.25–39.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listed pre-dialysis</td>
<td>125 (30%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Scores of patients comparing those calculated by an independent investigator with those calculated by the local units.

<table>
<thead>
<tr>
<th></th>
<th>Mean score independent (%)</th>
<th>Mean score local (%)</th>
<th>Median score independent (%)</th>
<th>Median score local (%)</th>
<th>P values independent vs local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listed patients</td>
<td>89.4</td>
<td>88.5</td>
<td>91.6</td>
<td>89.4</td>
<td>0.185</td>
</tr>
<tr>
<td>Unlisted patients</td>
<td>79.8</td>
<td>81.1</td>
<td>81.8</td>
<td>84.3</td>
<td>0.558</td>
</tr>
<tr>
<td>P values listed vs unlisted patients</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
for listing on the deceased donor kidney transplant list due to multiple comorbidities as assessed by the scoring algorithm. The remaining patients who were not listed had a significant comorbidity precluding transplantation despite a score of >70%. Sixteen (17%) of the cohort scored between 70–80%. Similarly the recorded data available from local units showed a calculated score of <70% in 11 (26%) of patients and a score of 70–80% in six patients (14%).

Correlation between the scores calculated by an independent investigator and those calculated by the local units is shown in Figure 1. The correlation coefficient between the independently calculated and locally calculated scores is 0.829881.

Discussion

This is the first report of the use of a survival algorithm in patients being assessed for deceased donor kidney transplantation. This algorithm has been in use since February 2013 and has been applied rigorously to all patients prospectively assessed in New Zealand over a six-month period.

This study demonstrates that the majority of patients who complete a full assessment for kidney transplantation and brought for discussion by the transplant groups in New Zealand are listed for deceased donor transplantation. On assessment of the currently used scoring algorithm, most patients listed meet the TSANZ recommendation of a predicted five-year survival of 80% post-transplantation and the majority also met the current New Zealand requirement of a 70% predicted five-year survival.

It was agreed that transplant units in New Zealand would not list patients with a predicted probability of five-year survival of less than 70%, unless in exceptional circumstances, and after discussion with and agreement of the Transplantation Subcommittee of the New Zealand Renal Advisory Board (subsequently replaced by the National Renal Transplant Leadership Team). It is important to note that patients with poorer survival may still benefit from kidney transplantation and are offered the option of living donor transplantation if they are otherwise suitable. Additionally, as the predicted probability of survival is only one tool in the assessment of a patient's suitability for transplantation, a predicted survival probability of 80% at five years after transplant does not guarantee listing in circumstances where there were other factors contraindicating kidney transplantation.

New Zealand has adopted an algorithm that has been validated in patients assessed for kidney transplantation in the US. Twelve variables independently predicting death were used to create the US model. There are
a number of key differences in a number of these variables between the US and New Zealand end stage kidney disease populations. These include ethnicity, in addition to a low exposure to peritoneal dialysis (PD) in the US (6.8%) compared to New Zealand, where 31% of patients are treated with this dialysis modality. PD is associated with a lower serum albumin due to protein loss through the peritoneum. Hypoalbuminaemia is a strong prognostic factor for death in the USRDS algorithm but we hypothesised that this may not be as relevant to patients on PD.

A comparison study of seven risk scoring algorithms for mortality prediction after kidney transplant in 2,033 patients across 64 UK centres, with seven-year follow up, showed that the score with the best predictive performance (the recipient risk score) was based on age, diagnosis of diabetes, ischaemic heart disease and dialysis duration < or >1 year. The primary outcome measure in this study was death with graft function and age was shown to be an independent predictor of mortality. There were low numbers of diabetic patients and those from ethnic minorities included and the grafts tended to be well HLA matched. Variables of albumin, employment status, hypertension and delay to transplant wait listing have been shown to significantly impact on survival previously and our findings support this. We were unable to identify any one factor or pattern of factors that reliably predict five-year survival after transplantation.

There are a number of limitations in this analysis. Only patients who completed a full assessment for kidney transplantation to the stage of discussion at a formal listing meeting were assessed. It is highly likely that other patients have been assessed by individual renal units and a contraindication to kidney transplantation has precluded full assessment and presentation for listing. Additionally, there are factors in the scoring algorithm that are open to interpretation. An example of this is employment where patients may be considered as employed if they are ‘homemakers’, however, no clear guidance is available.

Two listed patients demonstrated large discrepancies in scores when comparing those generated by the independent assessor and those generated by the local units. In both cases, the local units calculated the patients to be suitable for listing (scores of 73% and 84%), however, the independent assessor calculated the patients to be unsuitable for listing (scores of 46.6% and 49.6% respectively). The independent assessors’ scores were re-checked and also passed on to the senior supervising nephrologist for confirmation. We are unable to explain the reasons that the local scores were comparatively higher. One of these patients has been de-listed since the data was collected and the other remains on the waiting list. Though these two patients show a large discrepancy in score correlation, this does not translate into an overall statistically significant difference. This paper shows universal use of the risk calculator and only one patient listed for kidney transplantation with a locally calculated score of less than 70%. This case went through an appeals process and does not reflect the functionality of the scoring system. Our findings demonstrate acceptance of the algorithm in transplantation centres in New Zealand. We aim to examine this cohort again in five years in order to determine mortality and hence the efficacy of the risk calculator in this New Zealand cohort.
Competing interests:
Dr Pilmore reports grants from A+ Trust during the conduct of the study; personal fees from Abbvie Pharmaceuticals outside the submitted work.

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Gene expression profiling of breast tumours from New Zealand patients

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ABSTRACT

AIMS: New Zealand has one of the highest rates of breast cancer incidence in the world. We investigated the gene expression profiles of breast tumours from New Zealand patients, compared them to gene expression profiles of international breast cancer cohorts and identified any associations between altered gene expression and the clinicopathological features of the tumours.

METHODS: Affymetrix microarrays were used to measure the gene expression profiles of 106 breast tumours from New Zealand patients. Gene expression data from six international breast cancer cohorts were collated, and all the gene expression data were analysed using standard bioinformatic and statistical tools.

RESULTS: Gene expression profiles associated with tumour ER and ERBB2 status, molecular subtype and selected gene expression signatures within the New Zealand cohort were consistent with those found in international cohorts. Significant differences in clinicopathological features such as tumour grade, tumour size and lymph node status were also observed between the New Zealand and international cohorts.

CONCLUSIONS: Gene expression profiles, which are a sensitive indicator of tumour biology, showed no clear difference between breast tumours from New Zealand patients and those from non-New Zealand patients. This suggests that other factors may contribute to the high and increasing breast cancer incidence in New Zealand compared to international populations.

Breast cancer is the most common cancer among women and is the leading cause of cancer death in women worldwide. It is a multi-factorial disease, with considerable inter-patient heterogeneity, and complex aetiology involving genetic, endocrinological, environmental and lifestyle factors. New Zealand has one of the highest breast cancer incidences in the world. The age-standardised breast cancer incidence rate is 92.1 per 100,000 population, and there has been a steady increase in reported breast cancer incidence from 1978–2004, most likely due to improved diagnostic rates through breast cancer screening. Although breast cancer mortality in New Zealand has declined over the last 20 years, breast cancer remains a significant cause of death in New Zealand women, with an age-standardised rate of 20.3 per 100,000 population. While New Zealand breast cancer incidence is comparable to its neighbouring country Australia, New Zealand women appear to have higher breast cancer mortality, possibly due to the high cancer mortality rates for Māori and Pacific women, and the relatively slow funding of new drug treatments in New Zealand.

Gene expression profiling using primary breast tumours has transformed understanding of the molecular aspects of this disease, especially when gene expression data has been integrated with data about DNA mutation and copy number, epigenetic factors such as microRNAs and gene methylation, plus protein expression and in vitro experimental data. These integrated studies now have enabled a re-classification of breast tumours into 10 molecular subtypes from the initial five molecular...
subtypes,13,14 as well as an understanding of pathway signalling in breast cancer,15 association between DNA copy number variation, gene expression and patient survival,16 identification of drivers of proliferation in the luminal molecular subtype of breast cancer,17 confirmation of the heterogeneity of breast tumours18 and the development of molecular tests for breast cancer prognostication and stratified therapy.19,20

In this study, we aimed to generate gene expression profiles of breast tumours from a cohort of 106 New Zealand patients. We compared these profiles and their associated clinical and pathological data with data from non-New Zealand patient cohorts, and have made this new dataset available to the breast cancer research community (see Methods). We found that the statistical associations between gene expression profiles and clinicopathological parameters seen in New Zealand breast tumours are remarkably similar to the associations observed in breast tumours from non-New Zealand breast cancer cohorts.

**Materials and methods**

**Ethics statement**

All women provided written consent to their tissue being utilised and their clinical records accessed for this project. This study was approved by the New Zealand Multi-Region Ethics Committee (project MEC-09/06/060) and the Northern X Regional Ethics Committee (NTX-05/08/096). In addition, the study was reviewed by Auckland District Health Board Research Committee (project A+4567), the Christchurch Cancer Society Tissue Bank Board (project 10101PS) as well as the Māori Research Review Committees associated with the Auckland District Health Board and Cancer Society Tissue Bank.

**New Zealand primary breast tumour collection**

Breast tumour samples were obtained from 47 female patients (Auckland) and 59 female patients (Christchurch) who provided written consent (Supplementary Table 1). Patients included in the study were females aged ≥18 years with breast cancer, had no previous breast malignancies and had not received neoadjuvant treatment prior to surgery. Resected tumours ranged from 6–100mm in size, and were frozen at -80°C within 60 min of surgical resection. The Auckland samples were collected in two stages, 30 between 2005 and 2007, and 17 in 2010. The Christchurch samples were collected between 2003 and 2005. Clinical and pathological data, including up to eight years of follow-up data, were obtained from patient notes collected by the Auckland Breast Cancer Registry for Auckland (http://www.adhb.govt.nz/AucklandBreastCancerRegister/) and the Cancer Society Tissue Bank for Christchurch (http://www.otago.ac.nz/mackenzie-cancer/tissue-bank/).

The oestrogen receptor (ER) status of the tumours were determined using standard diagnostic immunohistochemistry (IHC) methods. The ERBB2 status of the tumours was also determined using IHC, and where the IHC results were equivocal, they were determined using fluorescence in situ hybridisation (FISH).

**RNA extraction and microarray hybridisation**

Breast tumour tissues were homogenised in TRIzol (Thermo Fisher Scientific Inc., Waltham, MA, USA), and total RNA was isolated from TRIzol homogenates using chloroform and purified using RNA affinity mini columns (manufacturer’s protocols; RNeasy Mini Kit, Qiagen, Germany; PureLink Pro 96 Total RNA Purification Kit, Thermo Fisher Scientific Inc.). RNA yields and purity were determined using the NanoDrop spectrophotometer (NanoDrop Technologies Inc., DE, USA). RNA integrity was assessed (Agilent 2100 Bioanlyser; Agilent Technologies Inc., CA, USA; Experion, Bio-Rad Laboratories, CA, USA) and the average 260/280 ratio of total RNA was 2.0 (range 1.8–2.2) and the average RIN/RQI was 8.68 (range 5.6–9.7). Total RNA was labelled, fragmented and hybridised to Affymetrix Human Genome (HG) U133 Plus 2.0 arrays (manufacturer’s protocol). For samples GSM900586-GSM900662 of Gene Expression Omnibus (GEO) record GSE36771, 100μg RNA was used (MessageAmp Premier RNA Amplification Kit, Thermo Fisher Scientific Inc.), for samples GSM900663-GSM900692 of GSE36771, 5μg RNA was used (Affymetrix GeneChip Kit, Affymetrix, Santa Clara, CA, USA).
Microarray data analysis

Raw and normalised microarray data together with clinicopathological annotations are available as GEO record GSE36771 (microarrays GSM900586-GSM900692). Quality assessment was performed using Affymetrix Expression Console and dChip to exclude low-quality samples. Data were analysed in R using the affy and limma packages. Briefly, the data was quantile normalised using the RMA method (without background correction), followed by differential gene expression analysis in limma using Benjamini and Hochberg false discovery rate control, followed by testing for functional enrichment using GeneSetDB, GATHER, and Ingenuity Pathway Analysis (http://www.ingenuity.com). Analyses of the New Zealand tumour gene expression data using limma showed no significant differences between Auckland and Christchurch tumours, or between tumour RNA purified using the RNeasy or PureLink methods (data not shown). Therefore no batch correction was applied to tumours collected from the two New Zealand regions in subsequent comparisons between New Zealand and non-New Zealand tumours described below.

Meta-analysis of microarray data from primary breast tumours from multiple cohorts

Microarray data for 1,034 primary breast tumours were assembled from raw Affymetrix HG U133 "cel" files from GEO records; the New Zealand cohort consisted of GSE36771 (n=106), and the non-New Zealand cohort consisted of cohorts: GSE1456 (n=159, Stockholm, Sweden), GSE3494 (n=232, Uppsala, Sweden), GSE4922 (n=40, Singapore), GSE6532 (London and Oxford, UK), GSE7390 (n=198, France), and GSE36772 (n=57, Singapore, unpublished) (Supplementary Table 1). Duplicate samples were removed from all cohorts and 22,277 probe sets common to the U133 Plus 2.0 and U133A arrays were used for this analysis, as described previously. Array quality assessment was performed using the ‘AffyQCReport’ package in R, and normalised using RMA (without background correction) and loess splining. Statistical meta-analysis was performed using the metaMA package in R, and differential gene expression was assessed from normalised microarray data using limma. Genes and probe sets were hierarchically clustered using Euclidean distance and the Ward agglomeration method of the hclust function in R. Molecular subtypes were assigned to each tumour using the Single Sample Predictor algorithm applied per cohort. The algorithm uses pre-computed subtype centroids and calculates the correlation between each tumour and each subtype centroid. A tumour was assigned the subtype that it was most highly correlated with, unless none of the correlations were above a certain threshold; a threshold of 0.1 was used. Differences between selected clinicopathological features of the New Zealand and the non-New Zealand cohorts were analysed using Pearson’s Chi-squared tests and Student’s t-tests. Principal components for the expression data were calculated by singular value decomposition using the svd function in R, after the data had been zero centered and scaled to unit variance. For visualisation purposes, expression values for each probe set were transformed into Z-scores by mean centreing the data then expressing variation above and below the mean on a scale of standard deviation, using the apply function in R. Differences in time to a distant metastastic event (up to eight years in New Zealand cohort and up to 12 years in the non-New Zealand cohort) were assessed visually via Kaplan-Meier curves and statistically via log rank tests and Cox proportional hazards models using the survival package in R. The visualisations for many of the analyses presented in this paper were scripted using the shiny package from R Studio (http://www.rstudio.com/products/shiny/shiny-server/).

Results

Analysis of gene expression profiles of New Zealand breast tumours

Using normalised gene expression data, we compared gene expression differences between two designated groups using limma, within the New Zealand cohort. We first compared the mRNAs differentially expressed between ER+ and ER- breast tumours, as determined using IHC in the clinic. This analysis identified 64 and 13 probe sets significantly differentially expressed at an absolute log fold
change ≥1.5, between ER+ and ER- tumours (adj-P≤1x10^{-12}). Due to redundancy in the microarray probe sets, these 77 differentially expressed probe sets represented 50 unique annotated genes (38 with increased and 12 with decreased expression between the ER+ and ER- tumours, respectively). The list of mRNAs differentially expressed between ER+ and ER- tumours are provided in Supplementary Table 2, and a heatmap depicting differentially expressed mRNAs between ER+ and ER- tumours are provided in Supplementary Figure 1. The proteins encoded by these differentially expressed mRNAs included known ERα targets such as the progesterone receptor (encoded by the gene \textit{PGR}), trefoil factor 1 (encoded by the gene \textit{TFF1}), anterior gradient 2 homolog (encoded by the gene \textit{AGR2}) and carbonic anhydrase XII (encoded by the gene \textit{CA12}), as well as proteins that function together with ERα such as forkhead box A1 (encoded by the gene \textit{FOXA1}), epidermal growth factor receptor 4 (encoded by the gene \textit{ERBB4}) and GATA binding protein 3 (encoded by the gene \textit{GATA3}).

Next, the mRNAs differentially expressed between 14 ERBB2+ (also known as \textit{HER2/neu}) and 48 ERBB2- tumours were compared; ERBB2 status was available for only 62 tumours. This analysis identified 28 and two probe sets (representing 18 unique annotated genes) that showed significantly increased or decreased expression respectively (adj-P=0.0001). The list of differentially expressed mRNAs are provided in Supplementary Table 3 and a heatmap depicting significantly regulated mRNAs between ERBB2+ and ERBB2- tumours are provided in Supplementary Figure 2. Interestingly, 17 of the 28 significantly upregulated probe sets in ERBB2+ tumours represented 10 mRNAs, including \textit{ERBB2}, located at locus 17q21 (encoded by the genes: \textit{CDK12}, \textit{CWC25}, \textit{FBXL20}, \textit{GRB7}, \textit{GSDMB}, \textit{MIEN1}, \textit{ORMDL3}, \textit{PCGF2} and \textit{PGAP3}).

When we compared the gene expression between tumours of histological grade 1 (n=11) and grade 3 (n=53), no differentially expressed genes were identified (adj-P≤0.05; data not shown).

**Comparison of the gene expression profiles of New Zealand breast tumours and international breast tumours**

We next compared gene expression profiles of New Zealand breast tumours with gene expression profiles of breast tumours from women recruited from other parts of the world: Sweden, Singapore, France and the UK (See Supplementary Table 1). Gene expression data from six published international breast cancer cohorts were combined (n=927; called “non-New Zealand”), and a number of clinicopathological characteristics were analysed to identify if there were any gene expression differences between the breast tumours from the New Zealand and non-New Zealand cohorts, based on the selected clinicopathological characteristics (summarised in Table 1).

The average tumour sizes (P=0.0001) and patients’ ages (P=0.03) in the New Zealand cohort were significantly larger than the non-New Zealand cohort (Table 1). There were also significant differences in the proportions of lymph node positive and lymph node negative patients between the New Zealand and non-New Zealand cohort (P=0.00001; Table 1). There were differences between the proportions of histological grade 1, grade 2 and grade 3 tumours between the New Zealand and non-New Zealand cohort (P=0.001; Table 1). Further analyses revealed significant differences in the proportion of grade 3 tumours compared to grade 2 (P=0.009), and in the proportion of grade 3 tumours compared to grade 1 (P=0.002), between the New Zealand and non-New Zealand cohort. Analysis of the composition of the cohorts based on ER status and molecular subtype showed that there were no significant differences in these variables.

We have previously reported that \textit{ESR1} (which encodes the ERα protein) mRNA expression progressively increased from basal-like to ERBB2 to normal-like to luminal tumours. After classifying our breast tumour gene expression data into their molecular subtypes using the PAM50
predictor (see Methods), we compared the distribution of ESR1 mRNA expression between the five molecular subtypes in the New Zealand and non-New Zealand tumour samples. We found that New Zealand and non-New Zealand tumours showed similar patterns of ESR1 mRNA expression within and between each molecular subtype, whereby ESR1 mRNA expression decreases from the luminal subtypes, to normal-like, to ERBB2 to basal-like tumour subtypes (Figure 1).

These box plots show the levels of ESR1 mRNA in each of the molecular subtypes in the New Zealand (A) and non-New Zealand (B) breast tumour cohorts. The molecular subtypes are shown on the x-axis, and the Z-transformed level of ESR1 mRNA (based on ESR1 microarray probeset 205225_at) is shown on the y-axis. The box plots show the medians, upper and lower quartiles, with whiskers extending to the 5th and 95th percentiles.

Table 1: Comparison of selected clinicopathological features of New Zealand and non-New Zealand breast cancer cohorts.

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>NZ cohort (n=106)</th>
<th>Non-NZ cohort (n=927)</th>
<th>P-value (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient age (y)*</td>
<td>60 (31–94)</td>
<td>57 (24-93)</td>
<td>0.0271</td>
</tr>
<tr>
<td>Patient tumour size (mm)*</td>
<td>29 (6–100)</td>
<td>24 (1–130)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tumour ER status*</td>
<td>Numbers (% of total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER positive</td>
<td>79 (74.5)</td>
<td>743 (74.5)</td>
<td>0.082</td>
</tr>
<tr>
<td>ER negative</td>
<td>27 (25.5)</td>
<td>168 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Histological tumour grade*</td>
<td>Numbers (% of total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>11 (10.4)</td>
<td>169 (18.2)</td>
<td>0.00121</td>
</tr>
<tr>
<td>Grade 2</td>
<td>42 (39.6)</td>
<td>403 (43.5)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>53 (50.0)</td>
<td>288 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Patient lymph node status*</td>
<td>Numbers (% of total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>59 (55.7)</td>
<td>225 (24.3)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Lymph node negative</td>
<td>45 (42.5)</td>
<td>528 (57.0)</td>
<td></td>
</tr>
<tr>
<td>Tumour molecular subtype</td>
<td></td>
<td></td>
<td>0.456</td>
</tr>
<tr>
<td>Luminal A</td>
<td>31 (29.2)</td>
<td>260 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Luminal B</td>
<td>23 (21.7)</td>
<td>187 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Normal-like</td>
<td>14 (13.2)</td>
<td>162 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Her2</td>
<td>8 (7.5)</td>
<td>92 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Basal-like</td>
<td>27 (25.5)</td>
<td>181 (19.5)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3 (2.8)</td>
<td>45 (4.9)</td>
<td></td>
</tr>
</tbody>
</table>

All calculations were using Pearson’s Chi square tests except *patients’ age and *tumour size, where a Student’s t-test was used. *Unavailable ER status information for four patients in GSE3494; exclusion of 12 ER+/PGR+ patients (GSE1456=6, GSE4922=5, GSE36772=1). *Unavailable tumour grade information for 67 patients (GSE1456=12, GSE6532=51, GSE7390=2, GSE3494=2); *Unavailable lymph node status information for 176 patients (GSE1456=159, GSE36771=2, GSE6532=6, GSE3494=9). See Supplementary Table 1 for patient clinical information.
We next determined whether a number of commonly-used gene expression signatures used to stratify tumours showed similar stratification of breast tumours from New Zealand women as from non-New Zealand cohorts. To do this we used the first principal component (PC) calculated from the expression data represented by the genes in the selected signature (see Methods) to act as an indicator of pathway activity of that gene signature. We assessed similarities and differences between cohorts in terms of the clinical features that correlated with the 1st PC of three well-known gene signatures (see Figure 2 for a short description of these gene signatures): (1) the PAM50 signature, (2) the Genomic Grade Index (GGI) and (3) the ER attractor. The results of the analyses were displayed as heatmaps (see Figure 3 for a description of heatmaps) where the tumours were sorted based on the magnitude of the 1st PC of each signature that was analysed.

Figure 1: The distribution of ESR1 mRNA expression levels in breast tumours stratified by molecular subtype are similar in the New Zealand and non-New Zealand cohorts.

Figure 2: Description of gene signatures.

**PAM50**
The PAM50 signature is a 50-gene subtype predictor that is used to identify the molecular subtype of breast tumours. It has recently been approved for use in the clinic (as the Prosigna diagnostic assay) to indicate long-term risk of recurrence in patients with ER+ breast tumours treated with endocrine therapy, in conjunction with other clinicopathological factors.

**Genomic Grade Index**
The Genomic Grade Index (GGI) is a 97 gene signature that is strongly associated with histological grade 1 and grade 3 breast tumours. It also stratifies histological grade 2 breast tumours into high and low risk of recurrence within five years and is currently being evaluated in clinical trials. The GGI is also able to identify better endocrine therapy-treated patients with very low risk of distant recurrence at 10 years, better than histological grade.

**ER Attractor**
Gene expression signatures can serve as surrogates of cancer phenotypes or signalling pathways. The ER attractor gene signature is a surrogate signature for the ER signalling pathway, and the top 50 ranked genes in this signature consist of numerous genes that are strongly co-expressed with ESR1, such as CA12, TFF1, XBP1, NAT1, GATA3 and FOXA1.
Figures 4A and B showed that the PAM50 signature did indeed stratify the New Zealand breast tumours into molecular subtypes (boxed in red), similar to that seen in the non-New Zealand cohort. For example, in both cohorts the basal-like breast tumours (boxed in red) were associated with a higher magnitude of the 1st PC (green) or higher inferred activity of the PAM50 signature and these tumours also tended to be histological grade 3 (Figure 4). Similarly, for both cohorts the luminal A tumours were mostly ER+, associated with a lower magnitude of the 1st PC (red) or lower inferred activity of the PAM50 signature, and tended to be of lower histological grade (Figure 4).

The expression profiles of 50 genes comprising the PAM50 signature are shown as heatmaps for (A) New Zealand and (B) non-New Zealand cohorts. The data are sorted by the magnitude of the 1st PC (principal component) of the PAM50 signature from low (green) to high (red). The PAM50 genes were hierarchically clustered using Euclidean distance and the Ward agglomeration method. Gene expression data were Z-transformed and expression levels mapped to colours on a red-black-green scale as indicated by the colour key at the top left of the plot. Shown above the heatmaps, indicated by multi-coloured solid bars are clinical and pathological information, with histologic grade, molecular subtype, ER status (IHC), PGR status (IHC), ESR1 mRNA expression (microarray), Ki67 mRNA expression (microarray; Ki67 protein is a marker of proliferation) and the 1st PC magnitude for the PAM50 signature genes for each tumour.

Figure 3: Guide to heatmaps.

Heatmaps are useful for visualising the expression (ie, the use) of a set of genes in a set of tumours. They show individual genes as rows and individual tumours as columns, with clinical features of each tumour such as ER status, tumour grade and molecular subtype indicated above the heatmap. For each gene in each tumour, heatmaps will show the level of expression (ie, the level of use) represented visually by a gradient of colours from red (high gene expression) through black (median gene expression) to green (low gene expression). In heatmaps the genes and the tumours are sometimes clustered based on their similarity, with the relationships between them summarised in the form of a tree diagram (dendrogram) at the top and/or side of the heatmap. Clinical and pathological information can be added to heatmaps, to visualise links between gene expression and clinicopathological information.
Analysis of the Genomic Grade Index (GGI) signature showed that this gene signature similarly separated both the New Zealand breast tumours and the non-New Zealand tumours into three molecular grades (boxed in blue) in Figures 5A and B. Similar to Figure 4, in both cohorts the basal-like breast tumours were associated with a higher magnitude of the 1st PC (green) or higher inferred activity of the GGI signature and these tumours also tended to be histological grade 3 (Figure 5).

The expression profiles of 97 genes comprising the Genomic Grade Index (GGI) are shown as heatmaps for (A) New Zealand and (B) non-New Zealand cohorts. The data are sorted by the magnitude of the 1st PC (principal component) of the GGI signature from low (green) to high (red). The GGI genes were hierarchically clustered using Euclidean distance and the Ward agglomeration method. Gene expression data were Z-transformed and expression levels mapped to colours on a red-black-green scale as indicated by the colour key at the top left of the plot. Shown above the heatmaps, indicated by multi-coloured solid bars are clinical and pathological information, with histologic grade, molecular subtype, ER status (IHC), PGR status (IHC), ESR1 mRNA expression (microarray), Ki67 mRNA expression (microarray; Ki67 protein is a marker of proliferation) and the 1st PC for the GGI signature for each tumour.

Analysis of the expression of genes associated with the ER attractor signature predominantly stratified both New Zealand and non-New Zealand cohorts of breast tumours by ER status, as indicated by both ER positivity by IHC and by expression of ESR1 mRNA (boxed in pink) in Figures 6A and B. As seen in Figure 6, almost all IHC ER-negative tumours were of the basal-like subtype.

The expression profiles of 50 genes comprising the ER attractor signature are shown as heatmaps for (A) New Zealand and (B) non-New Zealand cohorts. The data are sorted by the magnitude of the 1st PC (principal component) of the ER attractor signature from low (green) to high (red). The ER attractor genes were hierarchically clustered using Euclidean distance and the Ward agglomeration method. Gene expression data were Z-transformed and expression levels mapped to colours on a red-black-green scale as indicated by the colour key at the top left of the plot. Shown above the heatmaps, indicated by multi-coloured solid bars are clinical and pathological information, with histologic grade, molecular subtype, ER status (IHC), PGR status (IHC), ESR1 mRNA expression
(microarray), Ki-67 mRNA expression (microarray; Ki67 protein is a marker of proliferation) and the 1st PC for the ER attractor signature for each tumour.

We next evaluated how two of these prognostic signatures are associated with breast cancer patient prognosis in New Zealand women and in the non-New Zealand cohort. We analysed the 1st PC of genes comprising the PAM50 and GGI signatures. In both cases the PC magnitude was significantly associated with distant-metastasis events, as illustrated by Kaplan-Meier curves (Figure 7). These results showed that even with small numbers of New Zealand samples, both the PAM50 (Figure 7A) and the GGI (Figure 7B) signatures, were significantly associated with patient prognosis in the New Zealand and non-New Zealand cohorts. As described in the Methods, we assessed time to a distant metastatic event for up to eight years in New Zealand cohort (median follow-up time=4.43 years, n=106), and up to 12 years in the non-New Zealand cohort (median follow-up time=6.17 years, n=756). For this analyses, patients in each cohort (New Zealand and non-New Zealand) were divided into two groups based on the level of expression of each gene signature for both the PAM50 and GGI.

Figure 7: Kaplan-Meier curves showing prognosis of New Zealand and non-New Zealand breast cancer patients classified using the PAM50 and Genomic Grade Index signatures.
Kaplan-Meier curves were plotted using the 1st principal component (PC) of (A) the PAM50 or (B) the GGI signatures for patients from all treatment groups. Patients with tumours that have lower than the median 1st PC of either of the signatures (“low”) are shown as red curves (New Zealand n=53, non-New Zealand n=443), and patients with tumours that have greater than the median 1st PC of either the signatures (“high”) are shown as green curves (New Zealand n=53, non-New Zealand n=444).

Discussion

In this study, we have generated a gene expression dataset of 106 prospectively collected fresh frozen breast tumours from New Zealand women using standard RNA extraction methods and microarray analysis techniques. This dataset, with associated clinical data, is available for other investigators to use. Certain clinico-pathological parameters such as patient age, patient tumour size, lymph node status and proportion of histological grades differed significantly between this cohort and non-New Zealand cohorts (Table 1). However, when analysed at the level of mRNA gene expression, we observed that the New Zealand and non-New Zealand cohorts share multiple clinical associations with common gene expression signatures involving the ERα signalling pathway, the ERBB2 signalling pathway, proliferation-based pathways and distribution patterns of ESR1 mRNA expression between breast tumour subtypes.

Our study is the first to analyse the gene expression of breast tumours from New Zealand women. The gene expression data within our New Zealand cohort showed significant gene expression differences between histopathology-determined ER+ and ER- tumours, and ERBB2+ and ERBB2- tumours. The genes differentially expressed between ER+ and ER- tumours in our New Zealand cohort (Supplementary Table 2) consisted of genes that have already been described in the literature as differentially expressed in breast tumours dependent on ER status, such as PGR, TFF1, AGR2, CA12, ERBB4, FOXA1 and GATA3. Some of these genes are overexpressed in breast carcinomas (CA12, FOXA1, GATA3, TFF1, TFF3), some are co-expressed with the ER and PGR (EV1, SLC39A6, TBC1D9) and other genes have been shown to be GATA3 targets (DACH1, THSD4).

The genes differentially regulated between ERBB2+ and ERBB2- tumours included 17 upregulated probe sets, and represented 10 genes including ERBB2 itself, that were all located at locus 17q21 (CDK12, CWC25, FBXL20, GRB7, GSDMB, MIEN1, ORMDL3, PGF2 and PGAP3; Supplementary Table 2). These findings are consistent with other published studies that have shown that the genes on this particular locus, together with ERBB2 are both overexpressed and amplified in breast tumours, and breast cancer cell lines, when analysed using various methods: IHC, FISH, array comparative genomic hybridisation and gene expression. Many of these genes are also required for the proliferation and survival of ERBB2+ breast cancer cells.

Strikingly similar associations between each tumour’s pathology and underlying gene expression makeup were observed in a parallel analysis between our New Zealand patient cohort and a compiled international non-New Zealand cohort.

These similarities include multi-way relationships between the expression of breast cancer-associated gene sets (PAM50Genomic Grade Index and ER attractor), with ER status, histological tumour grade, ESR1 mRNA expression, molecular subtype and Ki67 mRNA (MKI67 gene; Figures 4–6). The expression of the Ki67 protein in breast tumours is a useful proliferation marker, and is used clinically to assess for prognosis and response to endocrine therapy in patients. Our analyses show that individually, the expression of MKI67 mRNA is associated with both histological grade and with the Genomic Grade Index, and inversely associated with ESR1 mRNA expression. We also noted similarities in expression patterns of ESR1 mRNA between the molecular subtypes in both cohorts (Figure 1) and similarities in patient outcome in both cohorts when stratified using the PAM50 and GGI signatures (Figure 7). However, despite this similarity between New Zealand and non-New Zealand tumours at the gene pathway level, a comparison between tumours of histological Grade 1 (n=11) and Grade 3 (n=53) in the New Zealand cohort failed to identify genes significantly enriched for proliferation-based functions, possibly due to the small cohort size.

We note that like many non-New Zealand breast cancer gene expression datasets, the New Zealand breast tumours were...
biased towards a larger size than the tumours commonly identified today by mammographic screening. Although tumour size appears not to strongly influence breast tumour gene expression patterns,\textsuperscript{57} it is possible that small breast tumours may have a different biology, which reduces their clinical progression.\textsuperscript{58} Therefore, additional prospective gene expression profiling studies using smaller tumours than were collected historically in New Zealand may be needed to fully understand the smaller and biologically different breast cancers detected by screening programs. As there might be difficulties in obtaining diagnostically spare tumour tissue from small breast tumours for research purposes, prospective studies that utilise tissue from biopsies such as fine needle aspiration (FNA) may need to be considered.

As previously mentioned, most of the studies on breast cancer in New Zealand have mainly focused on health system inequalities, various lifestyle factors, epidemiology and ethnic and socioeconomic associations for breast cancer risk. The small number of studies that have attempted to investigate any differences in breast cancer biology between the various ethnic populations such as between New Zealand Māori and New Zealand European women have been contradictory and inconclusive; albeit with small patient numbers for robust investigation.\textsuperscript{62–67} In the future, carefully designed and adequately powered genomic studies, using census-compatible ethnicity data may be able to exclude or confirm whether there are indeed biological factors associated with low breast cancer survival of New Zealand Māori women.\textsuperscript{68} However, given the past negative impact on Māori of some New Zealand genomic studies analysing ethnicity,\textsuperscript{66–71} future studies will require careful design to capture ancestry and ethnicity accurately, careful interpretation, and should be led by Māori researchers, to avoid inaccurate conclusions or misinterpretation.

In conclusion, in this study we describe the results of the first microarray analysis conducted on a large number of breast tumours from New Zealand women and make the data available for others to use. The clinical-gene expression relationships evident in New Zealand patients were consistent with published breast cancer gene expression data from outside New Zealand, highlighting the similarities between breast cancer in New Zealand and other regions. This consistency is reassuring, and it provides confidence that the gene expression data generated from our New Zealand cohort can be collated with other published, international gene expression cohorts and used in validation studies. With the introduction of internationally-developed genomic tests into the clinic in New Zealand, it is reassuring that breast tumours from New Zealand women exhibit similar molecular features to international cohorts, suggesting these tests should have the same relevance to clinical practices in New Zealand as they do overseas. Since the technically robust diagnostic test Prosigna (the PAM50 classifier) is clearly associated with ER+ patient prognosis in the clinic, our findings invite further investigation of the potential clinical utility of the Prosigna assay and related tests in New Zealand. We hope that future analysis of this New Zealand breast tumour data, potentially alongside non-New Zealand datasets, will provide valuable insights into breast cancer that ultimately improve patient outcomes in New Zealand.

**Clinical summary**

When analysed at the gene expression level, breast tumours from New Zealand and non-New Zealand cohorts share multiple clinical associations with common gene expression signatures involving ER status and ERBB2 status. These similarities include multi-way relationships between the expression of genes that constitute the PAM50 signature, Genomic Grade Index (GGI), and the ER attractor (an oestrogen pathway-associated gene signature), as well as similar distribution patterns of \textit{ESR1} mRNA expression between breast tumour subtypes and patient outcome using the PAM50 and GGI signatures.

Our findings suggest that breast tumours from New Zealand women exhibit similar molecular features to international cohorts, suggesting that genomic tests and gene expression signatures should have the same relevance to clinical practice in New Zealand as they do overseas.
Appendix

Supplementary Figure 1: Differentially expressed mRNAs between ER+ and ER- tumours in the New Zealand cohort.

Heatmap depicting significantly regulated mRNAs between IHC-determined ER+ and ER- tumours in the New Zealand breast cancer cohort (statistical cutoffs used for differential expression were adj-\( P \leq 1 \times 10^{-12} \) and absolute log fold change \( \geq 1.5 \)). ER+ tumours are represented by magenta bars above heatmap; ER- tumours are represented by light blue bars above heatmap. Probe sets were hierarchically clustered using Euclidean distance and the Ward agglomeration method (probe sets listed in Supplementary Table 2). Expression data for each gene was Z-transformed across tumours and expression levels mapped to colours on a red-black-green scale as indicated by the colour key at the top left of the plot.
**Supplementary Figure 2:** Differentially expressed mRNAs between ERBB2+ and ERBB2- tumours in the New Zealand cohort.

Gene expression in New Zealand breast tumours known by pathological analysis to be ERBB2+ (n=14) and ERBB2- tumours (n=48) was compared (adj-\(p=0.0001\)). ERBB2+ and ERBB2- tumours are represented by magenta bars above heatmap and light blue bars above heatmap respectively. Tumours and genes were hierarchically clustered using Euclidean distance and the Ward agglomeration method (gene probe sets listed in Supplementary Table 3). Gene expression data was Z-transformed and expression levels mapped to colours on a red-black-green scale as indicated by the colour key at the top left of the plot.
Competing interests:
Nil.

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Is cardiomegaly on chest radiograph representative of true cardiomegaly: a cross-sectional observational study comparing cardiac size on chest radiograph to that on echocardiography

Jane McKee, Katherine Ferrier

ABSTRACT

AIMS: To determine whether or not cardiomegaly identified on chest radiograph (CXR) is indicative of true cardiomegaly as determined using echocardiography (echo) as the gold standard tool, and therefore whether or not cardiomegaly on CXR should be investigated further.

METHODS: CXR and echocardiogram reports were reviewed for the presence of cardiomegaly in a population following non-ST segment elevation myocardial infarction (NSTEMI). Data was evaluated to determine whether cardiomegaly reported on CXR did indeed represent true cardiomegaly.

Exploratory analysis was undertaken to determine whether or not Body Surface Area (BSA) was a significant explanatory variable.

RESULTS: Data was collected for 244 patients. Thirty-nine were reported to have cardiomegaly on CXR, 22 of those also had cardiomegaly on echo, giving a true positive rate of 56% and a false positive rate of 44%. Fifty-five were reported to have cardiomegaly on echo, of which 33 (60%) did not have cardiomegaly identified on CXR. Sensitivity of CXR to identify cardiomegaly was 40% and specificity was 91% with a positive predictive value of 56% and negative predictive value of 84%.

BSA does not appear to be a significant explanatory variable for the discrepancy between the CXR and echo estimates of cardiomegaly.

CONCLUSIONS: In patients following an NSTEMI, the true positive rate of cardiomegaly identified on CXR is not too dissimilar to the false positive rate, thereby suggesting that reporting “cardiomegaly” based on CXR findings is inaccurate and rather reporting should simply focus on the cardiothoracic ratio and defining this as an enlarged cardiac silhouette rather than true cardiomegaly. In clinical practice the data indicates that the number needed to investigate to identify true cardiomegaly on echo is only two, thereby concluding that all patients post-NSTEMI with cardiomegaly on CXR should go on to have an echo, consistent with current national guidelines. As the study population were all post-MI, further study is necessary to evaluate whether this association holds true in a wider population.

It has long been accepted that a cardiothoracic ratio (CTR) greater than 50% on a posterior-anterior (PA) chest radiograph (CXR) is representative of cardiomegaly. An increased CTR on CXR has been associated with an increased rate of morbidity and mortality in middle-aged and elderly patients,1 with a linear association between increasing heart size and coronary heart disease risk factors as well as increased risk of mortality from coronary heart disease, stroke and all causes.2 Given this, individu-
als with such CXR findings are often referred for further investigations. Numerous studies have been undertaken to determine whether this association holds true, many producing negative findings.

In a resource-limited setting, therefore, it is important to determine whether or not further investigations are indeed warranted. Echocardiography is becoming a widely used tool as part of a workup for a multitude of conditions and complaints. It is therefore important that it is used appropriately to ensure patients truly requiring it are not subject to long waiting lists in order to receive appropriate assessment and management in a timely manner. In our district health board (DHB), we identified “cardiomegaly on CXR” as a reason for an increasing number of echocardiogram requests. Given the conflicting evidence as to whether or not an increased CTR on CXR is indeed representative of true cardiomegaly, we undertook this study to confirm or refute this hypothesis.

**Method**

The most likely patient group in our DHB that have both a chest x-ray (CXR) and an echocardiogram (echo) in close succession are patients who present with acute coronary syndrome (ACS), in particular NSTEMI. Therefore, all patients discharged with a primary diagnosis of “NSTEMI” were collated between 2011 and 2013. Patients were excluded if there was no CXR, no echo, or the timeframe between CXR and echo was greater than two months. If the CXR was an AP film and the radiologist was therefore unable to determine whether or not there was cardiomegaly, these too were excluded from the study. If the echocardiographic sonographer was unable to assess LV or RV size, these too were excluded.

The CXR reports of the remaining patients were reviewed for the presence of cardiomegaly, defined as a cardiothoracic ratio on the posterior-anterior view of greater than 50%. All CXRs were reported by experienced consultant radiologists. For those formal CXR reports where there was no comment on cardiac size, these were reviewed for the presence of cardiomegaly with an experienced consultant radiologist from the local department.

For each patient, their echo reports were then reviewed for heart size and deemed cardiomegalic if the left ventricle (LV) or right ventricle (RV) was reported as enlarged. Biplane echocardiographic measurements were undertaken by experienced cardiac sonographers with Australasian diplomas in echocardiography. The measurements and reports were then ratified by experienced consultant cardiologists. These measurements of chamber size and definitions of ventricular enlargement (ie, above the upper normal limits) were defined according to the internationally agreed guidelines and standardised to BSA. Data was recorded in a binomial fashion. Although left ventricular dilatation and right ventricular dilatation are two distinct conditions, for the purposes of this study no distinction was made between left and right ventricular enlargement, as either would warrant further investigation, and the question was simply to determine if CXRs were adequate at accurately identifying cardiomegaly, regardless of the ventricle or pathology involved.

BSA was recorded on the echo reports. The software calculated BSA using the Dubois formula, whereby BSA (m²) is calculated as weight (kg)⁰.⁴²⁵ x height (cm)⁰.⁷²⁵ x 0.007184.

Data was then evaluated to determine whether cardiomegaly reported on CXR did indeed represent true cardiomegaly, and therefore to determine whether cardiomegaly on CXR should indeed undergo further evaluation in the clinical context.

Exploratory analysis was undertaken to determine whether or not BSA was a significant explanatory variable for the discrepancy between the CXR and echo estimates of cardiomegaly in patients with NSTEMI.
Results

Four hundred and seven patients had a primary diagnosis of “NSTEMI” on discharge between 2011 and 2013 inclusive. Of these, 16 were wrongly coded and 163 were excluded for the reasons outlined above (Figure 1).

Basic demographics for the two groups are outlined below (Table 1). The mean ages of the study population and the population excluded were 67.2 and 71.7 years respectively (P=0.99).

Data was collected for the remaining 244 patients. Of those, 39 patients were reported to have cardiomegaly based on CXR, while 55 were reported to have true cardiomegaly based on the gold standard of echo.

Of those, 39 reported to have an enlarged heart on CXR, 22 (56%) did have true cardiomegaly based on echo, while 17 (44%) did not actually have true cardiomegaly (Table 2).

The kappa coefficient is 59%, indicating moderate agreement between these two tools.

<table>
<thead>
<tr>
<th>Study sample</th>
<th>Sample excluded</th>
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<tbody>
<tr>
<td>N</td>
<td>244 (62%)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>158 (65%)</td>
</tr>
<tr>
<td>Age (years) Mean (SD)</td>
<td>67.2 (12.6)</td>
</tr>
</tbody>
</table>
Using echo as the gold standard, CXR as a tool for measuring cardiomegaly was accurate in 80% of cases (95% CI 74.8–83.9%). The true positive rate was 56% with a false positive rate of 44%. The sensitivity of CXR to determine cardiomegaly was 40% (95% CI 27.0–54.1%) with a specificity of 91% (95% CI 86.0–94.7%). The positive predictive value was 56% (95% CI 39.6–72.2%) while the negative predictive value was 84% (95% CI 78.1–88.7%).

Of the 244 datasets collected, 206 had available BSA data. Of these, 163 (79%) did not have cardiomegaly on CXR, while 43 (21%) did have cardiomegaly. The mean BSA for these groups was 1.9 (SD 0.24 and 0.32 respectively). According to echo, 175 (85%) did not have cardiomegaly while 31 (15%) did have cardiomegaly. The mean BSA for these groups was 1.9 (SD 0.25) and 2.0 (SD 0.28) respectively.

Comparing these two groups, BSA does not appear to be a significant explanatory variable for the discrepancy between the CXR and echo estimates of cardiomegaly.

### Discussion

According to this study, the association between the CXR groups and the echo groups in reporting cardiomegaly in patients with NSTEMI is statistically significant, with BSA not appearing to be a significant explanatory variable in this population.

One hundred and forty-seven patients were excluded from the study. Twelve did not have a CXR. This is likely reflected in the rapid transfer of patients to a tertiary centre for angiography and/or percutaneous intervention. By the time they returned to the local facility for follow-up, an echocardiogram had been performed, rendering a CXR unnecessary. One hundred and eight did not have an echo. This is likely to reflect pragmatic local practice, where an echocardiogram would not have changed the patient's management, most commonly because the patients were more unwell or frail. There was no significant difference between the mean ages of the group studied and those excluded. Ethnicity and BSA data of the group excluded from the study were not recorded, however it is clear that there is a wide range of BSAs included in the study population (1.3–3.06m²) indicating that patients were not declined an echo based on size alone. Ethnicity likewise is not taken into account when a clinical decision is being made, so it is unlikely that there was any selection bias in the study.

Although 244 patient studies were analysed, representing a reasonable sample size, only 39 were reported to have cardiomegaly on CXR and it is this cohort that invokes the more interest as it is these patients who are referred on for further investigation. Taking just this cohort of patients then, the data shows that 22 (56% with 95% CI 40.4–71.6%) did go on to have true cardiomegaly, whereas 17 (44% with 95% CI 28.4–59.6%) did not have true cardiomegaly. Obviously with a much smaller sample size, the confidence intervals are much wider and clearly overlap quite significantly, suggesting that there may in fact be no significant difference between the two groups, but that cardiomegaly reported on CXR has roughly a 50% chance of indicating true cardiomegaly. This would suggest that reporting “cardiomegaly” based on CXR findings is therefore inaccurate and rather reporting should simply focus on the cardiothoracic ratio and defining this as an enlarged cardiac silhouette rather than a diagnosis of true cardiomegaly. In clinical practice, however, this can be interpreted as the number needed to investigate to pick up true cardiomegaly is two, therefore advocating that all patients post-NSTEMI with cardiomegaly on CXR should go on to have an echo. Current recommendations are that

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**Table 2: Comparing cardiomegaly on CXR with echo.**

<table>
<thead>
<tr>
<th></th>
<th>CXR</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>Y</td>
<td>Total</td>
</tr>
<tr>
<td>Echo</td>
<td>N 172</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Y 33</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>205</td>
<td>39</td>
</tr>
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Y = cardiomegaly; N = no cardiomegaly.
all patients presenting with NSTEMI should go on to have an echo, regardless of the CXR, therefore this does not actually add anything new in practice in terms of guidelines in this particular patient population.5

Our findings are similar to several previous studies. Satou et al looked at heart size on CXR as a predictor of cardiac enlargement by echocardiography in children (median age 5 years old). Sixteen out of 95 children were identified to have cardiac enlargement on CXR. The sensitivity of CXR identifying cardiomegaly by echo was higher than our study at 58.8%, but with a very similar specificity at 92.3%. The negative predictive value was a little higher at 91% with a similar positive predictive value of 62.5%. They similarly concluded that “the assessment of CE [cardiac enlargement] on CXR to predict CE by echocardiography has a relatively high specificity and negative predictive value, but a low sensitivity and positive predictive value.”6 And in another study by Biharas Monfared A et al, again a high specificity (84.5%) was identified with a poor sensitivity (34%).7

In comparison, in a study of 36 healthy children and 85 children with heart disease, Davidson et al concluded that cardiothoracic ratio and cardiac frontal area did not correlate with echocardiographic data but that such CXR estimates are unreliable.8 Clark and Coats suggest that a poor inspiration can give a spuriously raised cardiothoracic ratio, and the apparent size of the heart on a plain film can be very misleading. In their study of 91 patients, there was a poor correlation between cardiothoracic ratio and left ventricular size (r=0.32).9 Hammermeister et al looked at chest radiographs of 320 patients who had quantitative angiographic measurements of left ventricular volume. They found a poor correlation between cardiothoracic ratio and end-diastolic volume (r=0.29) and similarly poor correlations with other angiographic measurements of left ventricular overload. Interestingly they calculated a CTR of greater than 50% as having a specificity in the detection of left ventricular dilatation of only 41%.10

Schlett et al in a study of 45 patients likewise concluded poor correlation between CTR and end-diastolic left ventricular volume, mass or size, hypothesising that a possible explanation of such poor correlation may be related to the geometry of the thoracic shape and the right ventricle.11 Screaton in his editorial of the aforementioned paper, also hypothesised that other reasons for such poor correlation include the large cardiothymic shadow in infancy, the shrinking of the thoracic cage in later life, especially in elderly kyphotic females, congenital variations such as pectus excavatum and lung diseases such as emphysema.12

It may be, therefore, that our study produced a higher level of accuracy of the CXR at determining true cardiomegaly compared to these studies, due to our inclusion of right ventricular dilatation in the echocardiographic findings and definition of “true cardiomegaly”. One study by Baker et al looked at patients with structurally normal hearts on echocardiogram and then looked at cardiothoracic ratio on CXR and epicardial adipose tissue (EAT) by cardiac computed tomography (CCT) to determine whether enlarged cardiac silhouettes on CXR are being dismissed inappropriately. They concluded that an enlarged cardiac silhouette on CXR, despite a structurally normal heart on echo, can be caused by excessive EAT.13 This is interesting given the apparent lack of association in our study of increased BSA, which presumably would be present with increased EAT. Kaya et al looked at EAT volumes compared with BSA and other factors and found a positive correlation between BSA and EAT volume.14 Only three patients were excluded from our study due to no LV and/or RV measurements. These measurements were not obtained due to technical difficulties with the echocardiogram, but only two of these had a BSA indicative of obesity, therefore making bias in our results in this regard less likely. However, the fact that our population was post-infarct may explain the apparent lack in association.

Several studies have looked at the correlation between EAT and coronary artery disease and found positive correlations,13,14,15 although one Japanese study by Dagvasumberel et al only found this positive correlation in men.16 This was outside the scope of this study, as we were looking solely at echocardiograms requested purely for
cardiomegaly on CXR, not taking into consideration associated cardiac risk factors.

Limitations of the study

Given our patient cohort was a post-NSTEMI population and therefore by definition had known coronary artery disease, they may have been more likely to have cardiomegaly, therefore increasing the population prevalence in this study compared to the general population.

CXR reports were written by individual radiologists and reviewed for the presence of cardiomegaly. A potential weakness of the study was that the chest x-rays were not independently reviewed by two reviewers.

CXR reports were scanned for cardiomegaly based on the traditionally accepted cardiothoracic ratio of >50% on a PA film, and recorded as binomial data rather than actual cardiothoracic ratio. This has been a long accepted cut-off and we did not look at whether there was in fact a linear correlation between cardiothoracic ratio on CXR and cardiomegaly on echocardiograph and whether another cut-off value should be accepted. Likewise, ventricular enlargement on echo was recorded as binomial data rather than actual measurements, thereby not permitting a linear correlation to be made between echo and CXR measurements.

Although cardiac MRI may be the absolute gold standard for assessing cardiac size, with limited access, high cost and examination time, and problems of claustrophobia,12,17 in clinical practice echocardiography is considered the clinical standard and therefore was the tool used to determine “true cardiomegaly” in this study.

Conclusion

According to this study, in patients who have had a NSTEMI there is a statistically significant correlation between heart size on CXR and true heart size when measured by echocardiography. However, the data indicated that cardiomegaly on CXR was indicative of true cardiomegaly only 56% of the time. Therefore we can conclude that, in our population, a diagnosis of cardiomegaly cannot be made purely based on a cardiothoracic ratio on CXR of greater than 50%. In clinical practice, however, the number needed to investigate to identify true cardiomegaly on echo is only two, thereby concluding that all patients post-NSTEMI with cardiomegaly on CXR should go on to have an echo as per current guidelines. Further study is necessary to evaluate this association in a wider population.

Competing interests:
Nil.

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Health data research in New Zealand: updating the ethical governance framework
Angela Ballantyne, Rochelle Style

ABSTRACT
Demand for health data for secondary research is increasing, both in New Zealand and worldwide. The New Zealand government has established a large research database, the Integrated Data Infrastructure (IDI), which facilitates research, and an independent ministerial advisory group, the Data Futures Partnership (DFP), to engage with citizens, the private sector and non-government organisations (NGOs) to facilitate trusted data use and strengthen the data ecosystem in New Zealand.

We commend these steps but argue that key strategies for effective health-data governance remain absent in New Zealand. In particular, we argue in favour of the establishment of: (1) a specialist Health and Disability Ethics Committee (HDEC) to review applications for secondary-use data research; (2) a public registry of approved secondary-use research projects (similar to a clinical trials registry); and (3) detailed guidelines for the review and approval of secondary-use data research. We present an ethical framework based on the values of public interest, trust and transparency to justify these innovations.

Demand for data
Both the amount of data and demand for access to use this data for research are growing. These trends are apparent for health data and for other data collected by government, including welfare and social services data, justice, migration, education and taxation data. Better use of data underpins the New Zealand Government's 'social investment approach', which aims to increase the use of public sector data to drive innovation, save costs and better target services to people in need. It seeks to do this by applying rigorous, evidence-based investment practices backed up by big data.1

In the health context, secondary-use research involves the use of clinical data for purposes other than that for which the data was collected and which is therefore generally outside the original patient consent. This involves re-using, sharing and linking data to better understand New Zealand's health needs. This often involves access to initially identifiable health data for quality control purposes (ensuring the data is correct and complete). Researchers seeking to ensure accuracy and consistency of data from various datasets will require access to patient identifiers such as a National Health Index (NHI) number or personal patient information such as name and birthdate. There is increasing interest in establishing patient registries across the health sector and linking between registries, and from registries to other Ministry of Health (MOH) data. For example, research carried out by the New Zealand Treasury investigated the impact of eight different health conditions on the employment rates and incomes of working-aged New Zealanders.2 The study used the IDI, linking data from Inland Revenue, the MOH (including data on public hospital admissions and discharges, outpatient and emergency department treatments, pharmaceuticals dispensed, laboratory tests and enrolments at primary health organisations) and the Ministry of Social Development (MSD).

Broader context
There is increasing interest in the establishment of an expert national data ethics committee to oversee all significant data use in New Zealand, not just health data.
The collection and subsequent use of data must be undertaken with care. This has been recently highlighted by MSD’s ‘Data-for-funding’ policy, which required non-governmental organisations (NGOs) providing social services to disclose to MSD individual client-level data. The Privacy Commissioner’s report into this policy found the proposed data collection was excessive and inconsistent with privacy principles; and there was a lack of transparency about the purposes for which the data was being collected and for which it might subsequently be used. Roll-out of this data sharing program was delayed in April 2017 due to a security flaw in the information-sharing portal. The MSD situation provides a sober lesson regarding the need for data collection and use to consider both the interests of data subjects and stakeholder communities, as well as the needs of researchers and government.

The Integrated Data Infrastructure (IDI) includes de-identified microdata (information at the level of individuals) from government agencies, NGOs and surveys such as the Census. Researchers can access this data for economic, social or policy-related research. As of April 2017, there were 112 research projects listed by Statistics New Zealand which are using, or have used, data in the IDI, including projects for benefits and social services (12), business and employment (24), education and training (15), families and households (17), health and safety (24), housing (7), justice (4) and travel and migration (9).

Use of the IDI data requires approval from the Government Statistician according to the 5 Safes framework: safe people; safe projects; safe settings; safe data; safe output. While the ‘safe projects’ framework requires the Government statistician to sign off all research proposals and to ensure they are in the public interest, there is no independent ethics committee review of projects, no community input into determining what uses of data would be in the ‘public interest’ and no requirement for review of projects by Māori/iwi. We suggest that our proposals for the governance of health data could provide a useful pilot for such an expert data ethics committee.

In this paper we focus on the secondary-use of data in the health context and suggest ways in which the public interest may be served and trust preserved through expert oversight, public engagement and transparency. We propose an expert health-data research ethics committee, a public register of health-data research and expanded ethical guidelines for secondary-use.

Current New Zealand regulatory framework

The National Ethics Advisory Committee’s Ethical Guidelines for Observational Studies (NEAC Guidelines) permit some uses of health data without independent ethical review. Linking data for observational epidemiological studies is allowed without consent, provided that identity is only disclosed for linking purposes (NEAC guideline 8.11); and linking for audit and related activities needs no justification to an ethics committee provided that it is part of high-quality health care (NEAC guideline 8.12).

Access to potentially identifiable patient information for research generally requires approval from an approved research ethics committee. There is limited instruction available in the NEAC Guidelines for when ethics committees can grant access to identifiable health information:

NEAC guideline 6.43 provides that:
Access to identified or potentially identifiable data for research (without consent) may be justifiable when:

a) obtaining consent would cause either:
• unnecessary anxiety
• prejudice the scientific value of the study; or
• it is impossible in practice due to the quantity or age of the records; and
b) there would be no disadvantage to the participants or their relatives or to any collectivities involved; and
c) the public interest in the study outweighs the public interest in privacy.

The current regulatory approach is insufficient in a number of ways. Health and Disability Ethics Committees (HDECs) and...
other research ethics committees primarily review interventional or observational clinical research and some have questioned whether such committees have sufficient relevant expertise to review sophisticated data linkage projects. The current regulatory framework also lacks specificity. For example, there is no definition of ‘public interest’ or guidance on when consultation with Māori is required. And finally, the review system is fragmented, making it near impossible for the public, media or the research community to track who is accessing patient data and for what purposes.

Current regulations to guide the ethical use of health data continue to focus predominately on consent. Individual-level interests such as control of health information, confidentiality, privacy and personal disadvantage are well-articulated. Collective values such as public interest, solidarity, trust, equity and participation have been comparatively underdeveloped in the data governance literature and especially in research regulations and guidelines. This is true both in New Zealand and internationally. Consider the focus of NEAC’s primary guidelines on such matters, Guideline 6.43—it is first and foremost about consent. Public interest and potential disadvantage to communities are appealed to here but there is no definition of these concepts or guidance regarding how they should be interpreted.

A ‘consent’ approach is insufficient in the era of population-level research and big-data projects. Many current and future uses of health data—including population-level data analytics, predictive risk modelling and diverse data-sharing arrangements—make patient consent impractical, if not impossible. A framework that focuses primarily on consent is therefore inadequate to provide substantive guidance on which uses of health data are acceptable.

To resolve these challenges we propose the use of a framework based on three core values which should guide the secondary-use of patient data. We present three suggestions for developing the governance framework for health data research in New Zealand that is guided by these three values.

Core values

In standard clinical research, patient consent plays a major role in legitimising the research. As we have noted, there are a number of circumstances in which patient consent is not currently required for the secondary-use of health data. However, other values can legitimise research in the absence of consent: public interest, trust and transparency.

1. Public interest

The core value that should guide secondary use of health data is public interest. Ethics committees are acting as stewards for a public resource and need to ensure that those accessing the resource are likely to produce knowledge that will benefit the public. The current ethical guidelines in New Zealand require that research be in the public interest, and recognise that public interest includes both research and privacy interests, but do not define the concept further. In relation to data use, public interest (also sometimes referred to as public or common good) relates to collective interests such as national research priorities, equity and public access to the research results. We would argue for example that a public interest requirement is met when research addresses neglected diseases, health conditions with high social cost and/or sources of health inequality between different groups. Public interest may be undermined by research that involves the risk of surveillance of specific populations, individual or group discrimination, stigma and predictive privacy risk (where privacy invasions occur through inference rather than direct collection of personal data). The relative presence of these risks in a research project can decrease the public interest.

In a pluralistic society with diverse conceptions of wellbeing, a community engagement process can help answer the question of which data uses are in the public interest. Community engagement is especially important in the absence of individual consent.

Indigenous communities are increasingly calling for sovereignty over their data, including genetic material. In New Zealand, Te Mana Raraunga (the Māori Data Sovereignty Network) is advocating for Māori data...
sovereignty, arguing that data innovations are occurring in the absence of a robust Māori data governance partnership that is representative, enabling and provides clear lines of accountability back to Māori/Iwi. Te Mana Raraunga have argued that Māori data (including data about Māori, data used to describe Māori collectives and data about Te Ao Māori) are a living tāonga and should be subject to Māori governance. How to operationalise these sovereignty claims and how to ensure that data use serves the interests of Māori are complex questions that require more attention across the academic, government and private sectors.

2. Trust

There is widespread agreement on the importance of trust in medical research. Studies have shown that trust is fundamental to the successful conduct of research and is conditional. The Data Futures Partnership (DFP) has emphasised that maintaining trust is vital to ongoing data innovation and has warned that public trust in the data-use ecosystem is tenuous and, once lost, may be hard to restore. Trust is multi-dimensional, complex and contextual. Nevertheless, common qualities of trustworthy institutions include:

- integrity—the institution is fair and just;
- dependability—the institution will do what it says it will do; and
- competence—the institution has the ability to do what it says it will do.

It is essential to ensure that the public has adequate trust in the governance of secondary-use research, especially given the absence of individual consent. Both researchers and research ethics committees must demonstrate trustworthiness. Much of the trust that study participants place in researchers is associated with the reputation of researchers as a professional group, with associated standards of conduct and systems of independent oversight and review.

We believe that HDECs in New Zealand have built a reputation for integrity and dependability. We question however whether committees primarily designed to review interventional clinical research have the necessary competence to review complex data research. Ethical issues relating to the secondary-use of data for health research raise unique concerns which differ substantially from those raised by interventional research. Data research moves inquiry away from familiar categories of research harm, such as physical pain or psychological distress, to other categories such as surveillance, discrimination and stigma. Rapid advances in data research involve both a change in scale of the analytic tools—speed, capacity, continuous generation—as well as a change in the relationality, flexibility, re-purposing and de-contextualisation of data.

Internationally, calls are being made for “algorithmic literacy, transparency and oversight” because of the challenges of algorithmic biases. Algorithms reflect the biases of programmers and dataset, for example regarding race, gender and other variables related to social justice. Algorithms are biased towards what their writers understand to be ‘normal’. For example, a search for images of ‘professor’ results in pictures of white males, and to find images of women or people of colour, the search algorithm requires the user to include ‘woman professor’ or ‘Asian professor’; thereby reinforcing the assumption that a real professor is white and male. Overseeing data research requires specific expertise in information technology, computer science and topics such as data security, algorithms and data privacy. Appropriate oversight also requires specialist understanding of the risks data-harnessing may pose, including security failures and the wide-ranging ramifications for privacy, even absent security breaches. Ethical research with data therefore requires review by a committee which includes data specialists as well as lay members.

3. Transparency

Key features of transparency include visibility, accessibility and honesty. New Zealand has a strong track record of transparency in the context of HDEC ethical review—all meetings are open to the public and minutes are published on the website. This degree of transparency is not reflected in other countries.
Transparency helps facilitate community engagement because it allows other researchers and members of the public to see what is being done with patient data and by whom. In this way, transparency can help ensure accountability, secure trust and maintain the social licence for data research in the absence of patient consent.

Our three core values—public interest, trust and transparency—are consistent with the New Zealand government’s commitment to transparency, including the Declaration of Open and Transparent Government, which proclaimed that high value public data must, inter alia, be open, trusted and readily available. Our core values are also consistent with the four principles developed by the DFP of value, inclusion, trust and control.\textsuperscript{12}

**Data governance needs**

In light of these core values, we propose three recommendations for revising health-data governance in New Zealand.

1. **Guidance**

   We propose developing expanded guidance on the ethical uses of patient data in the absence of consent. This could consist of new independent guidelines or additional chapters within existing NEAC guidelines. The guidance should focus on defining the criteria for public interest and articulating the potential benefits and harms regarding secondary-use data research. Expanded guidance should consider use of patient data by academic researchers, NGOs, commercial or for-profit entities, public-private partnerships and government agencies. Research justified on the grounds of public interest should also be made publicly accessible and any power of commissioning agencies to limit the publication of results should be considered.

2. **Independent expert review**

   We propose establishing a specialist HDEC that reviews applications for secondary-uses of health data. The committee membership should include expertise in computer science, information technology, data ethics, privacy, as well as patient and community advocates; and should follow current HDEC policy and the HRC Guidelines regarding lay, gender and Māori representation.\textsuperscript{18,19}

   An alternative model would be to increase the data expertise on the existing four HDECs. However, given there are only eight members per HDEC, it would be hard to achieve the degree of expertise we advocate across all four committees, without either displacing existing categories of expertise or increasing the size of the committees. Our preference is therefore for a specialist HDEC committee but we acknowledge there are different ways of achieving the desired expertise during the review process.

   The Privacy Commissioner has spoken about the possibility of having an independent body to promote the ethical and safe use of data,\textsuperscript{20} as has the DFP which noted there is no independent trusted forum for an inclusive conversation on data use.\textsuperscript{21} Specialist ethics review committees are already part of the New Zealand ethical landscape—there is an Ethics Committee on Assisted Reproductive Technology and a Gene Technology Advisory Committee.

   There are four national HDECs and, as of 1 May 2017, none have a member described as having expertise in computer science or statistics; although some of the clinical research members will likely have expertise in data analytics due to their personal research programs.\textsuperscript{22} A specialist data ethics committee could develop expertise in judging issues such as public interest and potential population-level harms from the misuse of data, and may also provide greater consistency and predictability in the review process.

   Building on the HDEC model makes sense as this: (1) would prevent the siloing of a health data ethics committee outside the broader health research ethics review structure because Chairs of the HDECs meet regularly and discuss procedural and policy matters; and (2) leverages existing secretarial support services at the Ministry of Health. In addition there would be the advantage of a shared line of public accountability, statutory empowerment and a common regulatory framework.

3. **Registry**

   Third, we propose the development of a New Zealand data research registry that is public, searchable and based on the structure and content of clinical trials registries such as the Australian New Zealand Clinical Trials...
Registration should be a condition of receiving access to health data without consent. We have argued above that one strength of the New Zealand research ethics ecosystem is its relative transparency, but more needs to be done.

While HDEC minutes are published online, the applications are not categorised other than to indicate the title of the study, the principal investigator, the sponsor and the ‘clock-start-date’. To identify secondary-use data research studies, interested parties must read the full minutes of each meeting. The lists of applications in HDEC Annual Reports include a description of whether the study is observational or interventional, but there is no further categorisation and, at the time of writing, the Annual Reports are only available until 2013. The absence of any detailed and consistent coding of health research applications makes it difficult to determine how many data projects are occurring using patients’ health data, which agencies or researchers are accessing the data, what sorts of research questions are being pursued and where and when research results are being published. A core justification in the NEAC guidelines for approving access to patient information without consent is ‘public interest’. We argue that public interest requires public transparency.

A registry similar to the ANZCTR with settled and mandatory criteria with respect to data content, quality and validity, the assignment of unique identification numbers and advance searching capabilities would dramatically improve the transparency of secondary-use data research and its accessibility. A public registry is especially important in relation to tracking data research (as opposed to other observational research) because much data research does not have specific patient consent. A registry therefore provides a mechanism for the public to see who has access to their data and for what purposes.

### Conclusion

The governance framework for secondary-use health data research in New Zealand is piecemeal and underdeveloped. These deficiencies cannot be remedied by the established clinical research framework, which is not fully suited to dealing with the complexities raised by secondary-use data research. Our proposals to establish a specialist HDEC and a data research registry, combined with specific and expanded guidelines, would provide a robust governance framework for the secondary-use of health data, reflecting the core values of public interest, trust and transparency.

### Summary of key arguments

- The governance framework for secondary-use health data research in New Zealand is piecemeal and underdeveloped.
- Data use should be governed by the values of public interest, trust and transparency.
- An ethical framework focused on consent and individual control provides insufficient guidance for population and big data studies.
- We need expanded guidelines on the ethical uses of health information without consent that focus on collective benefits and harms.
- A specialist health data ethics committee would provide expert oversight and improve consistency of review.
- A registry of secondary-use health data research would increase accountability and transparency regarding the use of patient health data.
Competing interests:
Angela Ballantyne and Rochelle Style are current members of the Health and Disability Ethics Committees in New Zealand.

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URL:
17. Personal communication to Angela Ballantyne from research ethics experts in Australia, United States, Sweden, Amsterdam and the United Kingdom.


22. Details of the members of each of the four HDECs are available from: http://ethics.health.govt.nz/about-committees

Iron-pill inhalation
Matlawene J Mpe, William Diprose

Aspiration of iron tablets is rare but constitutes a medical emergency. It can induce severe and potentially fatal chemical injury to the tracheo-bronchial tree. Prompt recognition and management will minimise both the acute and chronic complications. The diagnosis can be challenging; symptoms and signs are nonspecific. Urgent airway examination is essential.

Case report
A 50-year-old woman presented with sudden-onset cough, chest pain, wheeze and vomiting. She had just taken ferrous sulphate with her evening meal and was concerned it might have gone down the “wrong way”.

Her examination was unremarkable, including normal vital signs and respiratory examination. Her chest x-ray (CXR) was normal. She was observed overnight and discharged with advice to see her general practitioner (GP) if symptoms deteriorated.

She re-presented four days later with continued wheeze and a hoarse voice. Her examination was again unremarkable except for new bilateral wheeze. Her CXR showed minor atelectasis around the horizontal fissure. She improved following a single dose of 40mg prednisone 2.5mg nebulised salbutamol and was discharged with a further three-day course of prednisone.

Eight weeks later she was referred to the respiratory service by her GP with persistent symptoms. She proceeded to bronchoscopy where rusty secretions emanating out of the right upper lobe were noted; with a denuded, friable and easy bleeding right upper lobe mucosa and necrotic debris (Figure 1). No tablet was seen.

Pathologic examination of the bronchial washings showed acellular pigmented material that stained strongly positive for iron with Perl's stain (Figure 2). A follow-up bronchoscopy 12 weeks after her original injury found almost complete occlusion of her right upper lobe. Subsequent rigid bronchoscopy and attempts at dilatation of the right upper lobe bronchus was unsuccessful. She remains asymptomatic but with permanent atelectasis of the right upper lobe.

Figure 1: Bronchoscopic view of the abnormalities in her right upper lobe.
It is estimated that 7% of all foreign body aspirations are medicinal pills.1 Pill aspiration represents a distinct clinical entity, requiring a high index of suspicion for a precise and timely diagnosis. Occasionally, serious and potentially life-threatening complications involving the airways can occur.2 The mechanism of airway injury depends on the properties of the pill; for example, inert tablets tend to have less severe complications that are easily dealt with by mechanical extraction.1

Iron tablet aspiration is the most commonly described, likely due to its severe and lasting airway effects.2 Iron tablets are chemically active, disintegrate quickly and rapidly dissolve into the airway mucosa. The suggested mechanism of injury is local production of cytotoxic oxidants and free radicals from oxidation of ferrous sulphate.3 The consequences can range from airway mucosal inflammation and tissue necrosis to bronchial perforation, haemoptysis, lobar consolidation and permanent airway stenosis.4,5,6 A case requiring lobectomy and a fatality have been described.7,8

Symptoms of aspiration are nonspecific and a good history and a high index of suspicion is essential. Chest radiographs are of limited diagnostic value.

Endoscopic airway examination is essential for diagnosis and evaluation of complications.1,3 An intact form of the ferrous sulphate tablet is rarely found. Histological examination of bronchial washings or biopsies may stain for ferric iron.9

With prompt tablet removal and supportive measures such as steroids, a favourable outcome can be expected even though the effectiveness of steroids in reducing airway complications has not been established.4,6 After the initial evaluation and management, surveillance bronchoscopy is recommended to identify complications in a timely manner when endobronchial therapies (bronchoplasty, stenting, etc) can be effective.2

Figure 2: Acellular pigmented material observed in the bronchial washings, which stained strongly positive for iron with Perl's stain.
Competing interests: Nil.

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I note with some alarm the debate about a proposed third medical school, purported to operate on quite different lines to the other two New Zealand medical schools and to be based in the Waikato.

The problem prompting the perception of a need for a third medical school is that of a lack of general practitioners in rural New Zealand, however it is a large assumption that doctors registered by the Medical Council of New Zealand, as the graduates of the proposed Waikato School presumably would be, would choose general practice over another career. Choice of medical school is different from choice of specialty.

The proposal appears not to take into account a steady increase in medical student numbers in Auckland and Otago over the next few years. The drive by successive governments to increase the numbers of Māori and Pacific students cited in the proposal for a third medical school conveniently skips over the efforts made by Auckland and Otago Medical Schools in that direction. Taking away Waikato DHB placements from Auckland medical students will do nothing to increase the overall number of doctors graduating. It has potential to be a zero-sum game—with resources diverted from one medical school to another, and no guarantee of a bigger total spend on medical education. Cui bono, except for Waikato University (which would stand to gain tens of millions of dollars per year)?

A lot of commentators have argued from statistics, logic and first principles when discussing this topic, and this is appropriate for those with a vested interest in the decision such as representatives of the existing medical schools. However, I believe that a full discussion of the proposal also needs to focus on Waikato DHB itself.

As a former employee of that DHB, and a more than casual observer of media reports regarding the DHB, I have a few observations to make. Waikato DHB is not good at retaining doctors they have trained, and frequently employs unknown overseas doctors rather than people who have been trained there. This is something I observed at first hand for several years as a trainee in psychiatry at Waikato DHB. Furthermore, the DHB is not sufficiently committed to the postgraduate training of doctors to maintain uninterrupted the training programme in obstetrics and gynaecology, another crucial specialty. The hospital’s accreditation for orthopaedic surgery training now hangs in the balance, and the Medical Council of New Zealand has criticised the training it gives to trainee interns.

Before a lot of taxpayers’ money is given to a new school to compete with established, quality medical schools, I would suggest that it work towards retaining a greater percentage of doctors who train there and demonstrating its commitment to postgraduate training of doctors. A rational step would be for the DHB to create dedicated rural roles, properly incentivised, for those interested. Taking a greater role in the training of GPs, for instance by supporting doctors to undertake training in the hospital system with credits towards the fellowship of the Royal New Zealand College of Urgent Care, for instance, would be far less costly and likely far more successful than the establishment of a competing medical school.
school, which would inevitably detract from the number of training places available to undergraduate medical students, essentially recreating a problem that has already shown up at the postgraduate level, where appropriate training places for specialist training programmes create a significant bottleneck. The government would be very wise to question the DHB's ability to train and retain doctors at the postgraduate level before entrusting them with the fate of a significant number of the nation's medical students, and I certainly hope that this is part of the discussion on the topic in future.

Competing interests:
Nil.

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URL:
New Zealand gastroenterologists’ perceptions, knowledge and experience of exclusive enteral nutrition to treat Crohn’s disease
Catherine L Wall, Richard B Gearry, Andrew S Day

Exclusive enteral nutrition (EEN) is a nutritionally complete liquid diet which excludes usual foods and fluids, and is recommended to induce disease remission in children with active Crohn’s disease (CD). The prescription of EEN, instead of corticosteroid treatment, by North American physicians has been shown to be influenced by their previous exposure to, and experience with, the treatment. EEN has not been widely used with, or recommended for, adults with active CD, however a New Zealand survey of 35 adults with CD attending out-patient appointments found that adults were interested in trying EEN as an alternative to corticosteroids. Given there is some patient interest in the treatment, we wanted to understand New Zealand gastroenterologists’ perceptions, knowledge and experience of EEN in the treatment of children and adults with active CD.

Methods
New Zealand gastroenterologists were emailed a web-based survey link from the New Zealand Society of Gastroenterology executive officer during July and August 2015. The survey questions were adapted from a survey sent to North American physicians to understand their attitudes and use of enteral nutrition to treat paediatric CD.

Results and discussion
The survey was sent to 110 New Zealand Society of Gastroenterology members, including scientists, up to 20 surgeons, 15–20 gastroenterology trainees and gastroenterologists. The survey was completed by 42 (38%) physicians, including 12 gastroenterology registrars.

The majority (90%) of New Zealand physicians were aware of EEN as a treatment for active CD and perceived that the treatment had various benefits, including avoidance of corticosteroids, improvement in patient nutritional status and growth improvements in children. Twenty-nine (68%) physicians had previously used EEN to treat active CD disease. In the previous 12 months, all six paediatric gastroenterologists reported that EEN was often or always considered as a treatment option for paediatric CD, whereas physicians who managed adults with CD rarely or sometimes considered using EEN for active CD. One-third of physicians reported that they were most likely to consider EEN for adults with newly diagnosed CD and mild disease, and 12 (33%) physicians caring for adult patients had used EEN with an estimated 1–8 patients in the last 12 months.
Common reasons that physicians had not used EEN were that in clinical studies patients struggle to maintain treatment adherence (65%), physicians had limited experience using EEN (41%) and patients had limited social support (33%). To increase their likelihood of using EEN, physicians required more scientific evidence of the efficacy of EEN in the treatment of adults and, alongside further evidence, clinical practice guidelines in conjunction with better multidisciplinary support.

New Zealand physicians perceived that the main disadvantage of EEN treatment was the need for treatment adherence. Other disadvantages included the need for adequate social support and a multidisciplinary approach. In North America, paediatric physicians were more likely to recommend EEN to their patients if they had worked/trained in a unit(s) that commonly used the EEN.2 Half of the New Zealand physicians had previously worked in a unit where EEN was used to treat active CD, and eight (19%) currently worked in a unit where the treatment was regularly used. Despite physicians believing that EEN has many potential benefits, the limited exposure of physicians to EEN treatment in clinical practice may impact their use of the treatment.

There are limitations with the results of this survey. The survey was sent to consultant gastroenterologists and gastroenterology trainees, and 12 (29%) of the respondents were trainees, therefore their experience with EEN may overlap with that of the consultant the trainee was working alongside. The results may overestimate the usage of EEN with adult patients for two reasons: more physicians with an interest in nutrition therapy may have completed the survey, and six of the 12 physicians who had used EEN with adult patients were from Canterbury where a clinical trial of EEN in adults with active CD had been conducted for the preceding 18 months.

Many adults with CD are interested in using EEN as an alternative to corticosteroids and there is increasing evidence of its efficacy in selected adults with active CD.4–6 The 2014 ECCO/ESPGHAN paediatric CD guidelines provide physicians with more practical guidance on the use of EEN with children.7 Such guidelines may be helpful for physicians and multidisciplinary teams working with adults interested in using enteral nutrition therapy.

Competing interests: Nil.

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Smokefree signage at New Zealand racecourses and sports facilities with outdoor stands

George Thomson, Nick Wilson

ABSTRACT
Smokefree signage is crucial to the implementation of smokefree policies for outdoor venues and for facilitating smoking denormalisation. Such signage helps to communicate the expected norms for not smoking at venues. Therefore, we aimed to identify such signage at racecourses and sports facilities that had outdoor stands. We surveyed the entrances of 25 racecourse and 25 sport facilities with outdoor stands, across New Zealand. There were smokefree signs at the main entrances of 40% of the sports facilities with outdoor stands, and at 16% of the 25 other entrances. None of the horse/greyhound racecourses had smokefree signage at any of their entrances.

Outdoor sports facilities with stands are a potential priority area for smokefree policies, given that people can be in relatively close proximity to each other and so can be exposed to secondhand smoke. The large number of attendees at stadium-related events (up to 50,000) also suggests that making these settings smokefree may contribute to denormalising smoking, which helps quitting and reduces uptake.1,2 The importance of sports within communities and within at-risk groups, coupled with the numbers of people, could provide both good ‘reach’ and strong impact for the intervention.

We found little research on the smokefree status of outdoor stadiums,3–6 with only one study using field observation of signage,3 and no relevant New Zealand research. Because there are smokefree policies for only some sports-related venues in New Zealand, and signage is crucial to the implementation of smokefree policies for outdoor venues, we aimed (i) to identify the extent and nature of smokefree signage at racecourses and sports facilities that had outdoor stands, and (ii) to pilot simple, replicable research methods for such studies. We also aimed to assess the utility of Google Street View (GSV) for studying smokefree signage at these type of settings. There is growing evidence for the value of GSV in such studies as per a recent review.7

Methods
Purposeful sampling was used to select sports facilities and racecourses (all having stands) from a range of urban and small town settings across different regions in New Zealand, so as to sample a wide variety of situations. We conducted field observations at 25 sports facilities (in 14 local authority areas) and 25 racecourses (April 2016 to April 2017). The sampling covered 23 out of the 67 local government districts in New Zealand (34%). The facilities were in 11 cities (over 40,000 population) and 12 small towns, from Gisborne to Southland. On these visits, we photographed any smokefree signage within 10 metres of all the entrances used by pedestrians or those driving to parking sites within the grounds. We counted the number of such signs per entrance type (main/other), and examined the signs found for the extent of the smokefree policy (stand only, or whole grounds), the placing of smokefree policies within other information, and the wording and language used.
Initial observations were made jointly by both authors to standardise methods and then by the authors separately. Both observers had previous experience in studying both smokefree and alcohol signage. So as to also test the usefulness of GSV, the same facilities were subsequently examined using GSV, with the field observations being treated as the ‘gold standard’ for comparisons (as per previous work).

**Results**

The field observations found that 40% (10/25) of this sample of sports facilities with outdoor stands had smokefree signage at their main entrances. The mean number of smokefree signs per main entrance was 0.72 (range: 0–5 signs). Only 16% of the 25 other entrances (4/25) at these facilities had smokefree signage (mean = 0.36, range 0–3). Four of these facilities were designated as smokefree throughout (ie, both grounds and stands). In two settings, the smoking restriction seemed to be about protecting the track or the artificial turf (see Figure 1 in the Appendix). Smokefree signage in Te Reo Māori was rare (see Figure 2 in the Appendix for an example).

None of the horse/greyhound racecourses (0/25) had any outdoor-place smokefree signage at any main entrances or any of the other entrances (0/14). A notice at one specified that function rooms were smokefree, but smoking was allowed outdoors (see Figure 3 in the Appendix).

The utility of GSV was poor for the smokefree signage at the main entrance of the sports facilities (eg, 10% sensitivity, albeit 93% specificity, see Table 1). The “missed” smokefree signs at main entrances on GSV were due to these being in small print, being too far away from the road or the GSV image preceding the smokefree sign being put up (ie, the GSV date stamp was always at least a year before the field observations, median: March 2015; range: December 2009 to August 2015). However, it was possible to view inside the grounds of one of the sampled facilities (in a ‘footpath view’ of GSV) and see smokefree signs within the seating area.

Many different sign designs were found. Of the sports facilities in 14 local authority areas, only two (in Upper Hutt and Wairoa) used signs from the former Health Sponsorship Council as part of their signage (see Figure 2 in the Appendix). The quality of the smokefree signage varied. For instance, sometimes there were words about prohibiting smoking included among a long list of activities not permitted in the facility (eg, Figure 4 in the Appendix). There was often a stark contrast between smokefree signs and the very much larger and bolder signage prohibiting taking alcohol onto the premises at the entrances to both sports facilities and racecourses (eg, Figure 5 in the Appendix for an example regarding alcohol). The degraded surface quality of some smokefree signs may also have reduced their impact (eg, Figure 6 in the Appendix). Some signs contained ambiguous wording, for instance in Figure 7 in the Appendix “we encourage you to comply with this request”.

**Table 1:** Sensitivity, specificity and predictive values of using Google Street View (GSV) relative to field observations of smokefree signage at the main entrances of the sports facilities with outdoor stands.

<table>
<thead>
<tr>
<th>Performance characteristic of GSV vs field observations</th>
<th>Smokefree signs seen at main entrance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives (number) [A]</td>
<td>1</td>
</tr>
<tr>
<td>True negatives (number) [B]</td>
<td>13</td>
</tr>
<tr>
<td>False positives (number) [C]</td>
<td>1**</td>
</tr>
<tr>
<td>False negatives (number) [D]</td>
<td>9</td>
</tr>
<tr>
<td>Total (number)</td>
<td>24</td>
</tr>
<tr>
<td>Sensitivity [A/(A+D)]</td>
<td>10%</td>
</tr>
<tr>
<td>Specificity [B/(B+C)]</td>
<td>93%</td>
</tr>
<tr>
<td>Positive predictive value [A/(A+C)]</td>
<td>50%</td>
</tr>
<tr>
<td>Negative predictive value [B/(B+D)]</td>
<td>59%</td>
</tr>
</tbody>
</table>

*That is within 10 metres within any direction from the main entrance, with the status of hard-to-read signs being assessed in terms of the balance of probabilities (for being a smokefree sign or not). One main entrance was not visible, hence a total of 24 settings.

**There is no doubt that the GSV image showed a smokefree sign in this ‘false positive’ case, but it was not visible in the field observations, which were used as the ‘gold standard’. Probably the sign had subsequently been removed or fallen down prior to the field observations.
Discussion

The results for this purposeful sample indicate the likely scope for the increased implementation of smokefree policies by local authorities, which typically own the sports facilities. There are also opportunities for health promoters and the wider health sector to work with horse racing clubs on smokefree policies. The introduction of a smokefree policy at the Hastings racecourse for one day of racing indicates one avenue for this.13

However, it would be more efficient and effective to amend the Smoke-Free Environments Act to require all venues with outdoor seating to be smokefree (as per the efficient and successful approach taken for smokefree school grounds),14 and to require signage of minimum size and quality. One option to ensure quality would be a standard sign that is noticeable, easily comprehended and tested to ensure a positive response. As Māori are more likely to smoke than other groups, signs that include Te Reo Māori could be considered, as some Māori may respond more positively to such signage.

The utility of GSV for studying smokefree signage at the sports facilities was poor (10% sensitivity), and substantially poorer than previous studies of smokefree signage at schools,8 and at public hospital campuses.9 Reasons for this are probably the legal requirement for prominent signs at school entrances and the typically large size of the signs at hospitals in New Zealand (which make them easily visible on GSV). Nevertheless, the situation for studying signs at sports facilities might improve with the expansion of the “footpath view” on GSV.

The purposeful sample means that the results cannot necessarily be generalised to all New Zealand sports facilities and racecourses with stands. We also recognise that signage at some sports facilities may also have changed during the data collection period, given the increasing interest by local governments in advancing smokefree environments.

Appendix

Figure 1: Smokefree sign to protect sportsground playing surfaces.
**Figure 2:** Example of use of Te Reo in smokefree sign (Wairoa District Council).

**Figure 3:** Racecourse notice regarding smoking.
Figure 4: Example of sign that includes ‘no smoking’ as part of a list.

Figure 5: Example of large size of alcohol-related notice.
Figure 6: Example of poor quality smokefree sign.

Figure 7: Sign containing ambiguous wording about the smokefree status of the facility.
REFERENCES:


Competing interests:
Nil.

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URL:
Risk of major congenital malformations in relation to maternal overweight and obesity severity

Does the risk of congenital malformations increase with maternal and overweight obesity severity? This is the proposition that is evaluated in this population-based cohort study.

Data derived from nationwide Swedish registries included information about more than 1.2 million liveborn singleton infants. 3.5% of them had some major congenital malformation; the most common subgroup was congenital heart defects. The incidence of the defects was correlated with the maternal body mass index.

The conclusion was that the risks of any major congenital malformation progressively increase with maternal overweight and obesity severity.

*BMJ* 2017; 357:j2563

Commencement of cardioselective beta-blockers during hospitalisation for acute exacerbations of chronic obstructive pulmonary disease

In patients with chronic obstructive pulmonary disease (COPD) and comorbid cardiovascular disease, emerging evidence suggests a benefit in commencing cardioselective beta-blockers.

In this retrospective cohort study it was noted that 36 of 1,071 hospitalised COPD patients were treated with beta-blockers. Atrial fibrillation and acute coronary syndrome were the commonest indications. Metoprolol was the most commonly prescribed beta-blocker. None of these patients suffered a significant decline in respiratory function during their treatment. One patient experienced symptomatic hypotension.

The conclusion reached was that the commencement of cardioselective beta-blockers during acute exacerbations of COPD appears to be well-tolerated. The researchers recommend that prospective studies would be appropriate.

*Internal Medicine Journal* 2017; 47:1043–1050

Health effects of overweight and obesity in 195 countries over 25 years

In this study the researchers analysed data from 68.5 million persons to assess the trends in the prevalence of overweight and obesity among children and adults between 1980 and 2015. They also quantified the burden of disease related to high body-mass index (BMI), according to age, sex, cause and BMI in 195 countries between 1990 and 2015.

High BMI caused four million deaths globally, nearly 40% of which occurred in those who were not obese. Two-thirds of the deaths were due to cardiovascular disease. A causal relationship to many cancers was also noted.

The rapid increase in the prevalence and disease burden of elevated BMI highlights the need for continued focus on surveillance of BMI and identification, implementation and evaluation of evidence-based interventions to address this problem.


URL:
Intestinal Obstruction by a Band in an Infant Nineteen Days Old—End-to-End Union—Recovery

By W. M. THOMSON, M.A., M.B.

On 1st September, 1917, I attended a primipara aet. 33. When I first examined there was already marked caput, and I wrongly diagnosed a normal presentation. After eighteen hours I applied forceps ineffectually. I could not move the head, and the forceps slipped off. Under deep anaesthesia, however, I found an ear, and found I had a persistent occipito-posterior presentation, pushed the head up, turned it into position, slipped up one blade of the forceps while still holding the head, then applied the other, and had the child born in about ten minutes without a tear of the perinaeum. He weighted rather over 9lb., had slight facial paralysis on the right side for about a week, and was unable to suck, but was fed on breast milk drawn off and given by a spoon. The midwife reported regular motions for two weeks; indeed, she never took a clean napkin off him. During the next five days his motions gradually ceased and he began to vomit green, slimy material resembling green motions. I was called in again on the 17th by the Plunket Nurse, and again on the 18th. On the 19th I examined him per rectum in the morning, but could feel no tumour. I saw him again at night, and finally decided
he must have obstruction, and sent him into hospital. He had been on water only for three days, and had had both stomach and bowel washed out on several occasions.

I operated the same evening, about 11 p.m., half expecting an intussusception, although the baby never had a crying fit (indeed, he had cried very little at any time), had no tumour, and had only passed a little blood and mucus once after the rectal examination. The incision was through the right rectus in the lower segment. A distended coil of small intestine presented at once. I inserted a finger into the abdomen, but felt no tumour, so began pulling out small intestine into a hot towel. After drawing out about eighteen inches of it I came across an obstruction caused by a band. This seemed to be attached by one end to the posterior surface of the mesentery, passed over the bowel, and was fixed by the other end near the root of the anterior surface of the mesentery. The bowel was rolled up on the mesentery and adherent a little to it.

In trying to divide the band the intestine tore clean through at the obstruction without any rough handling on my part, as I thought. I freed adhesions, lifted and clamped the divided ends, and as the bowel was of good colour did not excise any, but slit the antimesenteric border for about half an inch, and then sutured in the usual two layers. One of the Lembert’s stitches leaked, so I put a little purse-string round it, washed the bowel with saline, as there had been some escape of bowel contents, poured into the abdomen about a drachm of ether, and sutured the abdominal wall with six or seven through and through silkworm gut sutures.

The baby had water for twenty-four hours, to which peptonised milk was then added in slightly increased proportions daily. The child vomited a little green fluid once, and on another occasion a little curd, but otherwise made an uneventful recovery. He was given a tiny warm-water enema twenty-four hours after the operation and passed some flatus. For the next two days his motions were dark-brown, but by the seventh day he was passing normal baby motions, yellow and semi-solid. He was discharged from hospital on 4th October with his wound healed, bowels acting normally, no vomiting, and gaining weight. His mother had kept her breasts active and is now nursing him normally. His weight now is 7 1/2lb., and he seems to be gaining uniformly, to judge by his appearance.

I am sorry that I cannot state how far the obstruction was from the ileo-coecal valve, nor can I offer any suggestion as to the origin of the obstructing band, except that it may have been a free fibrous Meckel’s band which became turned up on the mesentery and adherent there, and so gradually caused the obstruction. I can only attribute the successful result to the presumably nearly sterile state of the interior of the bowel.