National Health Committee

Haematuria: Presentation, Diagnostic Pathway and Alternative Diagnostic Options

March 2015
National Health Committee (NHC)

The National Health Committee (NHC) is an independent statutory body charged with prioritising new and existing health technologies and making recommendations to the Minister of Health.

It was reformed in 2011 to establish evaluation systems that would provide the New Zealand people and the health sector with greater value for money invested in health.

The NHC Executive is the secretariat that supports the Committee. The NHC Executive’s primary objective is to provide the Committee with sufficient information for it to make decisions regarding prioritisation and reprioritisation of interventions and services. They do this through a range of evidence-based products chosen according to the nature of the decision required and timeframe within which decisions need to be made.

The New Zealand Government has asked that all new diagnostic and treatment (non-pharmaceutical) services, and significant expansions of existing services, are to be referred to the NHC.

In August 2011 the NHC was appointed with new Terms of Reference and a mandate to establish the capacity to assess new and existing health technologies. Its objectives (under Section 4.2 of its Terms of Reference – www.nhc.health.govt.nz) include contributing to improved value for money and fiscal sustainability in the health and disability sector by:

- providing timely advice and recommendations about relative cost-effectiveness based on the best available evidence;
- providing advice and recommendations which influence the behaviour of decision makers including clinicians and other health professionals;
- providing advice and recommendations which are reflected in resource allocation at national, regional and local levels; and
- contributing to tangible reductions in the use of ineffective interventions and improved targeting to those most likely to benefit.

In order to achieve its objectives under Section 4.2 and to achieve ‘Value for Money’, the NHC has adopted a framework of four assessment domains – Clinical Safety & Effectiveness; Economic; Societal & Ethical; and Feasibility of Adoption – in order that assessments cover the range of potential considerations and that the recommendations made are reasonable.

It is intended that the research questions asked will fall across these domains to ensure that when the Committee comes to apply its decision-making criteria, it has a balanced range of information available to it. When the NHC is setting those questions they will have the decision-making criteria in mind.

The 11 decision-making criteria will assist in the determination of the NHC work programme and in the appraisal and prioritisation of assessments.
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1 Purpose

This paper gives background information about haematuria (blood in urine). It outlines the clinical presentation and underlying causes of haematuria, and identifies interventions that could improve the pathway of care from the perspective of both patients and the health care system. Diagnostic options reflect the development of genomics as a diagnostic tool.¹

¹ As presented in the two Tier 1 documents; Genomics and Diagnostics discussed by the National Health Committee in February 2014.
2 Background

Haematuria can be visible or invisible but detected with diagnostic aids. It can come from different sources in the urinary or renal tract, including the kidney, collecting system, ureter, bladder, urethra and prostate. The components of the renal tract are shown in Figure 1.

Figure 1: Male and female renal tract

Source: National Cancer Institute (http://www.cancer.gov by permission)[1]

2.1 Underlying causes of haematuria

The frequency of underlying causes of haematuria is related to the part of the health care system in which a patient presents. People present first to primary care, where they receive initial assessment. The primary care diagnostic process can identify some causes of haematuria and raise suspicion of less common and more serious disease that needs further investigation. Potential presence of malignant disease and diagnostic uncertainty encourages primary care clinicians to refer to secondary care for further assessment. This means that in secondary care settings, the patients have already undergone selection, and therefore the frequency of diagnoses differs between primary and secondary care.

There are no New Zealand-specific data available on the presentation and underlying diagnoses of haematuria in primary and secondary care. However, there is no reason that the international evidence cannot be applied to the New Zealand context. Data are more readily available for secondary than primary care.
2.1.1 Primary care

Patients may present to primary care with haematuria either alone or with other symptoms for various underlying causes. The frequencies of particular diagnoses vary by the age and sex of the patients.

One retrospective analysis of a UK primary care clinical database containing routine clinical records identified adults who presented with visible haematuria. Following presentation, the records were analysed at set time points to determine the consequent diagnosis. Renal tract malignancy as an explanation for visible haematuria was found to be uncommon; 6% in men and 3% in women at six months after initial presentation.\(^{(2)}\)

Another study of the same primary care database took a similar approach. Diagnostic outcomes were analysed at 90 days and three years after the original presentation with macro-haematuria. A relevant formal positive diagnosis was found in 18% of men and 18% of women at 90 days, and 42% of women and 37% of men at 3 years.\(^{(3)}\) The attribution of the haematuria to a relevant diagnosis may be less certain at longer times from the original presentation. Clinical diagnoses vary between men and women. The frequencies of underlying causes for those with a formal diagnosis at 90 days are shown in Table 1.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td>51</td>
<td>82</td>
</tr>
<tr>
<td>Renal calculi</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Urinary tract cancer</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Benign prostatic hypertrophy</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>Menstrual disorders</td>
<td>–</td>
<td>9</td>
</tr>
</tbody>
</table>

Φ More than one possible.

As Table 1 shows, when there is a clear diagnosis, urinary tract infection (UTI) is the most common explanation, particularly in women. Renal tract cancers include both bladder and kidney sites, and overall are more common in men than women. However, the frequencies in Table 1 are for patients who had a definite diagnosis. In the about 4/5 of patients without a definitive diagnosis, it may be inferred that a serious diagnosis did not become apparent during the period of observation.

In a Belgium-based study with at least 18 months of follow-up, 10.3% of patients were diagnosed with urological cancer, 8.3% bladder cancer and 2.0% other cancers.\(^{(4)}\) A study of a primary health care service in the US found that of patients who presented with visible or invisible haematuria, 85% had microscopic haematuria and 57% had other symptoms present.\(^{(5)}\) UTI was a common diagnosis, in 26% of micro-haematuria and 51% of macro-haematuria.
2.1.2 Secondary care

Evidence about diagnostic outcomes is available from Australia and the United Kingdom. Most of the studies focus on malignancy, but other diagnoses have been reported. There is no known reason that the findings cannot be applied to the New Zealand population.

The services in these studies diagnosed using cystoscopy in combination with a variety of radiological methods. Cystoscopy is the visual examination of the bladder with a flexible camera and light source. The studies (shown in Table 2) report consistent diagnostic findings of patients with haematuria investigated in secondary care. The patients in the studies presented in primary care with both micro- and macro-haematuria. Bladder cancer was found in about 8–10% of patients. Transitional cell carcinoma (TCC), which can occur in the ureter and renal pelvis, was found in about 8–11% of patients. In one study, the histological type of TCC accounted for 88 of 90 cases (98%) of bladder cancer. Renal cell carcinoma was diagnosed in about 1% of patients. Malignancy of any type was more likely in patients who presented with visible rather than invisible haematuria. Renal calculus (about 6%) was another of the more common diagnoses. In 70–80% of patients, no specific disease was diagnosed.

<table>
<thead>
<tr>
<th>Population</th>
<th>Study period</th>
<th>Number of patients</th>
<th>Patients with macro-haematuria (%)</th>
<th>Bladder TCC (%)</th>
<th>Upper tract TCC (%)</th>
<th>Renal cell carcinoma (%)</th>
<th>Renal calculi</th>
<th>Prostate or urethral disease</th>
<th>No formal diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Australia</td>
<td>2008–11</td>
<td>500</td>
<td>60</td>
<td>10.2</td>
<td>1.0</td>
<td>1.0</td>
<td>3.5</td>
<td>12</td>
<td>69</td>
</tr>
<tr>
<td>UK(7)</td>
<td>1998–2003</td>
<td>4,023</td>
<td>52</td>
<td>10.3</td>
<td>0.3</td>
<td>1.5</td>
<td>8.4</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>UK(9)</td>
<td>1999</td>
<td>363</td>
<td>48</td>
<td>7.7</td>
<td>–</td>
<td>1.4</td>
<td>4.0</td>
<td>15</td>
<td>72</td>
</tr>
<tr>
<td>UK(6)</td>
<td>1993–98</td>
<td>1,046</td>
<td>37</td>
<td>8.4</td>
<td>1.0</td>
<td>1.3</td>
<td>4.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: 2013 NHC Executive literature search

2.2 Clinical presentation

Urinary infection typically presents with pain and increased frequency of passing urine. Severe abdominal pain and systemic symptoms such as fever can also develop.

Renal calculi (stones) typically present with one sided abdominal pain, nausea and haematuria.

Urothelial bladder cancer’s cardinal symptom is painless, visible haematuria, which occurs in more than 80% of patients at presentation. A smaller group of patients present with irritative infection-like symptoms in the absence of visible haematuria. Patients may present with micro-haematuria alone, and patients with upper urinary tract urothelial carcinomas may present with pain due to obstruction by the tumour.
Renal cell cancer can present with haematuria, but also typically presents with a more pronounced clinical picture of abdominal pain, weight loss, and reduced appetite; and a mass may be palpable at examination.\(^{(12)}\)

Glomerular renal disease typically presents with proteinuria in addition to haematuria. The degree of haematuria varies, although it is mostly microscopic. Other presenting symptoms may be non-specific but can include fluid retention and vasculitic changes including skin rash.\(^{(13)}\)
Diagnostic process for haematuria

There is no organised screening programme for bladder cancer. Clinical activity may be generated as a result of opportunistic screening, for example a simple urinalysis as part of a new patient check. Otherwise, presentation to primary care with haematuria and other urinary tract symptoms will lead to clinical assessment. The reporting of urinary symptoms usually triggers the easy detection of micro-haematuria, and immediate testing reagent test strips are easily accessible.

Clinical assessment aims to reach a final diagnosis. Clinical reasoning aims to determine whether the underlying cause of presentation is serious, to confirm a benign explanation, or to confirm or exclude a renal tract malignancy, particularly bladder cancer. If a patient has clinical factors indicating a higher risk of malignancy for which a less serious cause cannot be demonstrated, then clinical uncertainty and recognised baseline risk will lead to further investigation and possible referral to secondary care. Clinical assessment will involve detection of relevant clinical features, persistence of haematuria, features indicating urinary infection or intrinsic kidney disease, assessment of risk based on age and other factors, the assessment of renal function, and possible further imaging.

Further investigation of haematuria involves the history and examination, renal tract imaging, urinalysis, urine cytology and flexible cystoscopy. Figure 2 shows the assessment pathway recommended by a New Zealand clinical practice guide: initial investigation of visible haematuria using computed tomography (CT) urogram and a cystoscopy in any patient assessed as being at a higher risk of cancer; that is, haematuria, over 40 years of age or other factors such as positive smoking history. The combination of CT urogram and cystoscopy is considered the ‘gold standard’ and allows for both the direct examination of the bladder and assessment of the whole renal tract. However, the guide acknowledges that because access to CT urogram is incomplete, ultrasound and intravenous urogram have a diagnostic role in lower-risk patients. The guide also recommends investigation for urological causes of persistent and unexplained non-visible haematuria in high risk groups.
Figure 2: Clinical assessment pathway

Non-visible haematuria
- Asymptomatic
  - < 40 years
  - > 40 years

Visible haematuria
- Symptomatic

Consider nephrological causes of haematuria
- Measure blood pressure (BP), Test creatinine (eGFR), ACR/PCR.
- Request urine microscopy to detect dysmorphic RBCs and urinary casts

Ultrasound urinary tract

Urinary tract imaging where direct access permits:
- e.g. Intravenous urogram (IVU), Ultrasound, CTU

Negative
- Age > 40 years’ or Positive urine cytology?
  - Yes
  - Cystoscopy/urology referral
  - No

Positive
- Monitor for nephrological cause
  - Annually with urine dipstick, BP, eGFR and ACR/PCR while haematuria persists
  - Refer to nephrology if any of:
    - eGFR < 30 mL/min/1.73m²
    - eGFR < 45 mL/min/1.73m² if person has diabetes
    - eGFR declining by > 10 mL/min at any stage in last five years, or > 5 mL/min in last year
    - Proteinuria ACR ≥ 30 mg/mmol or PCR > 50 mg/mmol
    - Uncontrolled blood pressure (140/90 mmHg)

Monitor for urological cause
- Annually, for two years, with urine dipstick, eGFR, ACR/PCR and cytology.
- Refer back to urology if any of:
  - Haematuria persists
  - Urine cytology positive
  - Urinary tract symptoms develop or increase

Monitor in primary care
- Cause found

Source: http://www.bpac.org.nz (by permission)
Although urinary cytology is highly specific, it has a median sensitivity of only 35%. That is, it produces a high proportion of false negative test results, so it is good at confirming but not at excluding malignancy. Diagnosis cannot, therefore, rely solely upon urinary cytology.

CT urography has better detection rates for upper tract urothelial cancers. CT urogram is not necessarily used as a first line investigation because it is a limited resource, and of the desire to limit patients’ exposure to radiation. Ultrasound is a radiation-free imaging technique, readily available in both primary and secondary care, and is considered appropriate first-line investigation for lower-risk patients. If these patients’ symptoms persist after negative initial investigations, they may need intravenous urogram (IVU) or CT urogram. IVU allows anatomical assessment of the whole renal tract and can detect tumours, particularly renal tumours, from the presence of filling defects of the renal anatomy outline.

Patients referred to secondary services who are at higher risk of malignancy will have a cystoscopy. In the secondary care system, they may have further imaging to more clearly define the renal tract. Between 1998 and 2003 at one UK haematuria clinic, the primary investigations were plain x-ray, ultrasound and cystoscopy. Patients with negative initial results but on-going detectable blood in the urine had an IVU; while those with positive initial results had a CT urogram or IVU depending on the presumed diagnosis. IVU was performed in 46% of patients. Follow-up urological specialist review was required in about 4% of patients in another haematuria-focused clinic.

Some patients may not have had any imaging in primary care. In New Zealand, primary care access to imaging resources is variable, and direct cost to the patient can act as a barrier. If the patient is at sufficient clinical risk to need referral to secondary care, investigation at the patient’s expense may be thought to have limited benefit and not done in primary care.

Haematuria clinics offer a one- or two-step infrastructure to investigate patients with haematuria. In the UK, there is no standard protocol for investigations and varying permutations are practised. It is not clear whether there is a standard investigation pathway in New Zealand. Some conditions, such as UTI, are relatively straightforward to diagnose and offer access to immediate, safe and effective treatment. Some presentations indicate underlying intrinsic renal disease and need to proceed along the nephrology clinical pathway.

Clinical behaviour is driven by potential presence of malignant disease and uncertainty, and in both primary and secondary care, substantial diagnostic doubt is indicated by the data outlined above. For example, up to 80% of patients do not receive a final definitive diagnosis in primary care, and this is repeated after secondary care investigation. The absence of a diagnosis will encourage referral to secondary care for further assessment; this is reflected by the clinical guideline, which recommends referral of patients with persistent haematuria that is unexplained despite prior investigation. The particular need to exclude bladder cancer, and its relatively low prevalence in primary care, may explain the high proportion of patients in secondary care with no specific diagnosis at the end of assessment.
4 Epidemiology

Cancers can develop in any part of the renal tract from the body of the kidney, renal pelvis, ureter, bladder and urethra. The epithelial lining of the renal tract, provided by cell urothelium, is consistent from the renal pelvis to the bladder. Most cancers that form in the bladder, the renal pelvises, the ureters, and the proximal urethra are TCCs that derive from transitional epithelium.\(^{(18)}\)

4.1 Bladder cancer

American experience is that approximately 95% of bladder cancer is caused by TCC. The other 5% of cancers that make up bladder cancer behave in a clinically similar way to TCC.\(^{(18)}\)

In New Zealand in 2010, bladder cancer was the 11th most common cancer registration and the 14th most common cause of death from cancer. Registration rates remained relatively stable between 2005 and 2010, as did mortality rates for bladder cancer between 2000 and 2010. There are no clear differences in incidence or mortality between Māori and non-Māori.

Males have higher rates of bladder cancer than females for both registrations and deaths: in 2010 there were 389 new cases of bladder cancer with a male to female ratio of approximately 3.5 to 1. There were 126 deaths in males and 49 deaths in females caused by bladder cancer.\(^{(19)}\)

There is a strong trend in incidence of bladder cancer with increasing age, and strong evidence linking exposure to carcinogens to its development. Smoking increases a person’s risk of bladder cancer by up to four times the baseline. Certain occupational exposures have also been linked to bladder cancer; and higher rates of bladder cancer have been reported in textile dye and rubber tyre industries, among painters, leather workers, shoemakers, and those working with aluminium, iron, and steel.\(^{(20)}\)

4.2 Kidney cancer

Kidney cancer consists mostly of renal cell cancer (also called renal adenocarcinoma) and transitional cell cancer. Renal cell cancer develops from proximal renal tubular epithelium within the kidney, and accounts for about 90% of malignant tumours of the kidney. TCC accounts for most of the rest of renal tumours, either of the renal pelvis or ureter.\(^{(1)}\)

In New Zealand in 2010, there were 524 new registrations for renal cancer. The incidence in men was double that for women. There were 168 deaths due to renal cancer.\(^{(19)}\)

A New Zealand-based study using radiological diagnosis of renal stones (not all symptomatic), that covered secondary and primary care, estimated an overall population incidence of 1.05/1000 per year. About 70% of cases were male, and peak incidence was between the ages of 40 and 59.\(^{(21)}\)
In 2006 (the most recent available data) there were 4773 admissions for patients with a primary diagnosis of renal tract calculus, of whom 70% were males.

### 4.3 Benign prostatic hypertrophy

The prevalence of benign prostatic hypertrophy in New Zealand in 2010 was estimated from the New Zealand Health Tracker for the New Zealand Burden of Disease Study at 16.5/1000 males, with a marked increase from the age 50, equating to 41,500 men.
5 Disease burden

Disease burden is the impact of disease in terms of the death and living with disability. Health loss is estimated using disability-adjusted life years (DALY). The DALY combines information on both fatal (early death) and non-fatal (illness or disability) outcomes in a way that makes it possible to compare the effects of different diseases and injuries across population groups and over time.\(^{(22)}\)

The disability-adjusted life year (DALY)
The DALY is calculated as follows: \(\text{DALY} = \text{YLL} + \text{YLD}\).

YLL (years of life lost) measures health loss from early death, taking into account the age when death occurred.

YLD (years lived with disability) measures health loss from time spent in less than full health, taking into account the severity of ill health or disability.

The DALY, as a measure of health loss, provides additional perspective to data describing incidence, prevalence or mortality. A selected summary of results from the NZ Burden of Disease Study (which used 2006 as its time period of assessment)\(^{(22)}\) are presented for the conditions that are common diagnoses for the presentation of haematuria (Table 3).

| Table 3: Burden of disease for selected diseases by gender, 2006 |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                          | YLL                      |                          |                          |                          |
|                          | Male         | Female      | Male         | Female      | Male         | Female      | Total       |
| Kidney cancer            | 2423         | 1166        | 156          | 101         | 2578         | 1267        | 3845        |
| Bladder cancer           | 2067         | 786         | 240          | 76          | 2307         | 862         | 3168        |
| Benign prostatic hypertrophy | 129         | –           | 1625         | –           | 1754         | –           | 1754        |
| Urinary tract infections | 380          | 617         | 42           | 324         | 422          | 941         | 1362        |
| Renal calculus           | 37           | 98          | 45           | 19          | 82           | 117         | 199         |

Although the conditions in Table 3 can present with haematuria, these conditions have complex presentations which do not always include haematuria. The context of haematuria therefore affects applicability of the data. For example, benign prostatic hypertrophy presents mostly without haematuria, while malignant underlying causes are more likely to present solely with haematuria.

Renal tract cancers cause greater health loss for males than females. UTI affects females more than males. Renal stones contribute a relatively small health loss. Malignant diseases contribute a significant health loss (Table 4).
Table 4: Bladder cancer burden of disease counts, by gender, 2006

<table>
<thead>
<tr>
<th>Sex</th>
<th>YLL</th>
<th>YLD</th>
<th>DALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>786</td>
<td>48</td>
<td>834</td>
</tr>
<tr>
<td>Male</td>
<td>2067</td>
<td>151</td>
<td>2217</td>
</tr>
<tr>
<td>Total</td>
<td>2853</td>
<td>198</td>
<td>3051</td>
</tr>
</tbody>
</table>

Source: New Zealand Burden of Disease Statistical Annexe

In 2006, bladder cancer alone accounted for 3051 DALYs. The impact of bladder cancer increases with age, particularly for people aged 65 and over. Males have a higher number of deaths and years lost from bladder cancer than females; and non-Māori have more than Māori (Table 5).

Table 5: Bladder cancer burden of disease rates per 100,000 population, by ethnic group, age-standardised, 2006

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>YLL rate</th>
<th>YLD rate</th>
<th>DALY rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Māori</td>
<td>47.82</td>
<td>1.51</td>
<td>49.33</td>
</tr>
<tr>
<td>Non-Māori</td>
<td>47.17</td>
<td>3.54</td>
<td>50.71</td>
</tr>
<tr>
<td>Total</td>
<td>48.29</td>
<td>3.42</td>
<td>51.70</td>
</tr>
</tbody>
</table>

Source: New Zealand Burden of Disease Statistical Annexe

Table 6 shows the contribution of bladder and kidney cancers as a proportion of the total burden for cancers and shows the relative contribution of renal tract cancers to health loss.

Table 6: Burden for selected cancers in DALYs

<table>
<thead>
<tr>
<th>Cancer description</th>
<th>DALY</th>
<th>% of total for cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>28,570</td>
<td>17.1</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>17,870</td>
<td>10.7</td>
</tr>
<tr>
<td>Colon</td>
<td>15,907</td>
<td>9.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>9,786</td>
<td>5.9</td>
</tr>
<tr>
<td>Rectum</td>
<td>8,105</td>
<td>4.8</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6,909</td>
<td>4.1</td>
</tr>
<tr>
<td>Stomach</td>
<td>6,296</td>
<td>3.8</td>
</tr>
<tr>
<td>Ovary</td>
<td>4,046</td>
<td>2.4</td>
</tr>
<tr>
<td>Head and neck</td>
<td>3,851</td>
<td>2.3</td>
</tr>
<tr>
<td>Kidney</td>
<td>3,752</td>
<td>2.2</td>
</tr>
<tr>
<td>Bladder</td>
<td>3,051</td>
<td>1.8</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2,190</td>
<td>1.3</td>
</tr>
<tr>
<td>Cervix</td>
<td>1,591</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Source: New Zealand Burden of Disease Statistical Annexe
6 Primary care utilisation

No New Zealand data have been found about the presentation of haematuria in primary care or investigations in the subsequent diagnostic process. However, assuming there are similar patterns of underlying disease, there is no reason to believe that New Zealand frequency of presentation, diagnostic outcomes and the use of further investigation methods in primary care differ from overseas.

Estimating how many people present to primary care services with haematuria who may then be investigated further and referred onto secondary care services needs incidence data. Prevalence data for haematuria does not describe the rate of people presenting to clinical services. International incidence data on haematuria in primary care is sparse. Better quality data are available for the presentation of visible haematuria rather than micro-haematuria. The following estimates of incidence are available from the international literature:

- 400/100,000 person-years for those who present with either macroscopic or microscopic haematuria.\(^4\)
- 250/100,000 person-years in those aged 15 years or more. This is estimated using a large UK primary care database reliant on contemporaneous coding of consultations or those presenting with a new episode of macroscopic haematuria. Estimates of incidence are available by gender and age group that shows an increase in incidence with increasing age and a rate about 50% greater in males than females.\(^5\) The rate in this study may be an underestimate due to incomplete coding of consultations. Incidence is based on 11,138 patients with first occurrence of haematuria.
- 488/100,000 of adults from a Belgian study of a representative national network of general practice providers for those that presented with macroscopic haematuria.\(^4\) The data was collected prospectively and so may be a more reliable estimate of the true incidence. However, the estimate of incidence is based on 409 patients with first occurrence of haematuria.

6.1 Estimating numbers of patients presenting with haematuria in primary care

It is difficult to derive an estimate of the number of people presenting to primary care with haematuria in New Zealand from the international study data above. If the incidence and its age structure from the UK study for macroscopic haematuria is reflected in the New Zealand population, then about 4450 men and 3150 women aged 30 plus will present each year, a total of 7600. This may be a minimum, as it does not include microscopic haematuria. An alternative estimate for the incidence of haematuria, recognising that studies show that more than half of outpatients have micro-haematuria, is 500 per 100,000 for patients aged over 30. This rate produces an estimate that about 8900 men and 6300 women aged over 30 would present to primary care: a total of 15,200 patients per year.
Options for further investigation include simple labstix urinanalysis, a formal laboratory urine sample for microscopy and culture, blood tests and radiological investigations. There are no available data showing the proportion of patients in New Zealand that are investigated further.

One US study analysed the management of patients who presented with visible or invisible haematuria at a primary health care service. 85% had microscopic haematuria and 57% had other symptoms present.\(^5\) Further investigation included cystoscopy (9%), imaging (36%), repeat urinalysis (63%) and urine culture (62%). Imaging was more common in the macro-haematuria patients (42% v 34%) as was referral (60% v 15%). Renal tract malignancy was less common (1.1%) than found in other studies.

If the findings of this study are applied to New Zealand, the referral rate to cystoscopy would indicate that, about 14,000 patients would present to primary care with haematuria, of whom 3000 would be seen in outpatients (see later), and about 5000 would have further imaging.

These estimates suggest that the number of patients presenting to primary care because of haematuria ranges between 7600 and 15,000, and that up to 5000 would have renal tract imaging as part of their management.
Secondary care utilisation


More specific data was collected by the Auckland Regional Urology Service in Counties Manukau. This shows that for a 12-month period, 847 people had diagnostic cystoscopy, of which 75% were for the investigation of haematuria. If these data are assumed to be nationally representative and extrapolated to the whole of New Zealand, it provides an estimate of 3000 cystoscopies for the investigation of haematuria in New Zealand annually. These data would indicate that the NMDS data are an underestimate compared to the locally derived data, as the NMDS data indicated the Auckland Regional Urology Service performed only 440 and 500 first cystoscopies in total for each year.

An alternative approach to estimate the number of patients undergoing cystoscopy is to back calculate from the Cancer Registry data. The number of new registrations for bladder cancer has been identified for the years 2006 to 2010. The average annual count for the period is 360 (Table 7).

<table>
<thead>
<tr>
<th>Year</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>366</td>
</tr>
<tr>
<td>2007</td>
<td>348</td>
</tr>
<tr>
<td>2008</td>
<td>357</td>
</tr>
<tr>
<td>2009</td>
<td>382</td>
</tr>
<tr>
<td>2010</td>
<td>353</td>
</tr>
</tbody>
</table>


International data indicates that approximately 10% of individuals investigated for haematuria in secondary care are diagnosed with bladder cancer. This detection rate with the mean number of new diagnoses of bladder cancer produces an average annual count of patients investigated for haematuria annually of about 3600. Some not all of these patients would be seen in the public health care system as some would be diagnosed through the private sector.

The NHC Executive concludes that 3000 is a reasonable estimate of the number of patients who are seen and have a diagnostic cystoscopy performed in the public health care system.
8 Cost of haematuria diagnosis

8.1 Investigation activity

The following assumptions have been made regarding the number of patients presenting to primary and secondary care based on interpretation of the previously described evidence. The numbers assumed to undergo each activity are shown in Table 8:

- in primary care two-thirds of patients have a mid-stream urine specimen sent to the laboratory for microscopy and culture
- in primary care one-third of patients have a renal tract ultrasound performed
- in secondary care all patients have diagnostic cystoscopy
- in secondary care one-half of patients have an ultrasound performed that has not been done previously
- In secondary care one-third of patients have CT urogram performed.

<table>
<thead>
<tr>
<th>Table 8: Assumed clinical activities in the investigation of haematuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Numbers seen</strong></td>
</tr>
<tr>
<td>Primary care</td>
</tr>
<tr>
<td>Secondary care</td>
</tr>
</tbody>
</table>
8.2 Costs

Indicative costs for imaging were sought from a private provider. The costs of specialist activity have been taken from national prices for 2010/11 (Table 9).

Table 9: Cost of clinical activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP visit</td>
<td>35</td>
</tr>
<tr>
<td>Specimen to laboratory for microscopy and culture</td>
<td>20</td>
</tr>
<tr>
<td>Renal tract ultrasound</td>
<td>250</td>
</tr>
<tr>
<td>CT urogram</td>
<td>777</td>
</tr>
<tr>
<td>Cystoscopy performed</td>
<td>500</td>
</tr>
<tr>
<td>Urology first specialist assessment</td>
<td>271</td>
</tr>
</tbody>
</table>

8.2.1 Total costs

The total estimated costs for both primary and secondary care are shown in Table 10.

Table 10: Indicative costs ($) for investigation of haematuria by clinical setting

<table>
<thead>
<tr>
<th>Setting</th>
<th>Number seen</th>
<th>Specimen to laboratory for microscopy and culture</th>
<th>Renal tract ultrasound performed</th>
<th>CT urogram performed</th>
<th>Cystoscopy performed</th>
<th>Total ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care</td>
<td>15,000 x $35 = $525,000</td>
<td>10,000 x $20 = $200,000</td>
<td>5000 x $250 = $1,250,000</td>
<td>0</td>
<td>0</td>
<td>$1.98 million</td>
</tr>
<tr>
<td>Secondary care</td>
<td>3000 x $271 = $813,000</td>
<td>0</td>
<td>1500 x $250 = $375,000</td>
<td>1000 x $777 = $777,000</td>
<td>3000 x $500 = $1,500,00</td>
<td>$5.58 million</td>
</tr>
</tbody>
</table>

Figure 3 represents the numbers by final diagnoses for the estimated annual presentation to primary care of 15,000 patients; and Figure 4 provides an illustration of patient flows and costs by health care setting.

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2 The Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme (BODE³).
3 Canterbury Health Laboratory
6 National price
7 National price
Figure 3: Illustrative numbers for final diagnosis after assessment

Figure 4: Illustrative numbers and costs for diagnosis of haematuria

Source: National Health Committee Executive
9 Alternative interventions in the diagnostic assessment of haematuria

Some of the diseases that are common explanations of haematuria have a clearer clinical presentation and more accessible and acceptable investigation pathway than others. UTI is usually a clear presentation needing confirmation with basic further analysis. Nephrological disease needs clinical assessment, basic urinary examination and ultrasound before specialist assessment. Renal stones commonly have an acute presentation. Renal cell carcinoma often presents with other symptoms additional to haematuria, and various imaging techniques can successfully identify the tumour.\(^{(16)}\)

Bladder cancer and non-pathological explanations typically present with haematuria alone. The clinical uncertainty and risk of missing a malignancy with significant mortality and morbidity, which has a better prognosis at early stage of disease, drives referral for a specialist assessment including diagnostic cystoscopy.

If a diagnostic tool could effectively identify probable cases of bladder cancer when clinical uncertainty exists and other diagnoses have been excluded, it could offer both a significantly improved patient experience by avoiding an invasive procedure, and a reduction of demand on the health care system.
10 Potential role of biomarkers in diagnosis of bladder cancer

The limitations of cytology and the invasiveness of urethrocystoscopy for detecting bladder cancer has generated interest in non-invasive diagnostic tools. Upper tract cancers cannot be detected by cystoscopy alone. Cytology has an overall sensitivity of 40–60%, with considerable inter-observer variability, and needs specialised personnel.

10.1 Detection of urinary markers

The detection of urinary markers is a developing field. Commercial tests have been developed to analyse urine for molecular changes associated with bladder cancer, and the US’s Food and Drug Administration (FDA) has approved a number of tests including BTA stat, BTA TRAK, NMP22, Immunocyt and UroVysion. These tests measure either proteins associated with tumours such as bladder tumour antigen (BTA) and nuclear matrix protein 22 (NMP22); or chromosomal aberrations.

The BTA stat is a qualitative point-of-care test, whereas the BTA TRAK is quantitative. The NMP22 is both a qualitative point-of-care test and a quantitative test. The performance of both is affected by the presence of haematuria. Immunocyt detects cellular biomarkers on cytology slides with fluorescent antibodies. Reading requires a trained cytopathologist so is prone to inter-observer variability, but is less affected by the presence of blood and inflammatory conditions. UroVysion detects changes in chromosomes 3, 7, 9 and 11. It is intended to be used in conjunction with, rather than instead of, other diagnostic procedures.

Methods of detection using urine samples include:

- fluorescence in-situ hybridisation (FISH) for the detection of chromosomal anomalies (UroVysion)
- microsatellite analysis for the detection DNA repeat areas that show loss of variability in bladder cancer. Microsatellite alterations are detected in exfoliated cells using polymerase chain reaction for a panel of known markers
- immunocytology to visualise tumour-associated antigens in urothelial cancer cells (Immunocyt)
- determination of telomerase activity using polymerase chain reaction. Telomeres are sequences at the end of chromosomes that protect genetic stability during cell division; bladder cell cancers express telomerase that allows ongoing cellular replication
- bladder tumour antigen assay (BTA-stat and BTA-TRAK)
- hyaluronic acid (HA) and hyaluronidase assay. HA levels are higher in tumour cells including bladder tumours. Hyaluronidase is elevated in bladder tumour tissue and correlated with tumour grade
- nuclear matrix protein 22 (NMP22) is important for the regulation of mitosis. NMP22 is elevated in and released from tumour cells, allowing detection (NMP22)
• enzyme-linked immunosorbent assay (ELISA) to detect BCLA-4, a nuclear matrix protein that is overexpressed in bladder cancer. Promising initial studies show high sensitivity and specificity
• detection of cytokeratins, filaments that enable cells to withstand mechanical stress. Certain subtypes are associated with bladder cancer
• detection of excess levels of survivin, a protein involved in the regulation of cell death. Excess levels promote cell survival, and it is detectable in urine of patients with bladder cancer
• detection of epidermal growth factor receptor (EGFR).

10.2 Detection of genetic markers

Bladder-cancer-related mutations in individual genes may not be common, but detection of mutations in one or more genes through DNA analysis offers a higher detection rate. Detection of DNA methylation also is a potential approach. RNA controls the expression of genes and mRNA offers a potential diagnostic opportunity. Enhancement of protein markers is feasible by evaluation of multiple markers with multivariate algorithms, which improves performance.\(^{24}\) Cxbladder-detect is a multi-gene test developed by Pacific Edge in New Zealand. It uses PCR amplification to quantify five mRNA markers associated with bladder urothelial cancer.\(^{25}\)

10.3 Test performance

Biomarker test performance is considered here in terms of clinical performance. A more detailed analysis would also consider the implementation and cost of tests, and how well each test may (or may not) complement the current diagnostic laboratory economic model.

A systematic review of the performance of some urinary biomarkers for the detection of bladder cancer included studies published up to April 2008. These studies included randomised controlled trials (RCTs), non-randomised comparative studies and diagnostic cross-sectional studies of patients who were at risk of bladder cancer and who had had a history of bladder cancer. Of the studies that met the inclusion criteria, FISH was reported on by 14, ImmunoCyt by 10 and NMP22 by 41.\(^{26}\) Table 11 gives the pooled estimates for sensitivity and specificity of these tests, and draws data for other tests from another review.\(^{20}\) The data for Cxbladder-detect is taken from a study of 485 patients presenting with macro-haematuria in secondary care, which found a prevalence of urothelial carcinoma of 13.6%. This study reported an overall sensitivity of 82% and specificity of 85%, and noted 100% sensitivity for stage T1 to T3 disease; performing favourably compared with NMP22 (sensitivity = 69%).\(^{25}\)
Table 11: Sensitivity and specificity of urinary biomarker tests for the diagnosis of urothelial cancer

<table>
<thead>
<tr>
<th>Tests</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTA stat</td>
<td>68</td>
<td>74</td>
</tr>
<tr>
<td>BTA TRAK</td>
<td>61</td>
<td>71</td>
</tr>
<tr>
<td>UroVysion</td>
<td>77</td>
<td>98</td>
</tr>
<tr>
<td>FISH</td>
<td>76</td>
<td>85</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>84</td>
<td>75</td>
</tr>
<tr>
<td>NMP22</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>Cxbladder-detect</td>
<td>82</td>
<td>85</td>
</tr>
</tbody>
</table>

As previously noted, the driver for primary care referral for further investigation is clinical concern about potential bladder cancer. Any alternative diagnostic tool to be implemented would need to be effective in ‘ruling-out’ the presence of bladder cancer. That is, the test would need to demonstrate a high negative predictive value. Unless the test can do this, it will not function satisfactorily in the primary care setting.

10.4 Clinical setting for the use of biomarker tests

Urinary biomarkers have a potential role in the management of bladder cancer either in the initial diagnosis, or for patients who have a high baseline risk but negative preliminary investigations, or those who have been monitored but have a change of symptoms.

At initial diagnosis, a biomarker test could be used:
- to aid or modify the diagnostic pathway in secondary care for patients who have been triaged and referred from primary care; or
- as part of the diagnostic pathway in primary care to more effectively identify patients at risk of urothelial cancer and so selectively refer patients to secondary care and further investigation. This use could potentially reduce demand on secondary care urology services and avoid more invasive investigations in some patients.

Figure 5 below shows a simplified diagnostic flow of patients presenting with haematuria, based on the clinical guidance in Figure 2. Patient referral is recommended for urology specialist assessment if initial assessment is positive or if they have a high baseline risk for urothelial cancer with negative initial assessment. Patients can be followed up in the urology service after initial assessment; about 4% based on an Australian experience. Patients will undergo monitoring in primary care, which may generate specialist assessment if clinical circumstances eventuate.
The primary care approach potentially offers the greater impact on the diagnostic pathway for patients and the health system. However, the performance of a test is affected by the setting in which it used. The performance of a test is measured by its positive predictive value (PPV), the proportion of positive tests where the disease being tested for is present’, or ‘true positives’; and negative predictive value (NPV), the proportion of negative test where there is no disease, or true negative’s’ (see Table 12). The PPV and NPV are affected by the prevalence of the condition of interest.
Table 12: Measures of test performance

<table>
<thead>
<tr>
<th>Test result</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease status</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Test result</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Positive</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>Negative</td>
<td>a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>

- True positive results = a
- True negative results = d
- False positive results = c
- False negative results = b
- Total cases with disease = a + c
- Total cases without disease= b + d
- Total positive tests = a + b
- Total negative tests = c + d
- Sensitivity = a / a+c = proportion of true cases detected
- Specificity= d / b+d = proportion of true negative cases detected
- Positive predictive value (PPV) = a / a+b = proportion of all positive tests that are true positive tests
- Negative predictive value (NPV) = d / c+d = proportion of all negative tests that are true negative tests.

The probability of a patient who tests positive for a disease actually having that disease depends on the performance of the test used and on the underlying prevalence of the disease. The population prevalence in the is part of the pre-test probability of the patient having the disease, which, together with the test’s sensitivity and specificity affect how correct the test results are (or post-test probability) for an individual patient. Particular symptoms will increase the pre-test probability of the disease. In the secondary care setting, patients will have been selected by primary care clinical assessment as symptomatic. This means that the underlying prevalence of the disease in the secondary care population is greater than that in primary care, which in turn means that the likelihood increases of a positive test result being correct. Similarly, the nature of the presentation affects the likelihood of disease; for example, patients who present with macro-haematuria are more likely to have a malignancy than those who with micro-haematuria. Therefore, it is important to consider the population on which the test has been used to determine its effectiveness.

10.4.1 False negative results

Where a novel test replaces the established diagnostic method, there is concern about patients who have a false negative test result. That is, that the novel test does not detect the condition being tested for, but they actually have the condition and the standard investigation detects the condition. This is a particular concern in the case of malignancy.
If a test gives results as a continuous scale, this issue can be addressed by adjusting the cut-off point for a positive result, which would detect more cases of disease and improve the NPV. This promotes clinical confidence that important diagnoses are not being missed. However, the trade-off is that as the NPV is enhanced, the PPV is reduced, that is, there is an increase in false positive tests: more patients will have an initial positive urine result requiring further investigation that will ultimately be negative for disease.

Non-muscle invasive bladder cancer (NMIBC) is present in 70% – 80% of patients at initial diagnosis. NMIBC includes stages Tis, Ta and T1, \(^{(27)}\) as shown in Figure 6. The main treatment of NMIBC is transurethral resection of the bladder tumour (TURBT); but additional treatment options directly instilled into the bladder may also be required, such as Bacillus Calmette-Guerin (BCG) and cytotoxic agents.\(^{(11)}\)

**Figure 5: Bladder cancer staging (TNM)**

![Bladder cancer staging diagram](bladdercancerguide.com)

For those who present with or progress to muscle invasive bladder cancer (stages T2, T3 and T4),\(^{(11)}\) treatment is with radiotherapy, chemotherapy and radical cystectomy.\(^{(11)}\) A test can inform decisions about treatment. For example, the CxBbladder-detect test has an overall sensitivity of 82%. This includes a 68% sensitivity for stage Ta disease, and 100% for other stages. This means that a substantial proportion of the 56% of the diagnosed bladder cancer patients who have Stage Ta are not detected.

Adding a further step in the clinical pathway to allow repeat assessment could address missed diagnoses. For example, if a patient considered at higher risk of bladder cancer has a negative result to the initial urinary biomarker test, they could be reviewed after an appropriate period of time for further urinary testing. How successful this would be in terms of outcomes for patients would depend on the stage of disease incorrectly diagnosed, the clinical behaviour of that stage in terms of progression, and whether markers would be detected on repeat testing.
It is difficult to estimate the risk of disease progression for a person with a missed diagnosis, as data are only available from patients who have been diagnosed, staged and treated. Studies of treated patients show that several factors affect disease recurrence and progression to invasive bladder disease, including grade of disease, stage of disease and number of tumours.\(^{(28)}\) Risk of progression for: \(^{(29)}\)

- lowest risk patients, including those with low grade disease and stage Ta, is 0.2% after a year
- those with carcinoma in-situ is about 1% at 12 months post-treatment
- patients with Ta or T1 disease without carcinoma-in-situ (CIS) treated solely with TURBT is 9% risk of progression to invasive disease at five years
- patients with Ta or T1 disease with CIS is between 7 and 40% at 5 years.

These data suggest that a delay of a few months would be unlikely to risk disease progression to a state where treatment options are fundamentally changed. The impact on clinical outcomes of a delay of, for example, three months in diagnosis of bladder cancer should also be considered in the context of standard clinical care. Time to diagnosis includes the time from presentation in primary care, for initial investigation, referral to secondary care and waiting time until subsequent assessment. If the introduction of an alternative diagnostic pathway reduces the overall time to diagnosis, a delay of three months for a subset of patients may not have any difference from the status quo.
11 NHC Executive perspective

Haematuria results from varied clinical conditions that differ in the ease with which they can be diagnosed and their implications for future quality of life and survival. For a significant proportion of patients, no specific cause is found. Once specific conditions have been identified, a specific diagnosis still cannot be made for some patients. Clinical uncertainty and the possibility of bladder cancer result in referral to specialist care for further investigation. This is usually diagnostic cystoscopy, the standard method to evaluate the lower part of the renal tract, and a procedure which is invasive for patients and consumes significant specialist urological resources. A high proportion of investigations fail to detect any clinical pathology.

The aim of the diagnostic process is to filter and detect conditions with clinical consequences. The non-definitive diagnoses may be assumed to result from benign causes, but some of these patients will inevitably produce clinical concern and need monitoring in the primary and secondary care settings.

Testing for urinary biomarkers offers an alternative tool in the diagnosis of haematuria. Tests for urinary biomarkers have an advantage of being non-invasive. If used in the primary care setting, they have potential to successfully identify patients without bladder cancer, and avoid specialist referral and further investigation. Their impact on the diagnostic pathway will need to be clarified and assessed. The measured performance of any test depends on the population to which it is applied, so a suitably targeted population of patients with haematuria in whom other conditions have been excluded will need to be agreed. In the primary care setting, the use of new tests will need to meet the clinical requirement of successfully excluding malignancy. To do this, the evidence base for biomarker tests specifically in this setting will need to develop further; for example, how the tests perform in patients who present with the variety of clinical syndromes, macro-versus micro-haematuria, and with or without other urinary symptoms.

The NHC Executive considers further analytical work is appropriate on the use of urinary biomarker tests in the diagnostic pathway for haematuria, examining their effectiveness and cost-effectiveness. A particular focus should be on those tests that show high sensitivity.
References


National Health Committee (NHC) and Executive

The National Health Committee (NHC) is an independent statutory body which provides advice to the New Zealand Minister of Health. It was reformed in 2011 to establish evaluation systems that would provide the New Zealand people and health sector with greater value for the money invested in health. The NHC Executive is the secretariat that supports the Committee. The NHC Executive’s primary objective is to provide the Committee with sufficient information for them to make recommendations regarding the prioritisation and reprioritisation of interventions. The Executive do this through a range of evidence-based reports that are tailored to the nature of the decision required and timeframe within which decisions need to be made.


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