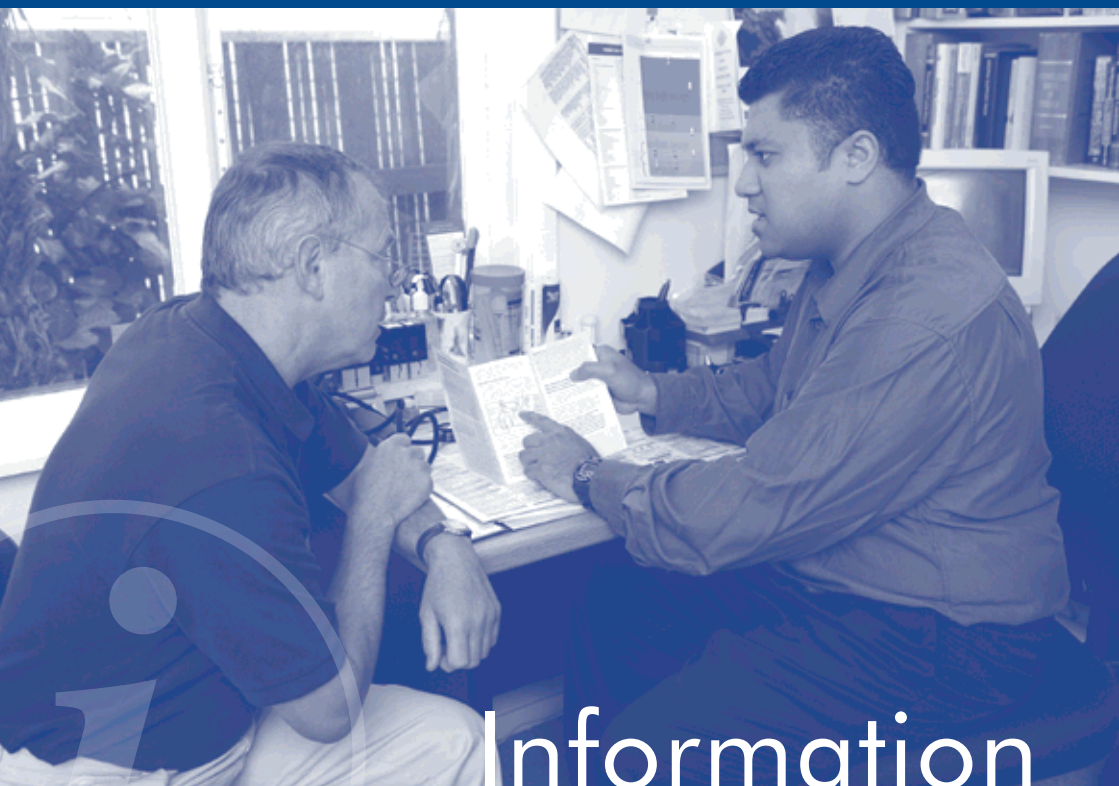


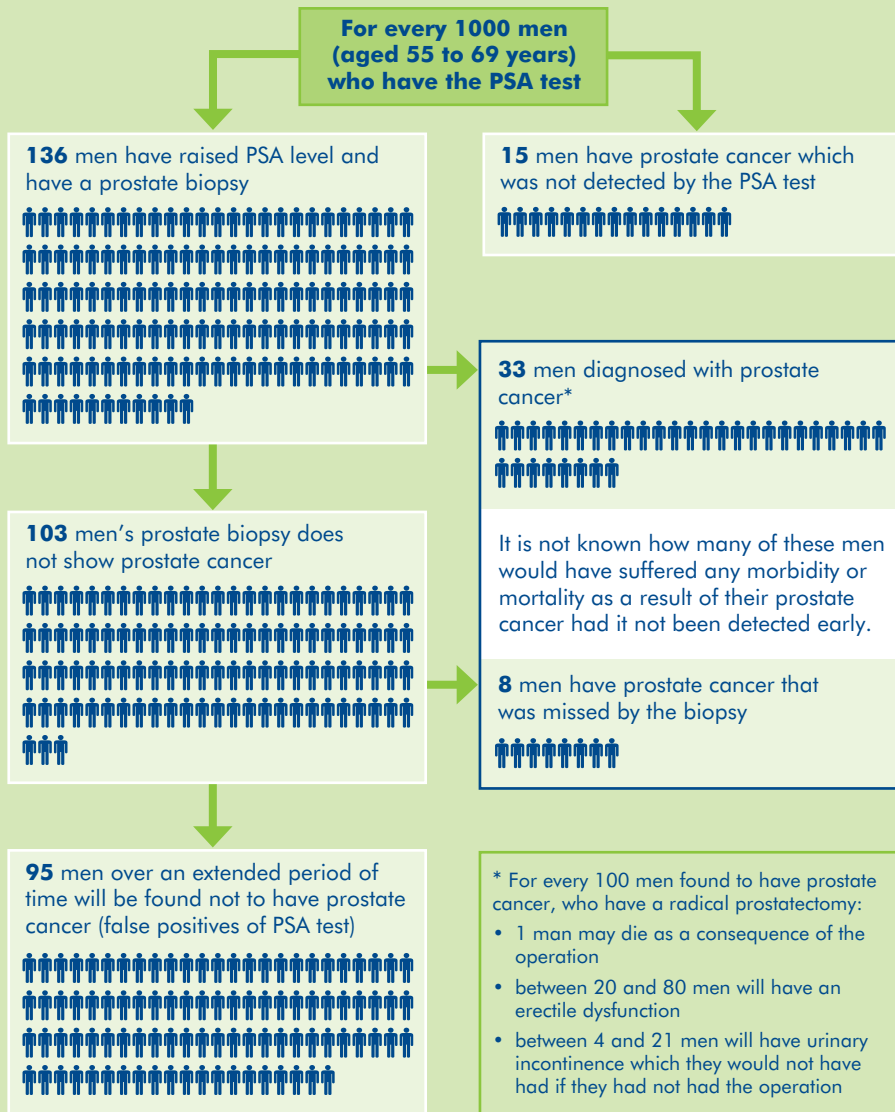
Screening for Prostate Cancer



Information for Health Care Practitioners

OUTCOME OF PSA TESTING IN 1000 MEN

The figure below is a simplified representation of what would happen to 1000 men who had a PSA test. The numbers are approximate and would be influenced by age and many other factors. The figure needs to be considered within the context of information provided earlier on the key issues surrounding the PSA test.



SCREENING ASYMPTOMATIC MEN FOR PROSTATE CANCER

Key messages

Screening asymptomatic men for prostate cancer in New Zealand is not recommended by the National Health Committee because of its lack of proven benefit and the potential for harm arising from unnecessary radiotherapy, surgery or other treatment. This concern applies to men of all ages.

- There is good evidence that PSA screening can detect early-stage prostate cancer, but mixed and inconclusive evidence that early detection improves health outcomes.
- Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies and potential complications of treatment of some cancers that may have never caused any morbidity or mortality.
- The NHC concludes that the evidence is insufficient to determine whether the benefits outweigh the harms for a screened population.
- The NHC does not currently support population-based screening for prostate cancer or opportunistic screening using PSA or DRE for asymptomatic men in New Zealand.
- However, concern over potential harms of screening is not sufficient reason to deny a man the test if he is fully informed and requests it.
- If a PSA test (or other screening test) is being discussed, the decision to use a screening test should be made by an individual, with his family, whānau and his doctor with full information of the benefits and harms associated with testing and the treatment choices he may face.
- Advice on the benefits and harms of prostate cancer screening tests will be reviewed as new evidence emerges.

1 BACKGROUND

In 2001, the National Health Committee contracted the New Zealand Guidelines Group to convene a Prostate Cancer Advisory Group to provide advice about prostate cancer screening in New Zealand. The group commissioned a review – ‘Population Screening for prostate cancer: A systematic review’, that is available at www.nzgg.org.nz

In September 2003, the Prostate Cancer Advisory Group published ‘A Consultation Document on Prostate Cancer Screening in New Zealand’. This summary is based upon that document.

Members of the Prostate Cancer Advisory Group were from varied disciplines including general practice, public health, radiation oncology, urology, pathology, epidemiology, as well as consumers, the Cancer Society of New Zealand, the Prostate Awareness and Support Society, and New Zealand Guidelines Group staff.

1.1 Ethical requirements of a screening test

There is an ethical requirement that the potential benefits of a screening test should clearly outweigh any potential risks or harmful effects.

- Screening involves otherwise healthy, asymptomatic individuals undergoing test(s) to identify a disease which they do not necessarily perceive that they are at risk from.
- When a well person is asked to undergo a screening test, there should be conclusive evidence that screening can alter the natural history of disease in a significant proportion of those screened.
- It is important that men understand (and agree to) the consequences of a positive or negative screening result before having any screening tests.

Health care practitioners have a responsibility to ensure men are fully informed of the potential risks of prostate cancer screening.

1.2 Risk factors for prostate cancer

The causes of prostate cancer are not known, although hormonal influences have a role to play in the development of the disease since tumours regress with androgen deprivation.

- A. Age:** Strongest risk factor; however, there is no evidence that tumour aggressiveness is influenced by age and there is no significant effect of age on cancer progression.
- B. Family History:**
- Approximately 5–10% of cases are thought to have a substantial inherited component.
 - The relative risk of prostate cancer is increased 2-fold with one first-degree relative diagnosed at age 70 or under and rises to 4-fold with 2 relatives (if one of them is diagnosed under the age of 65). The risk with three or more relatives affected is increased 7–10 fold.
- C. Ethnicity:** The incidence of prostate cancer is higher in African Americans (about twice that in white men) and lowest in Asian and Oriental men. The relative risk of Māori men is uncertain.
- D. Diet:** A diet high in animal fats and protein may increase the risk of developing prostate cancer.

Note: Benign prostatic hyperplasia is not a risk factor for prostatic cancer.

1.3 Clinically significant prostate cancer

Histological evidence of prostate cancer is very common and increases progressively with age. The majority of cases of this cancer will never cause any clinically significant disease. Post-mortem studies greatly over estimate the prevalence of clinically significant cancer.

The best estimates of the prevalence of localised prostate cancer that has the potential to progress to overt disease are 4.4% in men aged 50–59, 6.4% in men aged 60–69 years and approximately 12% in men aged 70 years or older.

Even these estimates are much higher than the age-standardised mortality rates for prostate cancer.

Screening for prostate cancer is therefore likely to detect many prostate cancers that would never have caused any morbidity or mortality.

Prostate cancer accounts for 3.8% of all male deaths in New Zealand.

Approximately two-thirds of deaths occur in men aged 75 years or older, 17% in men aged 70–74 years, 15% in men aged 60–69 years, 2% in men aged 50–59 years, and 0.2% in men aged 40–49 years.

1.4 Balance of benefits and harms in prostate screening

Although the identification of prostate cancer is sometimes suggested as a benefit of screening, it is only a benefit if there is an effective treatment that outweighs potential harms of treatment. There is no conclusive evidence that the potential benefits from prostate cancer screening outweigh the potential physical and psychological harms.

Potential benefits:

Prostate cancer screening detection rates varies with different populations and screening protocols, but an average detection rate is of the order of 3% (i.e. for every 100 men screened, then would be 3 cancers detected).

It is not known what proportion of those cancers that would be detected would have caused any morbidity or mortality.

While screening has the potential to cure some men before prostate cancer causes any problems, there is no good evidence that screening will reduce overall prostate cancer morbidity and mortality.

For example, the benefit of prostatectomy for screen-detected cancers has been estimated at only 1 prostate cancer death averted for every 100 operations. However, the remaining 99 patients would have been exposed to the potential harms of screening and treatment.

Potential harms:

The available treatments cause significant harm in a proportion of men and include:

- anxiety in men with false-positive results and false reassurance for men with false-negative screening tests
- prostate biopsy adverse effects
- death, impotence, urinary incontinence and diarrhoea from treatment for prostate cancer.

It is likely that some men will suffer these consequences as a result of treatment for a prostate cancer that would otherwise never have been detected or caused problems in their lifetime.

2 PROSTATE CANCER SCREENING TESTS

There are three recognised tests that have been evaluated for screening asymptomatic men for prostate cancer – Prostate specific antigen, Digital rectal examination and Transrectal ultrasound.

2.1 Prostate Specific Antigen (PSA)

Not recommended as a screening test in asymptomatic men.

Sensitivity and specificity: Best estimates are 74–84% and 90–94% respectively in screening for prostate cancer (the true values are likely to be at the lower end of the range).

The majority of men with a raised PSA do not have prostate cancer:

A man with a PSA result between 4.0 and 10.0 ng/ml has an approximately 1-in-4 chance of having prostate cancer.

A 'normal' PSA result does not exclude prostate cancer:

- There is no value that can be used to designate a normal PSA level below which no prostate cancer can be detected.
- The most frequently used cut-off level is 4 ng/ml, above which further investigation for prostate cancer is warranted.
- Screening using a PSA test ≥ 4.0 ng/ml, as the cut-off level for an abnormal result will miss approximately 25% of prostate cancers.

Other causes of a raised PSA: PSA is a tissue specific rather than cancer-specific serum marker and has been reported in increased amounts in other situations.

- A. Benign prostatic hyperplasia, prostatitis, prostate massage and prostatic needle biopsy.
- B. Ejaculation (commonly causes a mild elevation. After 48 hours, the PSA returns to baseline levels in most men).
- C. DRE (can cause a small elevation that is almost always clinically insignificant. As false-positive results are rare, it seems acceptable to perform a PSA shortly after a DRE).

- D. **Exercise** (case reports, e.g. a mild elevation in runners post-marathon and up to a 3-fold elevation in men after 15 minutes exercise on a bicycle ergometer).
- E. **Spontaneous variation** (reported to rise or fall by as much as 1ng/mL between consecutive measurements within a 90-day period).

Refinements of the PSA test do not add significantly to PSA efficiency in screening: While the free-to-total PSA measurement reduces the false-positive rate, it is doubtful whether this reduction would be sufficient to persuade many men not to have a prostate biopsy.

A. Free-to-total PSA measurements:

- A man with a PSA result between 4.0–10.0 ng/ml has an approximately 1-in-4 chance of having prostate cancer.
- If this same man then has the free-to-total PSA measured and the result is negative, this may reduce his chance of having prostate cancer to approximately 1-in-12.

B. Age-adjusted PSA cut-off levels: In younger men the specificity is reduced and the sensitivity is increased, and in older men, the reverse effect occurs with reduced sensitivity and increased specificity.

C. PSA velocity (change in PSA level over time): Increasing levels of PSA over a 1-year period have also been reported in men with no clinical evidence of prostate cancer.

D. PSA density (relationship of PSA levels in serum to the volume of the prostate gland measured by ultrasound).

Outcomes scenario per 1000 asymptomatic men screened with PSA

Assuming that the true prevalence rate of clinically significant localised prostate cancer in New Zealand is 5.6% in men aged 55 to 69 years, then a sensitivity of 74% and a specificity of 90% would produce the following results for every 1000 men screened (by PSA):

- 15 men with cancer would have a PSA <4.0 ng/ml and would be missed
- 136 men would have a PSA ≥4.0 ng/ml and would be referred for biopsy
- 33 men’s biopsy would show prostate cancer (in some of these men the cancer would not otherwise have become clinically evident in their lifetime)
- 103 men’s prostate biopsy would be negative for prostate cancer
- 8 men would have prostate cancer missed by the biopsy
- 95 men over an extended time would be found not to have prostate cancer (false-positive PSA).

2.2 Digital Rectal Examination (DRE)

Not recommended as a screening test in asymptomatic men.

Sensitivity and specificity: Best estimates are 55–69% and 89–97% respectively in screening for prostate cancer (the true values are likely to be at the lower end of the range).

Useful test if lower urinary tract symptoms or symptoms suggestive of metastatic disease:

- Allows assessment of the prostate for signs of:
 - cancer (a hard gland, often with palpable nodules)
 - benign enlargement (smooth, firm, enlarged gland)
 - other benign lesions such retention cysts, prostatic calculi, non-specific granulomatous lesions.
- Large tumours are easier to feel and are more likely to be clinically significant and to have spread beyond the prostate.

Limitations: Usually unable to detect tumours deep within the prostate and in many cases it is not possible to distinguish between benign lesions and prostate cancer.

2.3 Combined DRE and PSA

Screening using both DRE and PSA requires either a positive PSA test or a positive DRE as an indication for biopsy. It seems acceptable to perform a PSA shortly after a DRE as false-positive PSA results are rare.

Not recommended as a screening test in asymptomatic men:

- Small increase in the detection rate of prostate cancer but a larger increase in the false-positive rate (i.e. more unnecessary biopsies).
- Estimated that for every 1000 men screened, approximately 1 less cancer would be missed and 40 additional men would be wrongly identified as having cancer.

2.4 Transrectal Ultrasound

Provides a detailed image of the prostate gland and adjacent structures and prostate cancer usually appears as a hypo-echoic area.

Not recommended as a screening test in asymptomatic men:

- Many false-positive results (more unnecessary biopsies), with as many as 50% of lesions detected being benign.
- Resource intensive.
- Not available as a mass-screening instrument in New Zealand.

3 HARMS ASSOCIATED WITH SCREENING

An inevitable consequence of screening is that some men will experience the complications of diagnosis and treatment for a condition that would never have caused them any problem.

Psychological adverse effects: These include increased anxiety levels in men with false-positive results and false reassurance for men with false-negative results.

Prostate biopsy adverse effects: There is a false-negative rate of up to 20%. The reported complication rates vary widely with pain, bleeding and infection being the main adverse effects. Life-threatening infections occur in a very small proportion of patients.

One screening study of 1,687 transrectal ultrasound-guided systematic sextant biopsies identified:

- **haematuria or haematospermia:** approximately one-third of men in the 3 months post-biopsy
- **pain after the procedure:** 7.5% (126 men)
- **urinary retention:** 0.4% (7 men)
- **fever >38.5° C:** 4.2% (71 men), with 6 men requiring hospital admission with 1 man admitted to the intensive care unit with sepsis and shock
- **allergic reactions to the pre-biopsy antibiotic prophylaxis:** 0.12% (2 men).

Complications and side effects of treatment of prostate cancer:

- These are both the immediate mortality and morbidity of the treatment, and the possible long-term complications such as sexual dysfunction, urinary incontinence, and bowel dysfunction.
- For further details, see section 4.

4 TREATMENT OF PROSTATE CANCER

- The management of localised prostate cancer is central to the controversy surrounding screening for prostate cancer.
- Some men with localised prostate cancer are likely to benefit from active treatment.
- It is not possible to be certain, which localised tumours may become life threatening.
- There is no evidence from RCTs of any improvement in overall mortality for any active treatment compared with watchful waiting (active monitoring) for screen-detected cancers, although this may be demonstrated in the future by trials in progress.
- There is no strong evidence about the optimum treatment for localised prostate cancer, and there is continuing debate over patient selection for the different treatment options.
- Active treatments for prostate cancer have significant side effects, including death.

The 3 main treatments options are active monitoring, radical prostatectomy and radiotherapy.

4.1 Watchful Waiting (Active Monitoring)

In watchful waiting the patient is not treated and is followed up regularly by an urologist.

Rationale:

- This approach is based on the premise that there are some men with prostate cancer who, on the grounds of their age or co-morbidity or on the basis of having slowly progressing tumours will die from other causes and will not suffer significant morbidity from their prostate cancer.
- A decision to offer radical treatment (surgery or radiotherapy) may be made on the basis of a rising PSA level or a change in the DRE.

Watchful waiting survival rates:

- It has been estimated that 84% of screen-detected cancers would not prove fatal even if they were untreated.
- The disease specific 10-year survival rates for symptomatic cancers managed by watchful waiting disease are estimated at 87–92% for well- and moderately well- differentiated tumours and 44% for poorly differentiated tumours.

Advantages:

- Non-invasive.
- Avoids unpleasant side effects.
- Similar quality-of-life measures, physical and psychological wellbeing compared with men post-prostatectomy.
- A lower incidence of erectile dysfunction, distress from compromised sexuality, urinary leakage and distress from urinary symptoms compared with men post-prostatectomy.

Disadvantages: Some men will develop metastatic disease and some men may find the uncertainty of this approach very difficult to cope with.

Indications:

- This option should be discussed with all men whose cancer is believed to be localised.
- Often the treatment of choice for men with an estimated life expectancy of <10 years.
- However, it is also an option for men with greater life expectancies who wish to avoid the unpleasant side effects of surgery or radiotherapy.

4.2 Radical (Total) Prostatectomy

Aims to remove the entire prostate gland and to cure the disease. Not usually recommended for men with an estimated life expectancy of <10 years.

Benefits of radical prostatectomy:

It is likely that radical prostatectomy in men with localised prostate will prevent progression of disease and death from cancer in some men; however, it is not known which men will benefit.

Screen-detected cancers: It has been estimated the benefit of prostatectomy may be only 1 prostate cancer death averted for every 100 operations (possible range in a sensitivity analysis was 0–9 deaths averted per 100 operations).

Symptomatic cancer: It has been estimated that between 1-in-24 and 1-in-100 men would be prevented from dying from prostate cancer by treatment with prostatectomy.

There is currently no evidence from RCTs that radical prostatectomy compared with watchful waiting for screen-detected cancers, results in a reduction in overall mortality, although this may be demonstrated in the future by trials in progress.

Complications:

Mortality within 1 month of surgery:

- Age <75 years: <1%
- Age >75 years: almost 2%

Major cardiopulmonary complications:

- Age <75 years: 4–5%
- Age >75 years: almost 8%

Reduced sexual function:

- Ranges from 20–80%.
- Influenced by various factors (e.g. age, clinical and pathological stage and surgical technique).

Urinary problems:

- Difficult to quantify as there is wide variation in the definitions and assessment between studies.
- Ranges from 15–50%.
- Incontinence of varying degrees is common and other problems such as urinary strictures can also occur.
- Significant problem for many patients.

Complete tumour clearance is not always achieved:

- Up to 40% of patients who undergo surgery are found to have capsular penetration or positive resection margins. Approximately half of these men go on to develop biochemical or clinical recurrence of the disease.
- Recurrence does not necessarily equate with either significant health problems or death from prostate cancer.

4.3 Radiotherapy

Aims to cure the disease. This treatment is not usually recommended for men with <10 years life expectancy.

Benefits:

It is likely that radiotherapy in men with localised prostate will prevent progression of disease and death from cancer in some men; however, it is unknown which men will benefit.

There is currently no evidence from RCTs that radiotherapy treatment compared with watchful waiting for screen-detected cancers, results in a reduction in overall mortality.

Complications: Reported complication rates vary widely and are difficult to interpret.

Short-term complications: Mainly bowel and bladder problems from the radiation.

Longer-term complications: These include:

- reduced sexual function: 20–45%
- urinary problems: 2–16%
- bowel problems: 6–25%.

4.4 Brachytherapy

Involves the insertion of radioactive seeds into the prostate. It is appropriate only for certain types of prostate cancer and is currently only available in a few centres in New Zealand. The effectiveness of this treatment is not yet known.

4.5 Adjuvant Hormone Therapy

Uses LHRH analogues or anti-androgens to suppress growth of prostate cancer by reducing circulating androgens levels.

Indications:

- Increasingly used in conjunction with radiotherapy for apparently localised disease or after surgery in those with positive resection margins or poor prognostic factors.
- Can be used as adjuvant treatments to those outlined above and are also widely used in the control of metastatic disease.

Adverse effects: These include impotence, loss of libido, breast swelling and hot flushes.

4.6 Locally Advanced Cancer

Clinically advanced localised cancer cannot be eradicated by surgery alone.

- Patients with locally advanced disease mainly receive radiotherapy or hormone therapy, or a combination of both.
- Some men will live for many years with few symptoms, whilst others develop extensive disease quite rapidly.

4.7 Metastatic Prostate Cancer

Usually treated by hormonal therapy and once hormonal therapy fails by supportive or palliative care.

4.8 Monitoring Treatment Effectiveness with the PSA Test

PSA levels are used to monitor disease activity in those with established prostate cancer, giving an indication of response to treatments. It can also give an early indication of the progression of a cancer.

5 CONCLUSIONS

Prostate cancer is a health problem mainly affecting older men. There are problems around the early diagnosis and treatment options for the disease. While some men will benefit from treatment, there is currently no good evidence to say whether or not screening will reduce overall mortality.

Due to the uncertainties surrounding PSA and other screening tests, it is important that men who request a test receive balanced information to assist them in making an informed decision about being tested.

Further information is available from:

The New Zealand Guidelines Group, www.nzgg.org.nz. Copies of the Report to the National Health Committee, the Systematic review and other background documents are available on this site.

Further information

Doctors and other health care practitioners are obliged to provide a man with good information on the risks and benefits of prostate screening.

Additional copies of this booklet can be obtained through local public health services or ordered from Wickliffe on (04) 496 2277
Order number HP: 3796

Other useful information is available on the following websites:

www.nhc.govt.nz

www.cancernz.org.nz

www.nzgg.org.nz

www.nelc.org.uk

www.dipex.org

www.cancerscreening.nhs.uk

www.prostate.org.nz



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