Prostate - specific antigen utilization in Ontario - a feasibility study

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A thesis submitted in conformity with the requirements for the degree of Master of Science, Graduate Department of Community Health, University of Toronto.

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ABSTRACT


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This thesis examines the utilization of prostate-specific antigen (PSA) in Ontario in three phases. Phase I documents, by means of responses to a questionnaire, an exponential rise in PSA testing in Ontario laboratories, which performed over 300,000 tests in 1996. One-third of these PSA test data, together with patient identifiers, are computerised and accessible for additional study.

Phase II examines, in two laboratory databases, the proportion of PSA testing in three patient groups identified through record linkage with the Ontario Cancer Registry. Among those tested in these two laboratories, 8.5% had prostate cancer, 5.7% had cancer other than prostate cancer, and 85.7% were without cancer. These data are analysed with respect to testing frequency among the diagnostic groups and by patient age at time of testing; and with respect to PSA concentration in relation to time of diagnosis. These analyses reveal statistically significant differences, some of which are of clinical importance.

Phase III of this study examines, by means of responses to a self-administered questionnaire sent to attending physicians of patients undergoing PSA tests, the reasons for those tests. The PSA records were from a random sample of patients without prostate cancer as determined by Phase II. A 55% response rate was achieved, revealing that 64% of PSA tests were for screening for prostate cancer; 40% were for investigating symptoms of prostatism; and 33% were for following up other procedures, mostly digital rectal examination. Of those tests requested for screening, 64% were initiated by the patient. Most responses indicated multiple reasons for testing.

Limitations of the study are identified, and the results are discussed in the context of the feasibility of a province-wide study, and how they may affect public policy on PSA testing.
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INTRODUCTION

Thesis outline

This thesis assesses the clinical utilization of prostate-specific antigen (PSA) testing in Ontario. There are a number of features of this particular laboratory test, combined with features of laboratory test delivery and funding in Ontario, that led us to approach this utilization study in three phases. In Phase I, we documented the total number of PSA tests\(^1\) between 1988 and 1996, as reported in a questionnaire sent to all clinical laboratories in the province. We also assessed the extent to which PSA test data would be accessible for further studies of this nature. In Phase II, we linked records from databases of two laboratories with the Ontario Cancer Registry of Cancer Care Ontario, to establish the diagnosis of prostate cancer. The extent of PSA testing was analysed in three groups of patients: those who have prostate cancer, those with other cancer diagnoses, and those without any cancer diagnosis. In Phase III, we explored the use of PSA tests in a sample of physicians in the Greater Toronto Area, by means of a questionnaire mailed to physicians of patients who did not have prostate cancer. The questionnaire ascertained the reasons for PSA testing in this group of patients.

A brief introduction to prostate cancer and PSA testing is presented, followed by the rationale for this three-phase approach.

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\(^1\) For the purpose of this thesis, PSA tests refer only to tests carried out on patients, not to quality control or standardization tests.
Prostate cancer

Prostate cancer (PCa) is now the most frequently diagnosed cancer in men, and the second most common cause of death from cancer in men\(^1\). The increase in incidence over many years is partly the result of incidental detection following transurethral resection of the prostate (TURP) as a treatment for benign prostatic hypertrophy (BPH)\(^2\,^3\). It is also related to increased use of the PSA test in the detection of prostate cancer\(^4\,^5\,^6\,^7\), about which more will be said later. The prevalence of prostate cancer in men increases dramatically with age, rising from about 12% in men below 50 years of age, up to 43% in men aged 80 years and over\(^8\). This increase in prevalence of PCa is paralleled by an increase in BPH\(^9\,^10\), though the two conditions do not appear to be directly related causally.

Most cases of PCa are relatively indolent in their course; the ten-year disease-specific survival rate in Sweden for localized PCa without treatment has been reported as about 87%\(^11\); and 15-year survival data are 81%, with no difference between the treated and untreated groups\(^12\). Conservative management (observation and delayed hormonal therapy) has been shown, in an overview analysis of six non-randomized studies,\(^13\) to result in a ten-year disease-specific survival rate of 87% in patients with Tumour Node and Metastasis (TNM) Stage T1 and T2 tumours, and 34% with Stage T3 tumours. Knowing that low volume, low grade disease generally has good survival without treatment (or with conservative treatment) makes it important to be able to select which cancers are likely to develop aggressively, and which not; at present we are largely unable to do this.

Once a diagnosis of prostate cancer has been made, PSA measurements in serum are often requested for monitoring (i) after radical treatment (to detect recurrence before clinical
symptoms)\textsuperscript{14}; (ii) before treatment (when a rise in PSA suggests intervention in the so-called "watchful waiting" group is appropriate)\textsuperscript{15}; (iii) to assess the response to palliative (e.g. hormonal) therapy\textsuperscript{16}; and (iv) to assess prognosis after initial treatment with prostatectomy\textsuperscript{17}, radiation\textsuperscript{18} or hormonal therapy\textsuperscript{19}. Most prostate cancer patients are probably monitored with PSA; however the test is not funded for this purpose in Ontario.

**Prostate-specific antigen screening**

About three-fourths of patients presenting clinically with prostate cancer have incurable disease. To detect more cancers at an early stage, when they may be curable, screening asymptomatic men with PSA has been proposed. This is a highly controversial subject, with strong advocates and strong opponents\textsuperscript{20,21} Regular PSA measurements are proposed by the American Urological Association (AUA), and the American Cancer Society\textsuperscript{22} (ACS) for screening asymptomatic patients, although others are opposed to this use, including the U.S. National Institute of Health, and the Canadian Urological Association\textsuperscript{23} (CUA). The AUA and ACS screening guidelines suggest that screening begin at age 50 in the general population, but at age 40 in blacks and in patients with a family history of prostate cancer. There is some evidence of increased case-finding with PSA screening in high-risk families\textsuperscript{24}. However, there is no proven survival benefit resulting from screening these families.

There are many issues for both patients and their physicians who are interested in screening for prostate cancer to consider, including informed consent\textsuperscript{25,26} and patient preferences\textsuperscript{27}. Because there is no proven benefit for screening, and because the consequences of screening can involve significant morbidity and even mortality, it has been
suggested that neither a digital rectal examination (DRE) nor a PSA test should be offered to patients without informed consent\textsuperscript{25}. This raises issues surrounding the mechanism by which physicians are to be kept up to date in a rapidly changing field of new studies and the latest recommendations by learned societies; issues of the amount of time required by physicians to discuss these matters with their patients and remuneration for that time. There is also the matter of beliefs or preferences of an individual physician and an individual patient, which must be weighed against the benefits to society as a whole, when it comes to an intervention of unknown overall benefit \textsuperscript{26,27}. There are also "costs" in terms of time, follow-up of abnormal results, treatment and so on. The initial laboratory component of PSA is currently paid for (in an Ontario private practice setting) by the patient (at $15 - $30 per test). This represents a small amount in comparison to the costs of biopsies, ultrasound examinations, and repeat physician visits. However, this cost to the patient may reduce access to screening for some patients in a private practice setting. The cost of the test may also represent a strain on the global budgets of hospitals, which have not been specifically supplemented to cope either with PSA testing or with the consequences of testing (biopsies, treatment etc).

Several studies have shown that PSA screening leads to a greater detection rate than clinical examination or digital rectal examination, and in a greater proportion of the cases diagnosed by PSA screening the cancer is confined to the prostate (and potentially curable) \textsuperscript{28,29,30}. There is, however, controversy as to the best cut-off level for PSA screening\textsuperscript{31,32,33,34}. One reason for this is that benign prostatic hypertrophy (BPH) and other benign prostate diseases also lead to an increase in PSA levels. The test is quite tissue specific, but is not
cancer specific. Another reason is that we do not know the true sensitivity and specificity of the test, because most studies confirm the presence of prostate cancer by means of a biopsy, and in such studies most subjects had biopsies only with PSA > 4.0 ug/L. The test has poor to moderate sensitivity (40 - 80%) and specificity (60 - 90%) at the "normal" cutoff of PSA < 4 ug/L, depending on the study. As a result there are significant false negative and false positive rates, the latter from disorders such as BPH or prostatitis. Only when serum PSA > 20 ug/L, is the positive predictive value for PCa greater than 90%. Recent evidence from the European Randomized Study of Screening for Prostate Cancer suggests that the best screen might be to reassure all patients with PSA < 2.0 ug/L that they need no further investigation, thus avoiding further testing on 70% of the male population. This strategy would lead to only 6% of prostate cancers being missed (whereas a cutoff of < 4.0 ug/L would miss 20% of cancers); it would also avoid 36% of the follow-up biopsies initiated by PSA > 4.0 ug/L.

Screening has been pursued so vigorously in parts of the United States that recent evidence suggests that PSA-detectable prostate cancer is now actually on the decrease, as yields from screening decrease because of removal from the population of PSA-detectable disease. An interesting debate has arisen concerning whether patients with symptoms of prostatism should be investigated for possible prostate cancer. The difficulty is that patients with both benign and malignant conditions may have similar symptoms; both may have elevated levels of PSA; yet the prevalence of BPH is several fold greater than that of prostate cancer, and the treatments and consequences of these two diseases are very different. Given that the lifetime probability of dying from prostate cancer is quite small (estimates vary from about 1% to about 3%), should we even be offering DRE and PSA
testing for patients with symptoms of prostatism, especially as this is a normal part of aging?

There is also considerable controversy as to the types of tumours detected in patients. Small, low-grade foci of cancer are unlikely to cause death, especially in older patients with comorbidity; yet these tumours may be detected by PSA screening. On the other hand, recent work suggests that patients whose cancers were detected by PSA screening mostly have "biologically significant" or "clinically important" cancers. It is at present difficult to try to select those patients with positive screening tests and positive biopsies who need aggressive treatment, though some promising work has been done in this regard. A study of patients at the Mayo Clinic revealed that only one of 337 radical prostatectomies performed between 1991 and 1993 involved "clinically insignificant" cancer. However, one must be cautious about interpreting “clinically significant” cancer as implying the need for aggressive treatment in all cases, as shown by the survival studies referred to previously.

Present medical practice is reasonably efficient at arriving at a diagnosis of prostate cancer, with methods such as PSA screening. However, the consequences of that diagnosis frequently lead to aggressive treatment such as surgery or radiation, depending on the stage and grade of the disease. These radical treatments have significant side effects, including intra-operative death, impotence and urinary incontinence. Before implementing screening as a matter of policy, it is important to evaluate whether such interventions will do more good than harm.

Several decision analysis studies have been conducted to try to assess whether screening for PCa using PSA and other tests is likely to be effective. Some have suggested that screening with PSA does not improve life expectancy, and may actually decrease
quality-adjusted life years\textsuperscript{50, 51}; others have argued that there is an economic rationale for such screening\textsuperscript{52}. A recent overview has suggested that there is insufficient evidence to justify PSA screening\textsuperscript{53}. No randomised controlled trial data of PSA screening exist as yet, so it is difficult to estimate whether there is net benefit or net harm from screening.

The controversy is reminiscent of the debate over screening for lung cancer, which was implemented vigorously, before randomised controlled trials demonstrated that it provided no benefit\textsuperscript{54}. A case-control study for digital rectal examination (DRE)\textsuperscript{55} as a screen for PCa showed no increase in life expectancy for screened patients, although there were indications of diagnostic suspicion bias. A nested case-control study for PSA screening\textsuperscript{56}, using banked sera, showed that the test's sensitivity decreased the longer the period of follow-up, with specificity less significantly affected, and that these parameters were, in the authors' view, able to detect prostate cancer four years earlier than clinical diagnosis. However, the impact of screening on mortality was not addressed in this study.

Against this background of screening controversy, it is interesting to note two further publications. One reports on the great variability of practice patterns of family physicians surveyed in Arizona\textsuperscript{57}. Screening is being implemented over a wide variety of patient ages, with the average being 45 years. PSA levels ranging from 3.9 ug/L to 40 ug/L were considered abnormal levels for referral by the physicians who responded. Clearly there is no uniform standard of practice, and considerable physician education is required as to how to interpret, and respond to, PSA results. The other study documents large variations in the attitudes and practices towards screening for prostate cancer among urologists in Europe\textsuperscript{58}.
PSA testing in Canada

There is little information on PSA testing in Canada. A 1995 telephone survey indicated that about 20% of men over 50 years of age in Canada have had their PSA measured, suggesting that screening is well in place. There have been a few attempts in Canada to provide background information on PSA use, and guidelines for its use to physicians, including technology assessment reports to provincial governments in Saskatchewan and Quebec. The Saskatchewan report was able to evaluate over 90% of PSA tests performed in the province between December 1993 and February 1994. For men without prostate cancer, half the tests were performed on men under 50 or over 69 years of age, ages for which many proponents of PSA screening would not suggest it be used. Most tests were performed on patients attended by family physicians, about 60% of whom indicated that they used PSA for screening purposes. For about 5% of the patients without cancer who were tested for PSA, at least one additional procedure was performed (mostly a TURP or a biopsy); and of the 5%, about half had PSA values less than the traditional “normal” cutoff of 4.0 ug/L. Almost 90% of men who had biopsies, and also had a PSA < 4 ug/L, had BPH. About 61% of men who had biopsies and also had an abnormal PSA test result, had PCa. Because of the poor performance of the PSA test, the Saskatchewan report recommended against PSA screening for PCa in men of any age.

The Quebec report found that the numbers of PSA tests carried out in hospital laboratories increased tenfold between 1990 and 1993, though there was no information available on the extent of testing in private laboratories in that province. It was estimated that over 80% of PSA testing was carried out to screen asymptomatic men, and that about
84% of PSA screen-detected prostate cancer cases would not prove fatal even if untreated. This was the rate of over-detection of PCa by screening. It was also estimated in the Quebec study that a maximum of 9 out of every 100 surgical operations for prostate cancer might avert a cancer death, but that the actual probability of this happening was much lower. The report also documented that long-term complications of surgery were impotence in previously potent men (57%), urethral stricture (4%), severe urinary incontinence (2%) and rectal injury (0.3%). The most likely cost-effectiveness ratio was calculated as $214,000 per year of life gained, over a 10-year screening program.

**PSA testing in Ontario**

Laboratory testing in Ontario is divided between the private and public sectors. The former operates for profit, and recovers its costs by billing the Ontario Health Insurance Plan (OHIP). Private laboratory testing is usually carried out on patients who visit physicians in their private practices. The public sector comprises mostly hospital laboratories, which perform tests on patients admitted to the hospital, or visiting physicians in their hospital outpatient clinics. The hospitals must bear the cost of such testing out of their global budgets.

In Ontario there are no formal policy recommendations on screening for prostate cancer. Because PSA is not funded by OHIP in Ontario, patients must pay for the test if it is requested in a private practice setting. We do not know the extent to which PSA is used either in hospital or private laboratory settings. Moreover, data on this test are not readily available. The Laboratory Licensing Branch of the Ministry of Health, which has records of every laboratory's insured tests, does not keep records of uninsured tests such as PSA; only
the laboratories have such data.

There are almost no published data about PSA testing in Ontario. The number of measurements of PSA in Ontario exploded in the 1990s; a minimum number for 1995 was 165,000 tests per year. We clearly need to know how PSA is being used in Ontario, in order to establish appropriate guidelines and policy, for the following reasons. Because PSA is an unfunded test in Ontario, outside hospital settings patients pay for the test. However, a positive test leads to many consequences, as mentioned previously, with these costs being carried by the health care system. PSA is the best diagnostic test (with limitations that are well known) for prostate disease, yet the Ministry of Health has no stated policy on its use (other than permitting it to be measured in hospitals). The test is being used widely in Ontario; yet we do not know whether the test is being used more to monitor treatment of patients with prostate cancer, or to screen or diagnose patients with symptoms compatible with prostate disease. We also do not know the reasons that physicians request the test.

The present study

This thesis reports on a study carried out to assess the utilization of PSA in Ontario. The research questions are:

(1) How much PSA testing is there in Ontario?

(2) How much PSA testing occurs in patients with a diagnosis of prostate cancer as opposed to patients without a diagnosis of prostate cancer?

(3) Under what circumstances do Ontario physicians request the PSA test?

Because of the lack of centralized data on PSA in Ontario, the study was carried out in three separate phases, each designed to answer one of these questions. Phase I examined
the province-wide use of the PSA test on patients, in both hospital and private laboratories. during the period 1988 to 1996. Our hypothesis was that the number of tests per year would increase steeply as time progressed, possibly in an exponential manner, as might be predicted for the introduction of a popular new technology. We also hypothesised that the private laboratory test volumes would reflect mostly screening, and the hospital laboratory test volumes would reflect diagnosis and monitoring of patients with established cancer. To estimate the feasibility of a more detailed province-wide study in the future, we also assessed whether laboratories stored their PSA data on computers, and whether the data could be searched by PSA result, patient name, patient date of birth, and PSA test date. The method for this phase of the study involved a questionnaire which was sent to all clinical testing laboratories in the province.

Phase II was designed to answer the second question as a feasibility study. We examined the extent of PSA testing in patients with and without a diagnosis of prostate cancer, using two laboratory databases. The first database was from a tertiary-care teaching hospital with a regional cancer centre, and was hypothesised to contain mostly cancer-related testing. The second was from a large private laboratory, performing tests mostly for physicians' private practices, and it should have mostly testing on patients without prostate cancer. A significant component of this phase was the probabilistic linkage of patient PSA test records with the Ontario Cancer Registry, which allowed us to assign a diagnosis of prostate or other form of cancer. Our overall hypothesis, based on the Quebec report mentioned above, was that about 80% of PSA tests would be carried out on patients without a diagnosis of prostate cancer. To our knowledge, only one other study exists evaluating
PSA testing in a hospital setting, which relied on the laboratory information system (generally not very reliable), rather than record linkage, to assign diagnoses \(^6\).

Phase III of the study was designed to determine whether the PSA tests in a defined period of time (1995-1996) were requested for the diagnosis of symptomatic patients; to follow up on other diagnostic procedures or tests (such as a digital rectal examination or an ultrasound measurement); or to screen an asymptomatic patient for prostate cancer. This phase required a random sample of patients without the diagnosis of prostate cancer. From this sample, which was generated from data collected in Phase II, the physicians involved with the care of these patients were identified, and a questionnaire was sent to them regarding the purpose of the testing for that case. Our hypothesis was that the majority of PSA tests in patients without prostate cancer would be carried out by family practice or general practice physicians, and that most of the tests would be for screening patients without symptoms or signs of prostate cancer.
METHODS

Phase I - the Provincial PSA workload questionnaire

A questionnaire was sent to all laboratories in Ontario which carry out clinical testing, and undergo proficiency testing under the aegis of the Laboratory Proficiency Testing Program (LPTP), a mandatory program for all clinical laboratories. We sent a draft copy of the questionnaire to Clinical Biochemists in three teaching hospitals, three community hospitals, and two private laboratories in the Metropolitan Toronto area. Their feedback was incorporated into the questionnaire, which was then piloted at four more laboratories outside Toronto. Where possible the questions were restricted to yes/no, or numerical responses, which made it easier to complete and analyse.

The questionnaire contained eleven items (see Appendix 1). One item documented the number of PSA tests over the period since the test was introduced in Ontario (1988-1996), to the extent that this information was reported by the responding laboratories. We wished to avoid duplicate counting of the tests by laboratories that referred specimens on to other centres to do the test for them (so-called referred-in testing); this issue was assessed by the first two questions. Several items were designed to ascertain which laboratories have computerized data for PSA testing. It was desirable that the laboratory databases contained patient demographic information that would allow unique identification of the patient (such as name and date of birth). At the time of this survey, very few hospitals had Ontario Health Insurance Numbers (OHIN) in their records (because hospitals do not bill the OHIP reimbursement plan). Two other questions assessed the extent to which those institutions
with appropriate databases would be willing to make them available under approved research agreements. The questionnaire specified that information was “required only for patients residing in Ontario”; however total workload counts probably include all patient tests, and may be slightly increased by work done on patients outside the province.

Two major issues relating to the process of administration of this questionnaire were confidentiality of PSA test numbers, and the proprietary rights of the information. It was decided to conduct this phase of the study through an arms-length body, the Laboratory Proficiency Testing Program (LPTP) of the Ontario Medical Association. The LPTP was chosen because all laboratories are familiar with its methods of operation, with its staff, and its methods of communication. It also has an excellent reputation for confidentiality. The LPTP agreed to send out our questionnaire to every laboratory in the Province (in case there were recent PSA testers), to collect and collate the data, and to present them in aggregate form to our research team.

The “arms length” approach made it impossible to oversee data entry. Laboratories enter data of this nature on to LPTP forms several times a year as part of the proficiency testing in Ontario, making it a somewhat routine procedure for them. As documented below, some were unable to access all or part of their data, because of difficulty retrieving archived information.

Data were analysed as the total test count per year reported by each laboratory, summed over all laboratories, during the period 1988 - 1996. Because of the timing of the questionnaire, we could obtain data for only the first four months of 1996.
Phase II - PSA testing in patients with and without cancer

We linked records between two PSA laboratory databases and the Ontario Cancer Registry (OCR) to establish the diagnosis of prostate cancer and other cancers. In a study in a laboratory setting this is very important, as reliable diagnostic information is rarely obtained. Record linkage brings together information from two sets of records that are believed to be related. Appendix 2 provides a brief summary of the topic of probabilistic linkage, as initially developed by Newcombe, who based his approach on Bayes’ theorem of conditional probability. The question being asked is: what is the likelihood of two records belonging to the same patient given that one or more fields within those records agree? Individual patient records may be said to be linked (or matched) when the information in two sets of records is either identical or very close to being so; they may be said to be unlinked if they are different either completely or almost completely. A more rigorous mathematical approach was developed by Felegi and Sunter, based on conditional probability theory. Howe and Lindsay introduced further developments in relation to coping with the problem of partial agreement of identifying components of records. They explored methods of defining “blocking” factors for matching, a procedure for dividing large databases into smaller parts, making it easier to compare large sets of records.

In our linkage study we performed a “deterministic” match sometimes, and a “probabilistic” match more often. The former implies that only exact matches of fields having high reliability and uniqueness, such as health insurance numbers. The latter allows
for a margin of error, and is particularly useful when linkage depends on fields such as dates of birth or names, which are more prone to error.

There were two sources of PSA data. The first was a set of laboratory data from Dynacare Laboratories, a private laboratory; and the second a set of laboratory data from Sunnybrook Health Science Centre (SHSC), a hospital laboratory. SHSC has PSA data from a largely cancer population referred for testing from teaching hospitals in Metropolitan Toronto. The Dynacare database contains PSA data from all over Ontario. It was important to be certain of the diagnosis of prostate cancer applying to any particular patient, because the laboratory databases do not receive reliable diagnostic information, and patients could appear on more than one laboratory’s database. Research agreements were drawn up between the research team and the OCR and Dynacare, such that patient confidentiality was assured. All patient identifying information remained within the OCR’s secure area at all times.

Before carrying out the linkage, records on women and on all patients who had died before 1988 were removed from the OCR file (whose records start from 1964) because prior to this year PSA was not available in Ontario. This reduced the size of the OCR file to 242,063 records, making computing and clerical review faster and less subject to error. No out-of-province records were included.

Automatch software was used, as outlined in Appendix 3. The first stage, referred to as “unduplication”, involved drawing together those patient records with PSA test results which belong to the same patient. Once all of these records were linked together, the PSA test file was compared with the OCR patient file in a “many-to-one” match, which allowed
for the fact that about 4 - 6% of patients have more than one cancer diagnosis. Some cleaning up of the file was required, since some results were entered as missing values or as zeros, and some patient names were entered as blanks, etc.

The following is a summary of the steps by which Automatch was used to carry out our record linkage. Similar blocking variables and matching variables were used in the two stages of the linkage process.

i) The size of each record on each file was first specified as the number of characters on each line. A file name, including the full path, was also specified.

ii) Files are referred to as File A (the PSA file to be tested against a reference file) and File B (the OCR reference file). These were prepared so that all fields were of fixed length. For each file, the variable names were defined, and the location of each of these in the file specified. This was done in a simple DOS text editor, using ASCII format. It was important to specify whether there are any missing values, and different codes were assigned to different types.

iii) The combination of these variables constituted a data dictionary, one for each file, which was then compiled for further use.

iv) The next step was to select the blocking variable(s). Because the number of possible unlinked combinations of records was so large, it was most efficient to process this comparison in "blocks" of about 50 000 bytes. As an example, suppose there were two files of 1000 records each, that were divided into blocks of 10 each in file A and B. This would lead to 100 blocks x 10 records in file A x 10 records in file B, i.e. 10 000 pairs examined, rather than a million pairs without the use of blocking. The software automatically divided
the files up, based on our blocking variables, which were first letter of last name, first letter of first name, and patient year of birth, fields with relatively few missing values (see below).

v) After blocking variables were defined, the variables by which matching was to be carried out, were selected. Usually, such linkage studies involve several “passes” using different blocking criteria and different matching criteria. During the first pass, it is desirable to have fairly strict matching criteria, to create a high probability of linkage. We chose OHIN for the first pass. Perfect matches were considered reliable, and were not looked at again. The second pass included the same variables for matching as the blocking variables. This allowed the matching of many records in which OHIN was either missing (Sunnybrook data) or filled with zeros (some Dynacare records).

vi). An index for each pass was created, followed by a frequency analysis for each file, to keep track of what matches occur (during unduplication and during linkage).

vii). Matches were given positive weights, and non-matches negative weights, to separate records as far as possible into the two groups. It was necessary to define cutoffs for these weights that were to be regarded as matched, and for the weights that were to be regarded as unmatched, with a "grey area" in between, which was subjected to a clerical (manual) review. These cutoffs were assigned empirically, for each matching routine, based on a look at the bimodal distribution obtained, and comparison of some individual matched records manually - especially those immediately above and below the weight cutoff. Further detail about weights are given in Appendix 3.

viii). Those records with weights above the cutoff were regarded as linked; those below the cutoff, and those labelled as "residuals" after clerical review, were sent for a second pass
to seek a match using different blocking variables etc. Further passes used blocking variables defined by Ontario Health Insurance Plan (OHIP) number, NYSIIS\textsuperscript{2} code, and date of birth (see Appendix 2). Those records with weights below the lower cutoff were regarded as unlinked, and therefore considered not to have a cancer diagnosis. Those which were linked were assigned the cancer diagnoses in the OCR file.

During the linkage phase, it was important to have all patient names and demographic information available at all times. After completion of the linkage, all patient identifiers were stripped from the final file used for analysis. Because of the size of the data files, the SAS computer program was used, either on the Unix computer at the OCR, or on a pentium desktop computer.

The databases were first analysed to assess the completeness of the various fields. Further analysis was carried out comparing proportions of tests within diagnostic categories both within and across the two databases (Sunnybrook and Dynacare). Both approaches were required, because the two databases draw on different physicians and patients, although this distinction has become somewhat blurred in recent years, as Sunnybrook takes on a private laboratory character. It is more likely that testing practices within patient diagnostic group can be generalized to the province as a whole, particularly as regards patients without cancer of any kind, most of which reach Sunnybrook from other private laboratories and other hospitals. The numbers of PSA tests in patients with and without prostate or other cancers were counted, and the distributions of PSA tests by patient age (in decades) and by PSA test value, were documented. Some of this was done over the entire database, and

\textsuperscript{2} New York State Intelligence Information System, a phonetic software package
Data were analysed visually/graphically: univariate statistics such as mean and median are calculated; and the Mantel-Haenszel Chi-squared statistic was used to assess differences of distributions by diagnostic or other category. We recognise that, strictly speaking, the assumption of independence of events required for this test is not met; however the actual number of tests is close to one per patient, as will be seen later. The 95% confidence limits of a measured proportion (p), used to estimate sample size, were calculated according to the formula: 

\[ p \pm z \sqrt{pq/n} \]

where \( q = (1-p) \), \( n \) is the number of observations, and \( z \) is the standardized normal deviate (1.96 because the sample sizes were so large). Two proportions were compared by calculating \( z \) according to the formula:

\[ z = (p_1 - p_2) / \sqrt{pq[1/n_1 + 1/n_2]} \]

where \( p = (n_1 p_1 + n_2 p_2) / (n_1 + n_2) \) and \( q = (1-p) \).

We were interested in the proportion of PSA testing performed on patients with prostate cancer and without cancer. We were also interested in the proportions within these diagnostic categories performed by Sunnybrook and Dynacare laboratories. For sample size calculations, we could use either the estimate from Quebec\(^6\) that 80% of PSA testing is done on patients without a prostate cancer diagnosis, or that from Saskatchewan\(^6\) that 63% of physicians reported using PSA for screening purposes. The former proportion was used, because the methodology was also based on analysis of large sets of hospital PSA data, rather than a questionnaire. To estimate this proportion within 5%, using an alpha of 0.05, the sample size required is 246; to estimate it within 1%, the sample size is 6,150. We have sufficient data within our databases for the latter estimate.
Phase III - reasons for PSA testing in patients without prostate cancer

In this phase of the study, we obtained information, by surveying physicians regarding the reasons that they requested PSA tests on particular patients during the time period 1995-6. For sample size calculations, we used the proportion from the Saskatchewan study which found that 63% of physicians reported using PSA for screening purposes. The Saskatchewan study was also based on a questionnaire mailed to physicians, though the responses reflected physician-reported practice rather than patient-specific practice as in our case. With alpha = 0.1 for the 90% confidence limits of a proportion of 0.63, we needed information from 250 charts to establish this proportion within 5%. If we accepted a 60% response rate to the questionnaire, we required 418 mailings. Since we assumed that we would be unable to locate some physicians, we sent out about 500 questionnaires.

Confidentiality

Confidentiality was a major issue, for the patient, for the physician, and for Dynacare Laboratories, who did not want to upset their physician clients with an unexpected approach to participate in the research. This was one of the main reasons for sending the questionnaire by Dynacare’s courier to the (named) physician attending the patient. Our research agreement with Dynacare specified that no patient or physician information would be returned to the research team. The Ontario Medical Act stipulates that it is not a professional misconduct to release patient information, even without the consent of the patient, provided that the physician has been reasonably assured that the information will be kept confidential. We assured the physician, in our package, that we were interested only in
their specialty and in the specific patient-related responses; a study number was the only identifier on the returned questionnaire.

The ethics of using patient information (and even laboratory workload information) for research purposes was a major issue in this thesis, involving all three phases. The study was approved by the Ethics Review Board of Sunnybrook Health Science Centre prior to its initiation. It was also approved by the individual organizations involved in the research (the LPTP, the Ontario Cancer Registry, Dynacare Laboratories, and Intercounty Laboratories). Individual research agreements were drawn up between the research team and these organizations.

Selecting the physicians

The physicians were identified as those attending patients in 1995 and early 1996, to represent current practice. They were identified to us only by their practice postal code. The patient PSA results were identified as a random subset of 1,000 of the 1995 and 1996 patients without a diagnosis of prostate cancer, obtained in Phase II. These were restricted to the Greater Toronto Area by postal code, yielding 533 patient records. At the time we selected this subset, linkage with the OCR file was possible only up until December 31 1994; consequently there was a risk that some patients might have developed prostate cancer in 1995. To this sample of 533 was applied a linkage with the OCR pathology database, which gave a pathology diagnosis, was updated more quickly than the whole OCR file, and was about 95% complete. This two-pass linkage was based on blocking with (a) surname and first given name initials, and (b) date of birth, and yielded about 6% of the sample as having a cancer diagnosis, leaving us with a final 507 patient records as possible.
Because Sunnybrook does not have postal codes on its databases, only Dynacare patients were in the final sample. Of the 507 Dynacare PSA records, 79 were part of the London database, and could not be accessed by staff in the Brampton laboratory who were assisting us in the study (something we discovered only after the questionnaires were sent out). Thus our starting denominator was 428 for the main mailing.

**Questionnaire design and administration**

A self-administered questionnaire, rather than an interview with the physician, was selected as it was cheaper, easier and reasonably rapid, especially considering our sample size. It suited this phase of our study, which sought factual information from physicians, as opposed to seeking opinion or making judgements about individual patients. We did, however, allow for the possibility that information would be collected in person by a member of the research team. Draft questionnaires were sent to four family physicians and two urologists, to ensure appropriate content, clarity of wording, and design.

The Dillman method (adapted) was used because it has been well validated and usually delivers a good response rate. This normally involves an initial mailing of the questionnaire and a follow-up reminder letter two weeks later. However, the follow-up phone call required by this method, if no reply has been received, was not possible because of our research agreement. Due attention was given in our study to the appearance of the materials to attract the interest of the targeted provider of information, such as personal addressing of the envelope and letter, and an actual signature. To ensure a returned reply, we used a self-addressed, stamped return envelope. For ease of administration, the
questionnaire was coded for with a simple “yes” or “no” format, wherever possible. Where choices were applicable (such as the type of symptoms experienced by the patient), a list was provided, for physicians to circle those appropriate.

Page one of the questionnaire (see Appendix 4) ensured that the patient did not have prostate cancer, in case of an error during Phase II, and requested the physician’s practice specialty. The second page asked whether the reason for requesting the particular PSA test was to investigate symptoms; to investigate further the results of another procedure; to repeat a previous PSA test; to screen for prostate cancer in a patient without symptoms; or for other reasons. If symptoms were a cause for testing, we asked for their nature, and included a list which commonly occur in BPH. 76 77

The pilot and the main mailing

The questionnaire was piloted using 49 records, which were from the Sunnybrook database, and mostly came from Intercounty Laboratories. Of these, 47 records were confirmed to belong to patients within the desired area by the laboratory manager. A covering letter indicating that this was the pilot phase of the study was included. The covering letter requested information about the clarity of the letter to physicians and of the questionnaire, and how long the questionnaire took to answer. Very few of the responders answered the pilot-specific questions; those who did indicated that it took about 5-6 minutes to complete the questionnaire. A few suggestions were made which led to the wording being slightly altered. Replies were received from 35 of the 47 pilot questionnaires (72%), but only 27/47 (57%) could be analyzed because some physicians could not be reached and some could not find the required information in the chart.
Within two months of the pilot study, we delivered to each one of the physicians (see Appendix 4), courtesy of Dynacare Laboratories courier, a copy of a one-page summary of the research protocol, a copy of a letter to the physician (two sides of a single page) requesting her/his participation in the research; and a copy of the questionnaire (two sides of a single page). The letter to the physician was printed on University of Toronto letterhead. A stamped, self-addressed return envelope was provided to each physician, to help improve the return rate. As an inducement for busy physicians to complete the questionnaire, with each completed questionnaire there was one chance at five prizes of a weekend for two at a well-known local inn. With 500 mailings and an anticipated response rate of 60% this represented a 1/60 chance of winning.

A duplicate of the original test requisition, containing patient demographic information, was included with the package, because we were interested in the reason for a particular PSA test being requested (as opposed to the first test, or even the most recent test). This was important because PSA tests could have been done through other laboratories. The questionnaire, which was the only sheet returned, had only a unique study number, so that no patient- or physician-identifiable information reached the research team.

We combined the responses from the pilot study and the main mailing, in order to increase the number of responses we could analyse. The physicians mailed to were, in both cases, in the greater Toronto area; and, in both cases, were randomly selected. The minor changes in wording following the pilot did not affect the main questions asked. The analysis included calculation of a response rate, estimation of the proportion of PSA tests used for investigating symptoms of prostatism, the proportion used to follow up another diagnostic
procedure (such as DRE), to follow up a previous PSA test, for screening, etc. We obtained estimates of the proportion of testing carried out by the various physician specialties, and the age of the patients being tested.
RESULTS

Phase I - the Provincial workload questionnaire

The questionnaire was sent to 292 laboratories in Ontario, and replies were received from 272, of which 45 indicated that they carry out PSA testing “on site”. This is in accordance with the 45 laboratories which received LPTP testing samples during routine surveys for PSA at that time. Since many hospitals have several laboratories, it is probable that most of the apparent non-responders had in fact submitted replies. Further, LPTP testing in Ontario is compulsory, so it is unlikely that any testing sites were missed.

Our responses indicated that the laboratories doing referred-in PSA testing usually do not keep a separate count of hospital and private laboratory referred-in work, therefore we were unable to estimate the amount of work attributable to private laboratories and the amount attributable to hospital laboratories.

Of interest is that 11 laboratories reported sending their PSA specimens outside Ontario. While we cannot estimate what proportion of total PSA workload this out-of-province testing was, these data are included in the total count. In follow-up, one of these laboratories indicated that all of their testing (which was not reported) was for clinical trials studies only.

The annual test count for Ontario is plotted in Figure 1 for each of the years 1988 through 1995, with 1996 data projected from four months’ data multiplied by three. The actual counts, the number of laboratories indicating that they were testing, and the number testing and able to access their data, are indicated in Table 1, columns 2 - 4. From 1992,
only three laboratories performing PSA testing did not provide their annual test count, suggesting that the counts from that year onwards are more reliable. These data show that both the number of laboratories doing PSA testing, and the total number of PSA tests, increase steeply over time, and continue to rise in 1996.

An alternative way of evaluating the data in Table 1 is to calculate the average number of tests per reporting laboratory (column 6) based on the number of laboratories submitting data (column 4), and to multiply this by the number of laboratories indicating they were testing for PSA (column 3), yielding an average number of tests per testing laboratory (column 7). This process yields a higher test count for each year, because it takes into consideration missing data. However, it assumes that non-reporting laboratories test at the same rate as reporting laboratories. The overall trend remains the same, irrespective of the method used. The average number of tests per reporting laboratory, and the number of laboratories unable to access their data, stabilised from 1992 onwards.

The feasibility of obtaining access to the Ontario PSA data was assessed in the questionnaire. Of the 45 laboratories which reported doing PSA testing, 22 indicated that their records were computerized; 13 reported that they were not computerized and/or not searchable. Four computerized laboratories indicated they could not search for PSA results, and three did not respond to this question. Two others did not indicate whether they were computerized.

Of these 22 laboratories, 19 indicated that they would be willing to assist in further studies, and allowed their names and addresses to be sent to us. Of these, two were unsearchable, and three reported no test volume. The 14 remaining laboratories together accounted for about 117,000 PSA tests per year, roughly one-third of the Provincial workload.
Figure 1. The combined PSA test count of all reporting laboratories in Ontario, between 1988 and 1996.
Table 1 - number of PSA tests of participating laboratories, and ability to access data

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Patient Tests</th>
<th>Number of laboratories</th>
<th>Average number of tests per submitting lab&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Average number of tests per testing lab&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>testing for PSA</td>
<td>testing and submitting data</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>1,259</td>
<td>8</td>
<td>1</td>
<td>1,259</td>
</tr>
<tr>
<td>1989</td>
<td>8,554</td>
<td>10</td>
<td>4</td>
<td>2,139</td>
</tr>
<tr>
<td>1990</td>
<td>26,192</td>
<td>11</td>
<td>6</td>
<td>4,365</td>
</tr>
<tr>
<td>1991</td>
<td>52,654</td>
<td>11</td>
<td>7</td>
<td>7,522</td>
</tr>
<tr>
<td>1992</td>
<td>103,370</td>
<td>14</td>
<td>11</td>
<td>9,397</td>
</tr>
<tr>
<td>1993</td>
<td>159,054</td>
<td>21</td>
<td>18</td>
<td>8,836</td>
</tr>
<tr>
<td>1994</td>
<td>239,354</td>
<td>29</td>
<td>26</td>
<td>9,206</td>
</tr>
<tr>
<td>1995</td>
<td>278,187</td>
<td>37</td>
<td>34</td>
<td>8,812</td>
</tr>
<tr>
<td>1996&lt;sup&gt;5&lt;/sup&gt;</td>
<td>337,569</td>
<td>38</td>
<td>35</td>
<td>9,645</td>
</tr>
</tbody>
</table>

<sup>3</sup> This value is calculated by dividing column 2 by column 4.

<sup>4</sup> This value is calculated by multiplying column 5 by column 3.

<sup>5</sup> The 1996 data were projected based on four months of data multiplied by three.
Phase II: PSA testing in patients with and without cancer

Unduplication and linkage

A PSA test file was created from two sets of data, one from Dynacare Laboratories (147,511 PSA test records, between 1992 and June 1996), and one from Sunnybrook Health Science Centre (86,815 patient PSA test records, between 1988 and June 1996). The latter source had non-redundant data on two computers: a Sunquest (SQ) with 60,776 records and an Alpha Micro (AM) with 26,039 records. These were all combined to yield a PSA test file containing 234,326 records, which was used in the unduplication process as described previously. This represents about 19% of the Ontario PSA test records (from Table 1). At this stage we did not know the true number of patients these various records belonged to, because some patients probably had records on more than one database, and some had several records within one database.

An overview analysis of the combined PSA data file and the OCR data file was carried out. If information was entered either as blank spaces or as zeros, the data was regarded as missing. This is summarised in Table 2, giving percentage missing for the Alpha Micro (AM), Sunquest (SQ), Dynacare (DY) and OCR databases for the relevant fields that each carried.

Table 3 provides a summary of the results of the five passes for “unduplication” or grouping together of PSA records for each patient: out of the 234,326 PSA test records in the file, 95,503 are duplicates (i.e. have more than one PSA test done on the same patient) and 138,823 patients have at least one PSA result. Details are provided in Appendix 2. The first
blocking field, OHIN, yielded the second largest yield of duplicates, and required no clerical review because only exact matches were accepted (deterministic matching). This “second place” yield is related to the fact that the Sunnybrook databases did not have OHIN as a field. The second pass (names and date of birth) yielded the largest number of duplicates, and included some after clerical review. The third pass (using OHIP) produced no additional duplicates, largely because Dynacare’s data did not have this field. The fourth pass (NYSIIS) yielded 1,231 new duplicates, mostly at the stage of clerical review; and only 81 further duplicates were obtained in pass five. Note that only 6,485 records (2.8%) of all records were subjected to clerical review, so that any errors would not have a large impact on the outcome of the linkage.

Table 3 also contains a summary of the five passes for the linkage with the OCR file, which was current to the end of 1995 at the time of this linkage. The same blocking pattern and the same 5 passes were carried out, yielding 19,869 patients with a diagnosis of cancer of any sort, out of the 138,823 patients.

Some of the Dynacare PSA tests were repeated on the Sunnybrook database, because Sunnybrook did Dynacare’s PSA testing for a period of time. These redundant tests were removed from subsequent analysis. Patients would, however, occur on both Sunnybrook databases, and some on the Dynacare database; these were combined during unduplication. We also discovered non-numeric workload exclusion codes (such as NSR for “no sample received”) instead of results for 29 records, and 61 missing values, so that 90 additional records were excluded.
Table 2

Missing information (expressed as percent) on PSA and Ontario Cancer Registry Files

<table>
<thead>
<tr>
<th>Field</th>
<th>PSA Files</th>
<th>OCR File</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AM</td>
<td>SQ</td>
</tr>
<tr>
<td>Surname</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>First name</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Second name</td>
<td>94.9</td>
<td>71.5</td>
</tr>
<tr>
<td>OHIN</td>
<td>85.3</td>
<td>-</td>
</tr>
<tr>
<td>OHIP</td>
<td>97.1</td>
<td>-</td>
</tr>
<tr>
<td>Birth date</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Birth year</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Birth month</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Birth day</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Postal code</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vital status</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cause of death</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diagnosis ICD9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Date last seen</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- means that the field was not available on that file.
<table>
<thead>
<tr>
<th>Process</th>
<th>Unduplication (internal linkage)</th>
<th>Matching (i.e. have cancer)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-grey area processing</td>
<td>Post-grey area processing</td>
</tr>
<tr>
<td>Pass 1: deterministic match on OHIN records</td>
<td>234,326</td>
<td>Same</td>
</tr>
<tr>
<td>exact duplicates/matches</td>
<td>41,124</td>
<td></td>
</tr>
<tr>
<td>clerical review</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>residuals</td>
<td>193,202</td>
<td></td>
</tr>
<tr>
<td>Pass 2: last and first name initials and date of birth records</td>
<td>193,202</td>
<td>193,202</td>
</tr>
<tr>
<td>duplicates/matches</td>
<td>52,431</td>
<td>53,067</td>
</tr>
<tr>
<td>clerical review</td>
<td>1,128</td>
<td>0</td>
</tr>
<tr>
<td>residuals</td>
<td>139,643</td>
<td>140,135</td>
</tr>
<tr>
<td>Pass 3: OHIP</td>
<td>No matches</td>
<td></td>
</tr>
<tr>
<td>Pass 4: NYSIIIS phonetic code records</td>
<td>140,135</td>
<td>140,135</td>
</tr>
<tr>
<td>duplicates/matches</td>
<td>9</td>
<td>1,231</td>
</tr>
<tr>
<td>clerical review</td>
<td>4,404</td>
<td>0</td>
</tr>
<tr>
<td>residuals</td>
<td>135,722</td>
<td>138,904</td>
</tr>
<tr>
<td>Pass 5: records</td>
<td>138,904</td>
<td>138,904</td>
</tr>
<tr>
<td>duplicates/matches</td>
<td>8</td>
<td>81</td>
</tr>
<tr>
<td>clerical review</td>
<td>953</td>
<td>0</td>
</tr>
<tr>
<td>residuals</td>
<td>137,943</td>
<td>138,823</td>
</tr>
</tbody>
</table>

Totals: 234,326 records read in
95,503 duplicates (have more than one PSA record) 21,107 matches (cancer, any sort)
138,823 residuals (have at least one PSA record) 19,869 patients with one or more cancers

* The number of residuals is kept constant to allow for patients with multiple cancer records on the A file to be matched with a single patient PSA record on the B file.
Sunnybrook PSA data
Sunquest + Alpha Micro
(26,039) (60,776)

Dynacare PSA data
(147,511)

Standardized PSA data sets
produced by Autostan + Excel

SAS merge program
(234,326)

Internal linkage ("unduplication")
95,503 duplicates (i.e. patients with more than one test)
138,823 residuals (have at least one PSA test)

Linkage with OCR file
21,107 matches for cancer
19,869 patients with at least one cancer

Analysis

Patient breakdown: prostate cancer (11,867) other cancer (8,002)
without cancer (118,954)

Figure 2. Flow chart of the linkage of PSA and OCR files.
### The Ontario Cancer Registry cancer sites

<table>
<thead>
<tr>
<th>ICD9 Code</th>
<th>Site</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>185</td>
<td>Prostate</td>
<td>11,869 (59.7)</td>
</tr>
<tr>
<td>188</td>
<td>Bladder</td>
<td>1,379 (6.9)</td>
</tr>
<tr>
<td>153</td>
<td>Colon</td>
<td>1,332 (6.7)</td>
</tr>
<tr>
<td>162</td>
<td>Lung</td>
<td>1,155 (5.8)</td>
</tr>
<tr>
<td>189</td>
<td>Kidney</td>
<td>643 (3.2)</td>
</tr>
<tr>
<td>154</td>
<td>Rectum</td>
<td>625 (3.1)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>2,866 (14.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>19,869 (100.0)</td>
</tr>
</tbody>
</table>
The OCR file documents multiple cancer primaries at different primary sites. Of the 19,869 cancer patients (with 21,107 records) who had one or more PSA test results at any time (i.e. before or after diagnosis), site 1 (i.e. first cancer diagnosed) accounted for 18,702 out of 19,869 (94%) of the cancers; site 2 (i.e. two cancers) accounted for a further 1107 (5.6%) and sites 3, 4 and 5 a further 60 (0.3%), i.e. 5.9% of patients had more than one cancer diagnosis. The breakdown of these diagnoses was as outlined in Table 4 (only cancers featuring 3% or more of the database are specified); prostate cancer accounted for 60% of these PSA test records.

**PSA testing in the two laboratory databases**

The largest number of PSA tests were on the Dynacare database (147,430 or 63.9%), performed on 95,658 patients. A further 83,326 (36.1%), performed on 43,165 patients, were on Sunnybrook’s combined databases. The proportion of patients having at least one PSA test on both Dynacare and Sunnybrook databases was 7.9%. Thus the majority of PSA testing occurred within only one of the two databases. This is of interest in terms of the feasibility of tracking all of an individual patient’s PSA test results in future studies in the province. However, we cannot be sure that this is generalizable beyond these two databases.

The total number of patients with prostate cancer was 11,867, of whom 7,721 (65 %) were on the combined Sunnybrook databases, and 4,146 (35 %) were on the Dynacare database. Corresponding figures for patients with other types of cancer were: total 8,002, Sunnybrook, 3,540 (44 %) and Dynacare, 4,462 (56 %). There were 118,954 patients without a cancer diagnosis of which 31,904 (27 %) were on the Sunnybrook databases and 87,050 (73 %) on the Dynacare database. As a proportion of each laboratory’s patients, 7,721/43,165 (17.9%) of Sunnybrook’s patients had PCA; 3,540/43165 (8.2%) had other cancers; and 31,904/43,165
had no cancer diagnosis. The corresponding figures for the Dynacare database were, respectively: 4,146/95,658 (4.3%) PCa; 4,462/95,658 (4.7%) other cancer; and 87,050/95,658 (91.0%) no cancer. Overall, 118,954 of 138,832 patients (85.7%) undergoing PSA testing had no cancer; 11,867 of 138,823 (8.5%) had prostate cancer, and 8,002 of 138,823 (5.8%) had cancers other than prostate, i.e., 91.5% had no prostate cancer.

The situation for test records is very similar. As a proportion of all of Dynacare’s PSA records (147,430), only 2.8% related to patients with prostate cancer, 3.2% had another cancer, and the remainder had no cancer diagnosis. As a proportion of all of Sunnybrook’s PSA records (83,326), 32,486 (39.0%) related to patients without cancer of any sort 43,654 (52.4%) related to patients with prostate cancer, and 7,186 (8.6%) to patients with other cancers. Overall, 171,070 (74.1%) of PSA test results were on patients without cancer; 47,782 (20.7%) on patients with prostate cancer; and 11,904 (5.2%) on patients with cancers other than prostate.

These data support our initial hypotheses. Most PSA testing occurred on patients without prostate cancer and most of this testing was in the private laboratory database. Conversely, there was relatively little PSA testing on prostate cancer patients, and most of this occurred within the hospital setting. We cannot, however, generalize the above percentages to the Province as a whole, because we do not have a well-defined denominator. Further, Sunnybrook is not representative of the general hospital sector, being a regional cancer centre; and Dynacare may not be representative of other private laboratories.
The frequency of PSA testing within patients, by diagnostic category, was as listed in Table 5. This represents all PSA tests in the databases over the period 1988 - 1995 inclusive. The mean and median of the PSA distributions are higher in patients with prostate cancer than in patients with other cancers, or without cancer. About 70% of patients without cancer, and with cancers other than prostate, had a single PSA test, whereas only 36% of patients with prostate cancer had a single test. The 95th percentile is about 3 tests per patient in the former two categories, and about 17 tests in patients with prostate cancer. Some individual patients, however, had as many as 30 - 60 tests each. Several of those in the group without a cancer diagnosis had very elevated PSAs, and it is likely that these few patients were mis-classified, either because their diagnoses were not on file at the OCR, or through the process of linkage. In general, the testing intensity per patient is higher in the patients with prostate cancer, as might be expected. The Mantel-Haenszel Chi-squared test rejects the null hypothesis that the distributions are from the same population, considering all three diagnostic groups, and also comparing the two non-prostate cancer groups.

The frequency of testing between 1988 and 1995

The frequency of testing within these databases, by year of testing, is indicated in Figure 3. Overall, the steep slope of the curve for patients without cancer reflects that for PSA testing in the Province of Ontario as a whole. This confirms that most of the dramatic increase in PSA testing is in patients without prostate cancer. Given that a median of one test per patient is performed on these patients, these data suggest that an increasingly large fraction of the population is being tested (either for diagnosis or screening) with PSA

For patients with either prostate cancer,
or other cancers, the curve is much less steep, and levels off quickly. This suggests that the test was rapidly incorporated into the management of these groups of patients. It is also possible that the failure of the test numbers to continue to rise may be affected by a significant number of patients with cancer dying over time.
Table 5

The frequency (and cumulative percent) of PSA testing in the PSA test file (abbreviated)

<table>
<thead>
<tr>
<th># of PSA tests per patient</th>
<th>No Cancer</th>
<th>Other cancer</th>
<th>Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86,556 (72.7)</td>
<td>5,737 (71.7)</td>
<td>4,239 (35.7)</td>
</tr>
<tr>
<td>2</td>
<td>20,926 (90.3)</td>
<td>1,413 (89.4)</td>
<td>1,981 (52.4)</td>
</tr>
<tr>
<td>3</td>
<td>7,348 (96.4)</td>
<td>489 (95.5)</td>
<td>1,223 (62.7)</td>
</tr>
<tr>
<td>4</td>
<td>2,521 (98.6)</td>
<td>202 (98.0)</td>
<td>880 (70.1)</td>
</tr>
<tr>
<td>5</td>
<td>937 (99.3)</td>
<td>69 (98.9)</td>
<td>698 (76.0)</td>
</tr>
<tr>
<td>6</td>
<td>354 (99.6)</td>
<td>31 (99.2)</td>
<td>537 (80.5)</td>
</tr>
<tr>
<td>7</td>
<td>173 (99.8)</td>
<td>23 (99.5)</td>
<td>431 (84.2)</td>
</tr>
<tr>
<td>8</td>
<td>91 (99.9)</td>
<td>11 (99.7)</td>
<td>353 (87.1)</td>
</tr>
<tr>
<td>9</td>
<td>54 (99.9)</td>
<td>7 (99.8)</td>
<td>295 (89.6)</td>
</tr>
<tr>
<td>10</td>
<td>26 (99.9)</td>
<td>5 (99.8)</td>
<td>230 (91.6)</td>
</tr>
<tr>
<td>15</td>
<td>5 (100)</td>
<td>1 (100.0)</td>
<td>214 (93.4)</td>
</tr>
<tr>
<td>20</td>
<td>2 (100)</td>
<td>1 (100.0)</td>
<td>20 (99.0)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>6 (100)</td>
<td></td>
<td>5 (100)</td>
</tr>
</tbody>
</table>

Mean: 1.49 1.44 4.04
Median: 1 1 2

Total: 138,823 (100%) 8,002 (100%) 11,867 (100%)

M-H Chi-square (all three diagnostic groups, df = 26): = 28.767 (p < 0.0001)

M-H Chi-square (first two diagnostic groups, df = 13): = 47.3 (p < 0.001)
Figure 3. Number of PSA tests by year of testing, by diagnostic category.
Table 6 shows the PSA testing frequency in patients with prostate cancer and with other cancers, in relation to the time before (and after) a cancer diagnosis was made. In patients with prostate cancer, almost half of the pre-diagnosis tests were done within three months of the diagnosis date, consistent with a diagnostic use of the test, although screening for unsuspected cancer cannot be ruled out. For testing times earlier than this, it is interesting to speculate that these represent screening for prostate cancer, since most diagnoses would be made within a few months of an elevated test, though we have no direct evidence for this. The even distribution of testing as a function of time after prostate cancer is diagnosed is consistent with routine monitoring of patients, either to follow the response to therapy, or to screen for recurrence. As a proportion of all PSA tests done on patients with prostate cancer, 5,169/42,651 (89%) were done after diagnosis, indicating that the vast majority of testing in this group is for monitoring of established cancer. This proportion will likely change over time, as it is influenced by the extent to which PSA testing was available in the earlier years, and by the extent to which screening was in place (which is increasing rapidly).

In patients with cancers other than prostate, only 25% of testing is within three months of the diagnosis, consistent with screening for prostate cancer accounting for most of the testing in this group. The even distribution of testing after the diagnosis in this group of patients further suggests screening for prostate cancer as a possible second malignancy. The low rate of second malignancies (4 - 6%) in cancer patients makes this testing of doubtful value.

The above interpretation is confounded by the time frame of our analysis in relation to the time of diagnosis. In many cases, patients were diagnosed before PSA testing was available.
Table 6 - The frequency of PSA testing in relation to date of cancer diagnosis

<table>
<thead>
<tr>
<th>Time before/after diagnosis (y)</th>
<th>Prostate Cancer Frequency (%)</th>
<th>Other cancer Frequency (%)</th>
<th>Prostate Cancer Frequency (%)</th>
<th>Other cancer Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before diagnosis</td>
<td>After diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - &lt; 0.25</td>
<td>2,429 (47)</td>
<td>839 (25)</td>
<td>3,089 (7)</td>
<td>586 (7)</td>
</tr>
<tr>
<td>0.25 - &lt; 0.5</td>
<td>583 (11)</td>
<td>333 (10)</td>
<td>2,917 (7)</td>
<td>244 (3)</td>
</tr>
<tr>
<td>0.5 - &lt; 0.75</td>
<td>299 (6)</td>
<td>263 (8)</td>
<td>2,653 (6)</td>
<td>225 (3)</td>
</tr>
<tr>
<td>0.75 - &lt; 1.0</td>
<td>251 (5)</td>
<td>275 (8)</td>
<td>2,506 (6)</td>
<td>257 (3)</td>
</tr>
<tr>
<td>1.0 - &lt; 1.5</td>
<td>429 (8)</td>
<td>428 (13)</td>
<td>4,272 (10)</td>
<td>394 (5)</td>
</tr>
<tr>
<td>1.5 - &lt; 2.0</td>
<td>248 (5)</td>
<td>313 (9)</td>
<td>3,797 (9)</td>
<td>430 (5)</td>
</tr>
<tr>
<td>2.0 - &lt; 2.5</td>
<td>168 (3)</td>
<td>300 (9)</td>
<td>3,225 (8)</td>
<td>379 (4)</td>
</tr>
<tr>
<td>2.5 - &lt; 3.0</td>
<td>112 (2)</td>
<td>204 (6)</td>
<td>2,831 (7)</td>
<td>369 (4)</td>
</tr>
<tr>
<td>3.0 - &lt; 3.5</td>
<td>91 (2)</td>
<td>157 (5)</td>
<td>2,395 (6)</td>
<td>327 (4)</td>
</tr>
<tr>
<td>3.5 - &lt; 4.0</td>
<td>76 (1)</td>
<td>91 (3)</td>
<td>2,038 (5)</td>
<td>318 (4)</td>
</tr>
<tr>
<td>4.0 - &lt; 4.5</td>
<td>44 (1)</td>
<td>44 (1)</td>
<td>1,663 (4)</td>
<td>302 (3)</td>
</tr>
<tr>
<td>4.5 - &lt; 5.0</td>
<td>13 (0)</td>
<td>12 (0)</td>
<td>1,418 (3)</td>
<td>287 (3)</td>
</tr>
<tr>
<td>5.0 - &lt; 5.5</td>
<td>3 (0)</td>
<td>0 (0)</td>
<td>1,145 (3)</td>
<td>276 (3)</td>
</tr>
<tr>
<td>5.5 - &lt; 6.0</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1,114 (3)</td>
<td>261 (3)</td>
</tr>
<tr>
<td>&gt;6.0</td>
<td>1 (0)</td>
<td>2 (0)</td>
<td>7,588 (18)</td>
<td>3,916 (46)</td>
</tr>
<tr>
<td>Missing values</td>
<td>422 (8)</td>
<td>72 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>5,169 (100%)</td>
<td>3,343 (100%)</td>
<td>42,651 (100%)</td>
<td>8,571 (100%)</td>
</tr>
</tbody>
</table>

Note: percentages do not always add up to 100%, due to rounding.
The extent to which PSA testing occurs in patients as a function of their age (Table 7) is also of interest, particularly since guidelines for screening are age-dependent. This was evaluated as age to first PSA test in all three diagnostic groups. This approach was adopted because we did not wish to bias the extent of testing in the prostate cancer group, which had more tests per patient. The distributions by diagnostic category were statistically different by the Mantel-Haenszel chi-squared test, both among all three groups, and between the non-prostate cancer groups. Most patients having a PSA test were between the ages of 60 and 79, consistent with the age at which patients develop prostate cancer (median age at presentation in most studies is in the mid-sixties). Of men having their first PSA test, and not having cancer, 15% were under 50 years of age, and 22% were over 70. This is contrary to the recommendations of those who advocate PSA screening, as discussed earlier. This could reflect the fear of cancer in patients with relatives who have prostate cancer. The fact that 58% patients with prostate cancer undergoing PSA testing were over 70 years of age (16% were over 80) could be a reflection of the length of time that patients survive with prostate cancer, as well as diagnostic use of the test in older patients worried about having prostate cancer. These data have implications for PSA testing policy, as discussed later. Caution must be exercised in extrapolating this data too far, because additional testing may occur on other databases not accessible to us.

PSA testing by level of PSA

The distribution of PSA test results in the diagnostic groups is displayed in Table 8 by level of PSA. These are statistically different by the Mantel-Haenszel chi-squared test, both for all
three groups and for the two non-prostate cancer groups. (The small percentage of test results greater than 50 likely represents an inappropriate diagnosis as discussed earlier). This contrasts with only 53% less than 4.0 ug/L, and 9% greater than 50 ug/L in patients with PCa, the group in which higher test results are expected. At the other end of the scale, 18% of prostate cancer patients have results below 0.2 ug/L, compared with 5% and 3% in the other groups. This is consistent with the effect that would be produced by radical treatments such as prostatectomy and radiotherapy, and even hormonal therapy, being administered to these patients, leading to lower PSA levels.

Figures 4 and 5 are plots of the mean PSA level as a function of time five years before (negative values) and five years after (positive values) diagnosis, for patients with PCa and patients with cancers other than prostate. There is a fairly constant level of PSA in the non-prostate cancer patients, with most values occurring between 2 and 10 ug/L, as would be expected in this group. The 95% confidence intervals are wide, reflecting the small numbers of patients. Figure 4 shows that, in patients with prostate cancer, the mean PSA is between 5 and 25 ug/L before diagnosis, and rises to a mean of 55 ug/L at the time of diagnosis, and then falls back down within a year of diagnosis, presumably as a the result of treatment. Over the subsequent four years, there is a gradual rise in the mean PSA, to 46 ug/L by the fifth year, presumably reflecting relapse of disease.
Table 7

PSA testing: age at first test by diagnostic group

<table>
<thead>
<tr>
<th>Patient age at first test (years)</th>
<th>No cancer</th>
<th>Other cancer</th>
<th>Prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>2,618 (2)</td>
<td>56 (1)</td>
<td>5</td>
</tr>
<tr>
<td>40 - 49</td>
<td>15,832 (13)</td>
<td>284 (4)</td>
<td>61 (1)</td>
</tr>
<tr>
<td>50 - 59</td>
<td>36,128 (30)</td>
<td>1,158 (15)</td>
<td>825 (7)</td>
</tr>
<tr>
<td>60 - 69</td>
<td>38,218 (32)</td>
<td>2,806 (35)</td>
<td>4,020 (34)</td>
</tr>
<tr>
<td>70 - 79</td>
<td>20,404 (17)</td>
<td>2,612 (33)</td>
<td>5,012 (42)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>5,375 (5)</td>
<td>1,036 (13)</td>
<td>1,875 (16)</td>
</tr>
<tr>
<td>missing</td>
<td>489 (0)</td>
<td>3 (0)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>118,575 (100)</td>
<td>7,952 (100)</td>
<td>11,798 (100)</td>
</tr>
</tbody>
</table>

Note: percentages may not add up exactly to 100% due to rounding.

Mantel-Haenszel Chi-square (columns 2, 3 and 4): (DF = 10) = 12,058 \( p < 0.001 \)

Mantel-Haenszel Chi-square (columns 2 and 3): (DF = 5) = 3,364 \( p < 0.001 \)
Table 8

Results of testing in the three diagnostic groups, by level of PSA result

<table>
<thead>
<tr>
<th>PSA Result (ug/L)</th>
<th>No Cancer</th>
<th>Other cancer</th>
<th>Prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>&lt; 0.2</td>
<td>5,913 (3.5)</td>
<td>611 (5)</td>
<td>67 (1)</td>
</tr>
<tr>
<td>0.3 - 0.4</td>
<td>14,575 (8.5)</td>
<td>801 (7)</td>
<td>36 (1)</td>
</tr>
<tr>
<td>0.5 - 0.9</td>
<td>46,397 (27)</td>
<td>2,361 (20)</td>
<td>74 (1)</td>
</tr>
<tr>
<td>1.0 - 1.9</td>
<td>47,519 (28)</td>
<td>3,005 (25)</td>
<td>222 (4)</td>
</tr>
<tr>
<td>2.0 - 2.9</td>
<td>18,881 (11)</td>
<td>1,396 (12)</td>
<td>210 (4)</td>
</tr>
<tr>
<td>3.0 - 3.9</td>
<td>10,661 (6)</td>
<td>887 (7)</td>
<td>250 (5)</td>
</tr>
<tr>
<td>4.0 - 9.9</td>
<td>20,778 (12)</td>
<td>1,988 (17)</td>
<td>1,876 (36)</td>
</tr>
<tr>
<td>10 - 19.9</td>
<td>4,105 (2.5)</td>
<td>536 (4)</td>
<td>1,101 (21)</td>
</tr>
<tr>
<td>20 - 49</td>
<td>1,453 (1)</td>
<td>227 (2)</td>
<td>821 (16)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>403</td>
<td>98 (1)</td>
<td>512 (10)</td>
</tr>
<tr>
<td>Missing</td>
<td>22</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total tests</td>
<td>171,070 (100)</td>
<td>11,905 (100)</td>
<td>5169 (100)</td>
</tr>
</tbody>
</table>

Diagnosis: Before | After

M-H Chi-square (all diagnostic groups, df = 18): 52,195 (p < 0.001)
M-H Chi-square (first two groups only, df = 9): 960 (p < 0.001)
[prostate cancer columns were combined for the Chi-square analysis, changing df]

Note: percentages may not add up exactly to 100% due to rounding.
Figure 4. Mean PSA level (µg/L) as a function of time before and after the diagnosis of prostate cancer. Circles represent the mean PSA for each 4-month period, and error bars represent the 95% confidence intervals (provided once for each year to avoid crowding).
Figure 5. Mean PSA level (μg/L) as a function of time before and after the diagnosis of cancers other than prostate. Circles represent the mean PSA for each 4-month period, and error bars represent the 95% confidence intervals (provided once for each year to avoid crowding).
Phase III: Reasons for PSA testing

The random sample of 500 patients

A questionnaire was sent to physicians attending a random sample of about 500 patients without the diagnosis of prostate cancer. Figure 6 outlines the events that led to a final eligible number of 428 in the main mailing and 47 in the pilot phase for a total of 475.

Table 9 shows that a total of 320 physicians were involved with this sample of 507 patients; the majority of physicians had only one patient, but several had two or three patients, and one as many as ten. General practitioners (89%) and urologists (7.5%) made up the majority of physician specialties, as might be expected for this test (Table 9b).

Of the 475 questionnaires mailed out in the pilot and main mailings, responses were received from 262 (55.2%). Of these, 27 (10%) were unusable: 7 were associated with patients with prostate cancer at the time of the test; 5 physicians could not be reached; 5 physicians reported that the patient was not theirs; 4 forms were returned uncompleted; 3 could not find the information on the patient chart; and 3 were outside of the study area. Note that an average of 2.4 reasons per patient test were documented.

The results of all of the responses to the questionnaire (including the pilot study) are displayed in Table 10(a) and (b). For clarity, responses from the 160 family physicians, FP (61% of the 262 responses) and 42 general practitioners, GP (16%) have been combined, because their practices in PSA testing were very similar. In column 2, Table 10(a), the following proportions of responses applied to FP and GP respectively: symptoms (58/160 = 36% and 15/41=37%), procedures (29% and 39%), previous PSA (2.3% and 2.4%), screen (68% and 61%); of screens, those patient initiated (44% and 46%) and those as part of a routine examination (49% and 46%). None of these proportions were statistically different.
Main mailing

230,756 records
Sunnybrook and Dynacare

1,000 randomly selected

postal code restriction

533 (all Dynacare)

remove patients with cancer

507 eligible

remove London records
(inaccessible)

428 eligible for mailing

428 + 47 = 475 (total sample)

Pilot mailing

49 Sunnybrook records

remove 2 out of area

47 for pilot mailing

Figure 6. Flow chart for physician questionnaire selection.
### Table 9(a)  Number of patients per physician in the original Dynacare random sample

<table>
<thead>
<tr>
<th># of patients per physician</th>
<th># of physicians (by postal code)</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>215</td>
<td>215</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>320</td>
<td>507</td>
</tr>
</tbody>
</table>

### Table 9(b)  Breakdown of physician responses by practice specialty

<table>
<thead>
<tr>
<th>Specialty</th>
<th># of responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family /general practice</td>
<td>432 (85%)</td>
</tr>
<tr>
<td>Urology</td>
<td>59 (12%)</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>7 (1.6%)</td>
</tr>
<tr>
<td>General Surgery</td>
<td>6 (1.2%)</td>
</tr>
<tr>
<td>Dermatology</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>507 (100%)</td>
</tr>
<tr>
<td>Practice Specialty</td>
<td>Family/General Practice</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>Responses (n, %)</strong></td>
<td>201 (77%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Reasons for PSA test (n, % based on 235 usable responses)**

- **Symptoms**: 74 (78%)<sup>a</sup> | 16 (17%)<sup>a</sup> | 5 (5%)<sup>a</sup> | 95 (40%)<sup>b</sup>
- **Procedure**: 62 (79%)<sup>a</sup> | 13 (17%)<sup>a</sup> | 3 (4%)<sup>a</sup> | 78 (33%)<sup>b</sup>
- **Previous PSA**: 11 (79%)<sup>a</sup> | 3 (21%)<sup>a</sup> | 0 | 14 (6%)<sup>b</sup>
- **Screen?**: 134 (89%)<sup>a</sup> | 9 (6%)<sup>a</sup> | 8 (5%)<sup>a</sup> | 151 (64%)<sup>b</sup>
  - **Patient initiated?**: 89 (92%)<sup>a</sup> | 4 (4%)<sup>a</sup> | 4 (4%)<sup>a</sup> | 97 (64%)<sup>c</sup>
  - **Routine exam?**: 98 (89%)<sup>a</sup> | 6 (1%)<sup>a</sup> | 6 (1%)<sup>a</sup> | 110 (73%)<sup>c</sup>
- **Other reason?**: 15 (83%)<sup>a</sup> | 2 (11%)<sup>a</sup> | 1 (6%)<sup>a</sup> | 18 (8%)<sup>b</sup><sup>d</sup>

- **Column total**: 483 | 53 | 27 | 563<sup>c</sup>

<sup>a</sup> Percentage of row total

<sup>b</sup> Percentage of 235 usable responses

<sup>c</sup> Percentage of responses indicating screening (i.e. % of 151)

<sup>d</sup> Family history (4), patient fears cancer (4), BPH (2), monitoring prostatitis (2), impotence/pre androgen therapy (4), abnormal urinalysis tests (1), recommended by psychologist (1).

<sup>c</sup> There were, on average, 563/235 = 2.4 reasons per usable response
<table>
<thead>
<tr>
<th>Symptoms reported</th>
<th>Number (%)</th>
<th>Procedures</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>95 (100%)</td>
<td>Total</td>
<td>78 (100%)</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>27 (28%)</td>
<td>DRE</td>
<td>71 (91%)</td>
</tr>
<tr>
<td>Urgency</td>
<td>27 (28%)</td>
<td>TURP</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Nocturia</td>
<td>43 (45%)</td>
<td>Drugs</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Post-void dribbling</td>
<td>25 (26%)</td>
<td>TRUS</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Delayed emptying</td>
<td>24 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime frequency</td>
<td>12 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other symptoms</td>
<td>20 (21%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other symptoms:** not specified (19), weak stream (6), hematuria (6), hemospermia (5), groin pain (3), post-void pain (1), dysuria (1)

**Note:** Percentages are of column totals, and may add up to more than 100% because many patients had more than one symptom or procedure reported as a reason for the particular PSA in question.
One of the main issues to address relating to an incomplete response to a questionnaire is whether the responses are a reasonable reflection of the population sampled. This was approached by looking at the only indicators available to us, namely the distribution of practice specialties, the age distribution of patients, and the postal code distribution of physicians.

The breakdown of the 262 responses by practice specialty was a good reflection of that in the original random sample of 507 (see Tables 10 and 9b): 78% were from family and general practice physicians, compared with 85% in the original sample; 12% of responses were from urologists in both groups; and other known specialties were 3.1% and 2.8% respectively. These were not significantly different by the Mantel-Haenszel test (DF = 2, Chi-square = 1.0, p < 0.6).

The patient ages (by decade) of patients for whom we obtained responses, and of patients in the overall sample, are displayed in Table 11(a). They are comparable by the Mantel-Haenszel test, indicating that there is no significant bias in the patients for whom responses were obtained. The distribution of physicians by postal code in the total sample and of those who responded is shown in Table 11(b), again suggesting no bias by the Mantel-Haenszel test. We were unable to evaluate other patient or physician factors for bias.
Table 11 (a) The proportion of patients by age in the total sample and in respondents.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total sample, n (%)</th>
<th>Respondents, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 40</td>
<td>12 (2%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>81 (16%)</td>
<td>39 (17%)</td>
</tr>
<tr>
<td>50 - 59</td>
<td>161 (32%)</td>
<td>74 (31%)</td>
</tr>
<tr>
<td>60 - 69</td>
<td>150 (30%)</td>
<td>71 (30%)</td>
</tr>
<tr>
<td>70 - 79</td>
<td>88 (17%)</td>
<td>40 (17%)</td>
</tr>
<tr>
<td>Over 80</td>
<td>15 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Total</td>
<td>507 (100%)</td>
<td>235 (100%) *</td>
</tr>
</tbody>
</table>

Mantel Haenszel Chi-square (DF = 5) = 0.605 (p < 0.988)

Table 11 (b) The distribution of physician postal codes (total sample and respondents).

<table>
<thead>
<tr>
<th>Postal Code</th>
<th>Total sample, n (%)</th>
<th>Respondents, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>44 (9%)</td>
<td>27 (11%)</td>
</tr>
<tr>
<td>L</td>
<td>202 (40%)</td>
<td>82 (35%)</td>
</tr>
<tr>
<td>M</td>
<td>250 (49%)</td>
<td>117 (50%)</td>
</tr>
<tr>
<td>N</td>
<td>11 (2%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Total</td>
<td>507 (100%)</td>
<td>235 (100%) *</td>
</tr>
</tbody>
</table>

Mantel Haenszel Chi-square (DF = 3) = 4.00 (p < 0.262)

* Postal codes could not be found for 27 individuals at time of analysis
Symptoms and PSA

The presence of symptoms was listed as a reason for PSA testing in 40% of the responses. This is close to the figure of 40% reported in unselected men between the ages of 60 and 85 years\(^7\), though other studies\(^8\) suggest a lower rate (14 - 24%) of symptoms of “voiding complaints” in community-based subjects aged 55 - 74 age. The main symptoms in our patients leading to testing (according to their physicians) were nocturia (45%), hesitancy and urgency (28% each), and post-void dribbling and delayed emptying (24 and 25% respectively). The distribution of symptoms is somewhat similar to those in a study of patients with BPH\(^9\).

About 21% of responses indicated that symptoms were a reason for PSA testing, yet did not document even a single symptom. This makes one wonder whether some physicians did not understand the questionnaire; whether they were careless about completing the questionnaire; or whether they did not have the appropriate information in the patient chart.

The proportion of patients with symptoms seen by urologists, and by family or general practitioners, was 16/31 or 52% and 74/201 or 36% respectively. These proportions are significantly different ($z = 1.71, p = 0.044$), suggesting that urologists are more likely to measure PSA on patients with symptoms.

Procedures and PSA

The proportion of PSA tests related to follow-up of a procedure was 33%. This relatively high rate is mostly associated with the performance of a digital rectal examination (91% of procedures), and to a lesser extent with TURP (11%), monitoring the effects of drug therapy (5%) and TRUS (3%). The high rate of DRE is consistent with current screening recommendations to
do both the PSA test and a DRE. There are no data in the literature to compare this finding with; most studies have documented the extent to which other procedures were done on the same patient as a PSA test was measured, though the sequence is usually the reverse, with an abnormal PSA test leading to either TRUS or biopsy, as in the Saskatchewan study63. The proportion of PSA tests that were contingent upon a previous PSA test (5%) was lower than expected, considering the AUA and ACS recommendations for annual screening with PSA and DRE.

The proportion of urologists on the one hand, and general or family practitioners on the other, using PSA as a result of a procedure was 13/31 or 42% and 62/201 or 31% respectively. These proportions are not statistically different (z = 1.22, p = 0.11), suggesting that both groups utilize PSA tests to follow up other procedures to the same extent.

Screening

The proportion of PSA tests requested to screen for prostate cancer was 64%; this screening rate is comparable to the rate (63%) of self-reported practice by physicians requesting the PSA test in Saskatchewan63. Approximately 74% of our study PSA tests were requested as part of a routine examination, and 64% were reported as being initiated by the patient.

The screening guidelines suggest that men be screened between the ages of 50 and 70. Our data show that PSA testing occurred in patients under 50 in 93/507 (18%) of the original sample, and in 45/325 (19%) of the respondents; it occurred in patients over 70 in 103/507 (20%) of the original sample, and 45/235 (19%) of the respondents. Overall, approximately 64% x 40% or 26% of screening occurred outside the age range recommended by screening guidelines.

The proportion of patients seen by urologists and general/family practitioners, and
requesting PSA in the context of screening, was 9/31 or 29% and 134/201 or 67%, which are clearly different (z = 4.05, p < 0.0001). Thus PSA screening in this sample is predominantly being carried out by family physicians or general practitioners, who also outnumber urologists in Ontario. This is not surprising, since the former group see patients first, with urologists seeing mainly referred patients. The comparable comparisons for patient-initiated screening were: 4/31 (13%) versus 89/201 (44%), z = 3.32 (p = 0.0005) and for part of a routine examination 6/31 (19%) versus 98/201 (49%), z = 3.08 (p = 0.001). Family or general practitioners are more likely to request PSA in response to a patient initiative, and as part of a routine examination, then are urologists.

The data can be viewed as the proportion of tests requested for screening purposes by general and family practitioners (89/134, or 66%) compared to urologists (4/9 or 44%), which yields a z-value of 1.34 (p = 0.09). This reveals a trend, but it does not reach statistical significance.

The number of responses with both symptoms and screening identified as reasons for testing, was 29/151 (19%), which was coincidentally the same number and proportion identifying both procedures and screening as reasons for testing. This proportion is significant, and hard to interpret. It is possible that some physicians misunderstood the questionnaire (which states clearly that screening was on asymptomatic patients). It is possible that some are aware that symptoms of prostatism do not imply a diagnostic context, and are compatible with screening (i.e. they are more likely related to BPH than to PCa).

Other reasons for PSA testing comprised just 7% of the responses, and included a family
history of prostate cancer (usually the patient’s father had the disease) in 4, patient fear of prostate cancer in a further 4 (all were checked off as a screen on the questionnaire), BPH in 2, monitoring prostatitis in 2, treatment of impotence in 3, abnormal urinalysis testing in 1, and recommendation by a psychologist in 1 (this was included as a screen in the above analysis).
DISCUSSION

Phase I

The extent to which we were able to obtain information from all laboratories involved in PSA testing in Ontario was most gratifying. The amount of PSA testing occurring in Ontario far exceeded our expectations, based on the 1995 snapshot. The shape of the curve in Figure 1 suggests that testing will continue to increase. The rapid rise in PSA testing in Ontario is taking place without recommendations for testing, and without an OHIP fee code for the test.

Data summarised in Figure 3 indicate that 80% of PSA tests in our sample in 1995 were carried out on patients without prostate cancer. Figure 3 also shows that most of the increase in PSA testing is in patients without cancer. Table 10 shows that the proportion of PSA tests used for screening purposes was 64%. Table 1 shows that in 1995/6 an average of around 308,000 PSA tests were carried out per year. On the assumption that these proportions remain constant in the future, and that they are representative of PSA use in the province, then (308,000 x 0.8 x 0.64) i.e. 158,000 tests per year were carried out for screening purposes. The number of men eligible for screening in Ontario (for an overestimate, including men between 50 and 74 years of age) is 1.13 million. Thus, in 1995/6, 158/1,130 = 14% of the eligible population of men was potentially screened.

The extent to which laboratories, both private and hospital, regard their PSA workload count as private information was unexpected (especially for hospitals). It created some difficulty obtaining data, and forced us to adopt an arms-length approach via the LPTP. This, in turn, created difficulties in following up on certain issues, such as obtaining the reasons for not
providing workload in some instances.

The fact that PSA is an uninsured test also created difficulties, since the Ministry of Health does not have complete workload counts as it does for insured tests. There is also no incentive for laboratories to keep track of the source of tests (i.e. private or public referral). Knowledge of this public/private source breakdown for the Province as a whole could enable us to project, for the Province, the proportion of PSA testing done for screening (based on information from Phase II).

The extent to which PSA testing data is available on computer, and searchable by patient name and date of birth, is disappointing, though not surprising. Many clinical laboratories are not computerised at all, and many computer systems are designed for laboratory use, and are not linked to the laboratory’s patient demographic database. However, the fact that about one-third of the PSA data in Ontario could be part of an approved research project is encouraging for further work on PSA utilization.

This part of the study has limitations. The non-response of three laboratories as to their PSA workload between 1992 and 1996 makes it impossible to determine how much testing may have been associated with those laboratories. The inability of many laboratories to retrieve their results, especially in earlier years, makes those early counts less reliable. Overall, however, we have obtained a reasonably reliable count of PSA workload in Ontario during the study period.
Phase II

The linkage of the PSA records with the OCR documented that 60% of patients had prostate cancer. The main cancer sites (Table 4) are all likely, because of their location, to develop tumour bulk that may affect urine outflow. Such urine symptoms might prompt physicians to consider the possibility of prostate cancer as a cause, resulting in PSA testing. This may account for the site distribution observed.

Our data showed for the first time in Ontario that most PSA testing occurs in men without prostate cancer, even though the number of tests per person in this group was less than that for patients with prostate cancer. We confirmed that the steep rise in PSA testing over the period 1988 to 1996 occurred mostly in patients without prostate cancer. Most testing in men without prostate cancer occurred in the private sector. The bulk of PSA testing (89%) in patients with prostate cancer during the study time period occurred after the diagnosis was made, and most of this testing was in the hospital sector. The number of tests per patient was greater for patients with prostate cancer than other patients. These proportions will probably change over time, particularly in earlier years, because of the limited availability of the PSA test.

The extent of PSA testing beyond the age range of 50 - 70 (indicated by most screening guidelines) was unexpected. This finding was confirmed during Phase III, and is discussed later.

This phase of the study has some limitations, the first of which is the extent to which the databases were complete for the important fields desirable for linkage. The lack of OHIN on the Sunnybrook side was a major drawback here; its presence would have led to a much easier and probably more reliable linkage. However, this is a reflection of the situation in all Ontario
hospital laboratories. Lack of OHIN, and lack of availability of several other fields, may have led to errors in the linkage of PSA records to the OCR for diagnosis, a fact suggested by the high PSA levels (and large numbers of tests) observed in a few patients identified after linkage as being without prostate cancer. However, as a proportion of all records linked, this was very small.

The second limitation is the inability to generalize our results to the Province as a whole, because we do not have a well-defined denominator, defined either geographically (such as Metropolitan Toronto) or in terms of workload (such as proportion of hospital or private laboratory workload). However, our results are likely a reasonable approximation for the province as a whole when looked at by patient category, whether that be diagnosis group or age.

If this study were broadened to include the other 14 laboratories willing to participate in further research, identified in Phase I, we could potentially access about a third of the Ontario PSA data. Most accessible data would be in the more recent years. It is unclear whether increasing the amount of data would provide us with any better denominator, either by patient population or by geographic area, since at least two-thirds of the data would not be accessible.

**Phase III**

This part of the study allowed us to document, for the first time in Canada, the reasons that PSA tests were requested in patients without prostate cancer. We also demonstrated that there are some differences in the testing practices by specialty type. A greater proportion of PSA tests requested by urologists were associated with patients with symptoms than was the case for family
and general practice physicians; a smaller proportion were associated with screening. There were
a number of limitations to this phase of the study.

Response rate

It was unfortunate that we were unable to access the patient records for as many as 79 PSA
tests because of their being associated with the London laboratory. With hindsight, this is
something that could have been avoided by checking that all numbers in the random sample were
accessible before the mailing.

The limited response rate (55%) was somewhat disappointing, though better than some
other current physician surveys in Ontario. It was almost certainly affected by the climate of
negotiations in existence at the time, between physicians and the Ministry of Health, though to
what extent is impossible to say. It was also unfortunate that our research agreement with
Dynacare made it very difficult to follow up our mailed questionnaire with a phone call, both to
encourage a better response rate, and to find out the reasons for those not responding.

Bias

Physicians answered the questionnaire themselves. The questionnaire and the letter
requested that they check the chart for reasons leading to a particular test. The 21% of responses
that did not document any symptom type suggests that many physicians either did not have this
information in their charts, or that they were going by memory rather than checking the reasons
for the particular test identified by the questionnaire.

The only indicators of bias in responses that we could evaluate (physician specialty,
physician location by postal code, and patient age at the time of the PSA test) did not suggest any
bias in the non-respondents compared to those who were contacted.

Symptoms

The symptoms identified in our study as leading to some of the PSA tests were documented by physicians, and did not necessarily reflect the patient's reason for testing, nor the "degree of bother" of the patient by those symptoms. However, a more important issue is whether PSA testing in response to symptoms is really a different process (diagnosis) from PSA testing in the absence of symptoms (screening). This debate is beginning to appear in the literature, and is discussed further below.

Generalizability

There are two significant issues relating to how generalizable this study is to all of Ontario. First, the sample was obtained from a database serving the Greater Toronto Area, and was confined to the GTA by postal code. It is quite possible that screening and diagnosis practices in the GTA are different from those in other parts of Ontario. Second, the fact that the majority of patients were associated with one private laboratory may have an effect on the results. Private laboratories often send material (such as newsletters) to their physician and laboratory clients relating to utilization of laboratory tests, and this may have an effect on practice.

General discussion

Feasibility

The data obtained and analysed by us in this study show that it is indeed feasible to obtain a reasonably reliable count of total laboratory workload in Ontario, within the limitations
discussed above. It is not, however, possible to arrive at a breakdown of how much work is done through private practice and how much through hospital practice, when considering laboratory records of PSA workload.

It proved feasible, also, to link the PSA records from two large laboratories to the OCR to carry out both internal linkage and to assign a cancer diagnosis to the patients undergoing PSA testing, again within the limitations discussed above. The availability of a Province-wide database, with common patient identifiers including OHIN, would greatly facilitate such work.

The third part of our study showed that it was feasible to obtain an estimate of the reasons for which physicians requested PSA tests on patients without prostate cancer. A major difficulty with this part of the study related to the private laboratory's perception of confidentiality, which prevented us from directly contacting physicians in follow-up, either to improve the response rate, or to learn the reasons for not responding.

Policy

The continued rise in PSA tests across the Province of Ontario, which we have shown is largely related to screening or investigation of symptoms of prostatism in patients without prostate cancer, raises many policy issues. From our study, private laboratories appear to handle the majority of PSA tests, but are not licensed to perform the tests in their own laboratories. This leads them to refer the testing to hospital laboratories, which are happy to do the testing, because this provides them with additional revenue. However, this referral creates additional administrative and transportation work in order to get the test done. The Ministry of Health needs to consider allowing private laboratories to do PSA testing themselves, since denying them the
licence is probably not reducing the total workload. It is possible that the private laboratories wish to avoid adding further tests such as PSA to their licences, because the total number of tests they can do is fixed ("capped") by an agreement between them and the Ministry of Health.

The impact of PSA testing on hospital funding should not be overlooked. Hospital laboratory testing comes out of the hospitals' global budgets. Most hospital programs get increased funding if they can demonstrate increased activity. However, PSA testing has not been identified as a separate item, and some hospital laboratories have struggled to perform this unfunded testing.

Overall, the cost of the PSA test is small compared to the cost of follow-up of positive tests (most of which will not identify prostate cancer). Not insuring PSA may not be a significant cost-saving device for the province.

Another consequence of confining laboratory licences for PSA testing to hospitals, is that patients visiting family physicians in hospitals get the PSA test free of charge; but patients visiting family physicians outside of hospitals have to pay for the test, at a rate that varies between $15 and $30 per test. This inequity could force more patients to visit hospitals to avoid paying for the test (putting more strain on the hospital laboratory budgets), and could deny some patients equal access to what is becoming a more widespread practice.

Third, a decision needs to be made on the circumstances in which PSA testing will be funded by OHIP. PSA is requested under three main circumstances: (a) in patients with prostate cancer, for monitoring therapy and to detect early recurrence; (b) for diagnosis of symptoms (some of which are associated with the natural process of aging in men) that might be related to
the prostate, and which could be prostate cancer, BPH or prostatitis; and (c) screening patients without symptoms.

In relation to (a) there is no demonstrated benefit in terms of either longevity or quality of life for measuring PSA to monitor response, as opposed to monitoring response with symptoms. However, it has become the standard practice, and does provide prognostic information for patients, and monitoring for recurrence in other cancers (such as breast and colorectal cancer) occurs. Much cancer monitoring takes place in a hospital setting, but some patients are monitored for part of their care either by urologists or by their family physicians, many of whom are in private practice where the test is not covered. This again raises the issue of equity if payment for PSA is a financial burden for some. A recommendation is that, until we have evidence that suggests to the contrary, all cancer-related PSA tests should be free of charge to the patient. Our study shows that the burden of this testing is not very great.

In relation to (b), Hall et al \(^5\) point out that symptoms of prostatism are more likely the result of benign disease rather than prostate cancer, though there are few good studies addressing this point. There is evidence\(^3\) that the specificity of the PSA test for PCa in patients with symptoms of BPH is significantly decreased (65%) compared to patients without those symptoms (98%). Further, BPH is 3-4 times more common than prostate cancer\(^4\), and occurs with a similar age distribution. There does not appear to be a causal relationship between BPH and prostate cancer. It is arguable that the distinction between screening in asymptomatic patients and diagnosis in patients with signs and symptoms of prostatism is negligible, especially since prostatism is part of the process of aging.
We need further research to show whether the use of PSA to diagnose symptoms of prostatism is different from screening patients without symptoms. Our study shows that investigation of symptoms was a reason for testing in 36% of patients, a significant proportion. In any particular practice, it will be difficult to identify what testing is for diagnosis and what for screening, and it is probably not practical to use this distinction as a means of deciding on whether the test should be covered by OHIP or not.

In relation to (c), there is no evidence of benefit, either in terms of longevity or quality of life, from PSA screening, and randomized controlled trials currently under way will only provide answers in several years time. But it appears that screening is taking place on a widespread scale. Patients’ wishes are being consulted to an increasing extent, and 37% of the PSA tests in our study were initiated by the patient. The bulk (134/151 or 89%) of screening is being carried out by family and general practitioners, according to our study, and fewer of their patients have symptoms of prostatism. One approach is that PSA testing be funded only if patients are being treated in hospitals or by urologists, in order to decrease screening. This approach, however, will probably overload urologists in Ontario, and could cause patients to visit outpatient clinics in hospitals, overloading them also. An expert group, or a consensus conference on PSA funding, with all major stakeholders involved, is probably needed to decide on an appropriate utilization and funding model. In the United States, Barry et al. recommended against Medicare coverage of PSA screening.

The results from Phase II revealed that a significant amount of PSA testing occurs in patients without cancer under the age of 50, and over the age of 70. It is likely that many were for
screening, and this is contrary to the guidelines of those bodies in favour of screening, suggesting that there is a need for education of both physicians and patients about screening guidelines.

A fourth issue, relates to the interaction between physician and patient. PSA screening is associated with morbidity and even a mortality risk, as detailed earlier. Other studies have shown that patients know very little about the test and its consequences, and that physicians are very inconsistent in their interpretation of PSA test data. A physician-patient interview needs time for all the questions to be explored. It would appear that patients and physicians would benefit from education materials that would assist them in arriving at an informed decision about whether to undergo PSA screening for prostate cancer. Consideration needs to be given to reimburse physicians appropriately for the time needed to counsel their patients.
The following summary relates to the two PSA testing databases in our study, and may not apply to Ontario as a whole. We have determined, for the first time, the extent of PSA testing in the province of Ontario, during the period 1988 and 1996. This first part of our study indicates that PSA testing is still increasing rapidly, with little sign of tailing off at the 1996 value of 338,000 patient tests per year. This observed rate is consistent with the introduction of a new technology. The pattern is also consistent with screening patients for prostate cancer, rather than an increase in diagnosis or monitoring of patients with prostate cancer.

In this first part of the study, we have further ascertained that approximately one-third of Ontario’s PSA testing data could be made available for further study in the context of an approved research protocol.

In the second part of our study, we have determined, for the first time in Canada, the extent to which PSA testing is performed on patients with prostate cancer, with other cancers, and with no cancer. There is a greater number of PSA tests per patient with prostate cancer than in the other two categories, consistent with regular monitoring of therapy, and monitoring for early recurrence. However, the greatest number of PSA tests occurs in patients without any cancer, simply because of the greater number of patients being tested. This is consistent with what one expects from screening in the general population.

Prostate cancer was present in 60% of patients who have undergone PSA testing and who had cancer. Just under 6% of these cancer patients had additional malignancies. There were significant differences in the distributions of PSA testing among the three diagnostic groups.

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mentioned above, by testing frequency per patient, by patient age at time of diagnosis and/or time of first test, and by PSA level (in ug/L). The breakdown of patients undergoing PSA testing by diagnostic group was as follows: 85.7% had no cancer diagnosis, 8.5% had prostate cancer, and 5.8% had cancer other than prostate.

We demonstrated that PSA testing on patients without any cancer rose exponentially during the period studied, mimicking the total provincial workload count found in Phase I, and suggesting that the rapid rise in PSA testing provincially is largely on patients without cancer. There was also an increase in PSA testing in patients with prostate cancer and in patients with other cancers, but this tapered off with time.

In patients with prostate cancer, we were able to document the expected rise and fall of PSA levels as the group approached the time of diagnosis; the fall in PSA levels after the presumed implementation of therapy; and the subsequent rise over five years in the PSA level, presumably as the result of recurrence of the disease in some men.

Fully 64% of the PSA tests in our file came from the Dynacare database, which serves largely physicians in general and family practice. Just under 8% of PSA tests were on both Dynacare and Sunnybrook databases. However, because we have used only two databases, we cannot be sure that this would be generalizable to the Province as a whole. This has repercussions for tracking patients’ PSA results in other studies. The proportion of PSA tests on the Sunnybrook database was 65% for patients with prostate cancer; 44% for patients with other cancers, and 27% for patients with no cancer (this latter group is mostly from tests referred in from other institutions). The PSA test records on the Dynacare database comprised just 2.8% of patients with prostate cancer, 3.2% of patients with other cancers, and 94% patients without
In Phase III of this study, we have determined, for the first time, the reasons that physicians request the PSA test in patients without prostate cancer in Ontario. We have found (within the limitation of a 55% response rate, and with 10% of responses being unusable) that 64% of PSA tests were requested with a view to screening patients for prostate cancer. This screening rate is the same as that of 63% reported by physicians in Saskatchewan. The majority of these screening requests come from family and or general practice physicians. PSA tests were to investigate symptoms in 40% of responses; were in response to other procedures 33% of the time, and in response to a previous PSA test only 6% of the time.

These results have been discussed in relation to the feasibility of expanding this work to include data from other laboratories in the Province, and in relation to PSA testing policy. We have shown that we may be able to access up to a third of the Provincial PSA testing data, together with patient identifying information, such as name and date of birth. We have pointed out some of the difficulties associated with such a study, including the “proprietary” nature of laboratory test workload, and the confidentiality of laboratory data, especially in the context of the relationship between private laboratories and their physician clients.

In the area of policy, the majority of studies investigating third party funding of screening for prostate cancer with PSA supplemented with other procedures such as DRE, have recommended against screening. However, screening is going ahead, with patients paying for the test, but funding agencies (OHIP in Ontario) cover the consequences of the test. There is a paradox if the smallest component of screening (the laboratory test) is not covered, but all the
consequences are. The Ministry of Health needs to arrive at a funding policy for PSA testing, physician counselling of patients, and the provision of educational materials for patients and physicians. Physicians need to be educated on PSA screening, and patients need to provide informed consent if they elect to pursue screening.
CONCLUSIONS

We can make the following conclusions based on this study:

* PSA testing in Ontario increased rapidly between 1988 and 1996, and continues to increase.
* This exponential increase in PSA testing occurred largely in patients without a diagnosis of prostate cancer, though there was some increase, with a levelling off, in patients with cancer.
* PSA testing occurs more frequently in men between the ages of 50 and 80; in patients with prostate cancer testing occurred at a slightly older age than in patients with other cancers or in patients with no cancer. In men without prostate cancer, a significant amount of testing occurs outside the age range (50 - 70 years) recommended by those guidelines advocating screening.
* In patients with prostate cancer, most (89%) of the PSA testing occurs after the diagnosis has been made.
* The Dynacare database contained PSA records mostly on patients without cancer; the Sunnybrook database contained slightly more PSA records on patients with cancer than on those without, the latter coming largely from work referred in from other institutions.
* The main users of PSA testing in the Dynacare database were family practice/general practice physicians (77%), followed by urologists (12%).
* PSA testing is being carried out in the private practice setting for the following reasons, in order of decreasing frequency, screening (64%), of which 64% was initiated by the patient; investigation of symptoms (40%); investigation of other results of other procedures (33%); investigation of previous PSA tests, and other reasons.
* The proportion of screening carried out on patients visiting family and general practitioners was
(81%) compared with those visiting urologists (6%); a greater proportion of urologists (53%) requested PSA testing on patients with symptoms than family and general practitioners (37%).

* A larger study on PSA utilization could be carried out in a similar manner over a larger proportion of the PSA database (possibly as much as a third).

* The reasons for testing in other parts of Ontario could be investigated by means of a questionnaire, possibly allowing for comparisons of practice in different areas of the Province.

* The data have relevance to various aspects of policy, as discussed above, including matters of laboratory funding, physician funding, accessibility to PSA testing, patient and physician education, and informed consent to undergo PSA screening. An expert panel or consensus group are probably needed to arrive at a decision on these policy matters, even though there is probably insufficient evidence to support OHIP coverage of PSA screening.
Due Mail@: 8.7.6. Do your 5.4.3. Do you RECORD-KEEPING TEST WORKLOAD PLEASE

1. Is your laboratory currently performing PSA testing (i.e., in-house)?
   - Yes ☐ No ☐

2. Is your laboratory currently reporting results for PSA tests performed in laboratories outside Ontario? ☐ Yes ☐ No
   If NO to both of the above, please sign and return questionnaire.

RECORD-KEEPING
3. Do you keep records of your laboratory’s PSA patient workload?
   - Yes ☐ No ☐
   If NO to the above, please sign and return questionnaire.

4. Are all or part of your PSA data computerized?
   - Yes ☐ No ☐

5. Please specify years for which PSA data are computerized: ____________________________

6. Do your PSA records include patient name and date of birth?
   - Yes ☐ No ☐

7. Is the database searchable for some or all PSA results?
   - Yes ☐ No ☐

8. If YES, for which years are data searchable: ____________________________

WORKLOAD
9. Please provide the following volume data for each year since your laboratory initiated PSA testing. To avoid double counting, please report workload only if performed in your laboratory (in-house), or if testing is performed outside Ontario but is reported from your laboratory (this applies to a few private laboratories). NOTE: Required only for patients residing in Ontario.

<table>
<thead>
<tr>
<th>Year</th>
<th>Testing Performed but Data Not Accessible (N/A)</th>
<th>In-house Tests</th>
<th>Out-of-Provience Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989</td>
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<td></td>
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<td>1995</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* For 1996, please provide data for January 1 to April 30, inclusive.

10. This questionnaire fulfills the first of three stages of the study. Would you be willing to assist in this project further by providing access to your laboratory’s computerized PSA data? A copy of the research proposal, approved by Sunnybrook Health Science Centre’s Ethics Review Board, could be supplied. The researchers assure both patient confidentiality and laboratory name confidentiality.
   - Yes ☐ No ☐

11. If yes, would you allow LPTP to pass on the name of your laboratory so that the researchers can contact you? Your laboratory’s name will NOT be attached to any workload data, but will be forwarded on a separate list to the researchers.
   - Yes ☐ No ☐

Thank you for your time and anticipated assistance. If you require help in capturing the requested data, please contact Peter Bunting, of the research team.

Peter Bunting Telephone: (416) 480-6100, ext. 3616
J. Ivan Williams e-mail: peterb@ices.on.ca
Vivek Goel
Neill Iscoe
Eric Holowaty

Please provide the name and telephone number of a contact person in your laboratory.
Name: ____________________________________________ (Please print)
Telephone No.: ______________________________________
Appendix 2  General theory of record linkage

Newcombe's approach is based on Bayes' Theorem of conditional probabilities. For the purposes of this thesis, one set of records was the Ontario Cancer Registry (OCR), which has information on all patients with a cancer diagnosis in Ontario, including patient specific identifiers such as date of birth and OHIN, and cancer diagnosis by ICD9 classification. The second set of records was obtained from two laboratory databases containing testing information for PSA measurements. Individual patient records may be said to be linked (or matched) when the information in two sets of records is either identical or very close. The records may be said to be unlinked or unmatched if they are different either completely or almost completely. The term "probabilistic linkage" enters into the matter because most of these linkages are not perfect, but may agree with each other either to a very high, or a very low extent, or somewhere in between. The selection of appropriate cutoff weights is used to decide this separation between linked and unlinked records.

The degree of certainty of a linkage depends on the specificity or uniqueness of individual values (data fields such as name, date of birth or OHIN) being compared in the two sets of records. If several identifier fields agree completely we have no problem: the two records are linked or matched. But sometimes there will be errors (often of a clerical nature) and sometimes certain fields are unavailable, which make perfect matching difficult. When comparing two fields - for example a person's last name in one data set with the last name in another data set - one is trying to answer the question: "How likely is it that such a comparison produces a linked pair of records, compared to the likelihood of that comparison existing in a pair of records that are unlinked?". The latter is best thought of as the probability of agreement if a pair of records is brought together at random.

The probability (Pr) of linkage (L+) conditional on agreement (A+) for a particular data field may be written as \( \text{Pr}(L+/A+) \). Similarly, the probability of no linkage (L-) given agreement for a particular field may be written as \( \text{Pr}(L-/A+) \). From Bayes' Theorem, we can write the likelihood ratio (LR) for linkage given agreement as follows (for a given variable or field):

\[
\text{LR}(+) = \frac{\text{Pr}(L+/A+)}{\text{Pr}(L-/A+)} = \frac{\text{Pr}(A+/L+)}{\text{Pr}(A+/L-)} \times K
\]

where \( K = \frac{\text{Pr}(L+)}{\text{Pr}(L-)} \)

If we assume independence across several variables being compared, the combined LRs are the product of the individual LRs.

If we are comparing a thousand records in File A with a thousand records in File B, there can only be a thousand true matched pairs or linkages; and there will be a thousand times a thousand minus a thousand ie just under

80
a million unmatched or unlinked pairs. The large number of possible combinations of records brought together from two large files creates some difficult problems of handling data, some of which are explored later in discussing the Automatch software.

For any particular letter in a patient's last name, one would anticipate that the frequency of a random occurrence of such a letter would be one in 26 at each letter of the name. However, if one considers five-letter names such as Brown or Smith, which are two of the most common names occurring in Canada, and then one considers another five-letter name such as Scuda, then the frequency of the occurrence of the name Brown (in for example the Canadian Mortality list), is about 0.39% and the frequency of occurrence of the name Scuda is about 0.0004%. These numbers refer to value-specific frequencies. The same concept applies to an individual letter (e.g. a patient's initial). For example the letter "J" occurs in the same death file with a frequency of 15.5% compared to the letter "Z", which has a frequency 0.1% and the letter "Q" with a frequency of 0.023%. For each individual reference list, in this case reference file B, one needs to take into account the value specific occurrence of various letters if a name is being considered. These frequencies will differ by language (French vs English), and by geographic area (Toronto, being very cosmopolitan, compared to more uniformly Anglo-Saxon parts of Ontario). Linkage is much more likely (and is therefore assigned a higher weight) if agreement occurs in a name or letter which has a low frequency of occurrence in the records being compared. Similar considerations apply to various numbers. For example, if a hospital file number or date of birth is being considered for linkage, agreement by OHIN is much more likely to imply a positive linkage than agreement by date of birth, and is accordingly assigned a higher weight.

During record linkage, it is necessary to consider the degrees of similarity which are acceptable. For instance a date of birth differing by one year from the true date of birth has been found in about 15% of linked files in the death record referred to above, and about 2% of unlinked records. (This is probably because patient age is often all that is available, and the guessed date of birth has been incorrectly calculated). Full agreement of date of birth was found in about 77% of linked records and about 1% of unlinked records. Because any one field has a certain error rate, it is usually necessary to compare as many fields as possible in order to arrive at a final decision as to whether two records, one in File A, one in File B, actually are linked.

Due account was taken of partial agreements which will ordinarily form a relatively high proportion of comparisons of a number of field types, using value-specific frequency ratios for partial agreement. Some examples are given by Newcombe:

Comparing last names can be done using letter comparisons for each letter of the last name. However it is likely that some phonetically similar portions of the name will be substituted for others. For instance the name Anderson could end in "son" or "sen", depending on the origin of the name (whether it be Anglo-Saxon or Nordic for
In order to take this into account, exact matches are sought first and if they are found counted as exact matches. Then in a second pass, phonetic matches are allowed in order to take into account this possible mistake in recording last names. This can be done using software packages for phonetics, including Soundex or the NYSIIS (New York State Intelligence Information System, being somewhat better for names originating in the so-called “far east”, for instance, which frequently occur in large cosmopolitan cities like Toronto). The error rate in similar sounding names has been found to be approximately 2% in large data bases.

For given names one needs to treat the two sexes separately because the sound errors will be different. It has been found best to compare the two records initially for the first letter of the given names and then if there is a match on initials, to compare the remainder of the name. There are several reasons for this. For example, a name such as "Samuel" might on some occasions be recorded in a health encounter as simply "Sam" with three missing values. In the PSA database, I noticed frequent interchange of first and second name, and even changing of Giuseppe to Joseph.

Similar problems arise in looking at date of birth. If we consider the year of birth, the distributions of years of birth on a file are unlikely to be uniform over time. It is general practice in record linkage to look at the year of birth separately from the month and day of birth, which would be expected to be fairly uniformly distributed. In the death list referred to above, Newcombe has found full agreement of year of birth to occur 72 times more commonly in linked record pairs than in unlinked pairs. Differences in date of birth by one year have been found to occur 7 times more commonly in linked pairs as in unlinked pairs; and so on. If one considers day and month having a uniform distribution then the chance occurrence of each number is easy to calculate: each day would occur by random chance one in 30 times approximately and each month once in 12 months. There is also a chance of these being reversed by mistake (eg June 11th could be written as 0611 or 1106).

This sort of comparison of records can only be done using computers. Recently a highly efficient and rapid automated program for comparing two sets of records has become commercially available. This program has been marketed by Matchware Inc. and is called AutomatchH7, a generalized record linkage system. One of the main contributors to development of this field 88 89, plays a significant role in this company. It is this software, available at the Ontario Cancer Registry, that was used to carry out the linkage in the PSA research project.
Appendix 3  How cutoff weights are assigned using Automatch

For a match, the probability that a field agrees given that the record pair is a match pair is the \( m \) probability; and the probability that a field agrees given that it is an unmatched pair is the \( u \) probability. The first (\( m \)) corresponds to \( \Pr(A+/L+) \) and is generally 1 minus the error rate. The second (\( u \)) is the random chance of its occurrence, i.e. \( \Pr(A+/L-) \).

Let us consider using sex and a seven-digit number as two matching variables. The \( u \) probability for sex is 0.5; that for the seven-digit number is \( (1/10)^7 \), or one in ten million.

Suppose that the error rate for sex is 10%; then a reasonable estimate for its \( m \) value is 0.9.

Similarly, suppose that for the Number the error rate is 40%, then its \( m \) value is 0.6. The weights for these variables are the base 2 logarithms of the ratios of the \( m \) and \( u \) values. This would make the weight in favour of a link, conditional on agreement on sex, \( \ln_2(m/u) = \ln_2(0.9/0.5) = 0.85 \).

Conversely, if there is a disagreement on sex, the weight in favour of being a link is \( \ln_2(0.1/0.5) \) or -2. This negative weight favours the pair as not being linked. Eventually the distribution of weights can be displayed graphically, with the less likely links having negative or low weights, and the more likely links having positive and higher weights. By analogy, for the variable Number \( \ln_2(0.6/0.0000001) = 22.5 \). This confirms the better utility of the 7-digit number as a matching variable, compared to sex, because it has a much higher positive weight for linkage, conditional on agreement.
Dear Practising Physician:

27 January 1997

RE: Patient with ID#

Our recent research has shown that, in Ontario, over three hundred thousand PSA tests are performed on patients each year. However, there is no reliable data as to the reasons that these tests are being requested. What proportion of PSA tests are used to assist in diagnosing patients with symptoms of prostate disease? for follow-up of other procedures or therapies (such as digital rectal examination, transrectal ultrasound, etc)? or to screen asymptomatic patients for prostate cancer?

I am writing to invite your participation in this PSA Utilization Study, being carried out by researchers at the University of Toronto. Your involvement is the completion of the enclosed one-page questionnaire relating to your patient's PSA test result on the attached requisition; this will require information from the patient's chart. To encourage your participation, we offer, for each completed questionnaire, a chance at winning one of five (5) prizes of a weekend for two at the Millercroft Inn*. The winning entries will be drawn randomly from the completed and returned questionnaires, and the winners contacted by April 30 1997.

The patient names have been arrived at from a random sample of patients in proximity to the Toronto Area, without a diagnosis of prostate cancer, and having a PSA test done within the past two years. A participating laboratory has forwarded the questionnaire to you on our behalf. In terms of our research agreement, we and that laboratory will protect the confidentiality of your patients and you; only the study ID number comes back to us (on the questionnaire). We do not need to know your identity, but would like to know your practice specialty.

* Near Orangeville; two nights accommodation, including one evening meal and two breakfasts
A one-page summary of our protocol is attached. The study has been approved by the Ethics Review Board of Sunnybrook Health Science Centre. It is a feasibility study, and we are relying heavily on voluntary assistance, including your participation. It is very important to receive your completed questionnaire, in order that our findings reliably reflect current practice. Please note that we are interested in the reasons for a particular PSA test on your patient, on or around the date indicated on the accompanying requisition.

The questionnaire should take about 6 - 8 minutes of your time to complete, and requires information from your patient's chart. Please return the questionnaire to Dynacare Laboratories via their courier, who will send it on to our research team. Alternatively, you could fax it back directly to us. If you prefer, we can send someone to review the patient chart and complete the questionnaire: please contact us as indicated below to participate in this way. Any information that we receive will be treated in strict confidence. Results from this research will be published in aggregate format so that it will not be possible to identify individual physicians or patients.

Thank you, in anticipation, for your assistance in this research. If you require further information, or if we can assist in any other way, please contact me as indicated below.

Yours sincerely,

Peter S Bunting, PhD DCC FCACB

Project Director

for the PSA Utilization Study Group

P.S. If you would like a copy of the final results of the research, please send under separate cover a return name and address for us to mail it to (or include this information with the questionnaire when you return it).

Phone: 416-480-5854 (has voice mail for messages)
Fax: 416-480-4651
E-mail: peter.bunting@sunnybrook.on.ca
Re: Patient with STUDY ID #
(name and test date are on accompanying requisition)

INSTRUCTIONS -
according to the situation for the patient named on the accompanying letter,
please circle A or B below:

A. I am returning the completed questionnaire, with the following information:
   I have seen this patient in my capacity as (please circle as appropriate):
   a) family physician
   b) general practitioner
   c) urologist
   d) other (please specify).................................

B. I am returning the questionnaire, uncompleted, because:
   a) This is not my patient.
   b) I do not have the time, but will allow you to view the patient chart;
      please call for an appointment at (phone no).........................................................
   c) This patient had biopsy-proven prostate cancer before the date of this PSA test.
   d) Other (please specify) ................................................................................................

    /... (page 2)
1. Does this patient have biopsy-proven prostate cancer at the present time? 
   Y N P U

2. For patients without prostate cancer at the time of the test (see sheet one):
   
   was the reason for the test (more than one response may apply):
   
   a) To investigate symptoms related to prostate disease which existed before the test was done (circle those applicable)? 
      Y N
      - hematuria
      - nocturia
      - post-void dribbling
      - delayed emptying of bladder
      - other (please specify)

   b) To investigate further the results of another procedure or therapy (circle those applicable)
      i) a digital rectal examination (DRE)
      ii) transurethral resection of the prostate (TURP)
      iii) drug therapy (e.g. anti-androgen treatment for BPH)
      iv) suspicious ultrasound result (TRUS or other)
      v) other procedure or therapy (please specify)

   c) To repeat the PSA based on results of a previous PSA test 
      Y N

   d) To screen for prostate cancer when the patient had no symptoms. 
      Y N
      - if (d) is YES, was this at the patient's own request? 
        Y N
      - if (d) is YES, was this part of a routine periodic exam? 
        Y N

   c) Other reason for PSA test (please specify)

   f) Reason unknown 
      Y N

THIS IS THE END OF THE QUESTIONNAIRE; THANK YOU FOR YOUR ASSISTANCE.
PLEASE RETURN THE QUESTIONNAIRE IN THE ENVELOPE PROVIDED.
The Study: This is a three-part feasibility study of the utilization of PSA testing in Ontario, which has been approved by the Research Ethics Board of Sunnybrook Health Science Centre. A copy of the full protocol can be obtained by contacting Peter Bunting as indicated below. In brief, the first part of the study determined the total number of patient tests performed on patients in Ontario. The second part measured the frequency of PSA testing in two large laboratory databases, in patients with prostate cancer, and in patients without cancer. The third part of the study involves the attached questionnaire for physicians requesting the PSA test on certain patients. It is very important to have your response so that our conclusions reliably reflect the current use of the PSA test.

Objective: The first part of the study has shown that over 300,000 patient PSA tests are requested annually in Ontario, but we have no reliable data as to the reasons for these tests being requested. The objective of this third part is to establish the proportion of patients for whom the PSA test was requested under certain circumstances:

(i) in a diagnostic context (i.e. the patient had symptoms of prostatism before the test);

(ii) to follow up on results of another procedure (such as a digital rectal examination, trans-rectal ultrasound, biopsy, etc) or a previous PSA test;

(iii) to screen patients without symptoms for prostate cancer (as part of a periodic examination, or at the request of the patient, for example).

Method: This third part of the study involves the random selection, from the above-mentioned two databases, of 400 patients in the Greater Toronto Area, without the diagnosis of prostate cancer (as determined by record linkage with the Ontario Cancer Registry). The number 400 was based on appropriate sample size calculations. We require access to physician records of these patients, in order to establish the reason that the particular PSA test identified, was requested. We do not require individual physician name, nor individual patient name. Access to the patient record would be most easily carried out by you, the patient's physician; however we are available to obtain the information if you prefer.

This study fulfills part of the requirements for an MSc in Clinical Epidemiology for Peter Bunting. Other members of the research team include J Ivan Williams, Vivek Goel and Eric Holowaty, all from the Department of Preventive Medicine and Biostatistics; and Neill Iscoe from the Department of Medicine. This is a feasibility, study, and we are relying heavily on voluntary assistance. Any questions can be directed to:

Peter S Bunting, Project Director.

Phone: 416-480-5854 Fax: 416-480-4651 e-mail: peter.bunting@sunnybrook.on.ca

Appendix 5 The reminder letter for the survey
Dear Practicing Physician:

A few weeks ago, we mailed a questionnaire to you concerning one or more of your patients, for whom a prostate-specific antigen (PSA) test was performed. The purpose of the questionnaire was to determine the current situations in which this test is being used in Ontario, on patients without a diagnosis of prostate cancer.

If you have already completed and returned this questionnaire, then please accept our sincere thanks, and ignore this follow-up note. If you have not completed the questionnaire yet, then please do so this week, if at all possible. It is important that we have your response, so that our results will reliably reflect the current use of the PSA test in Ontario. You are still eligible for the vacation prize (one chance per questionnaire completed and returned, roughly 1/60 chance to win), and you should have a copy of the questionnaire and a return stamped and addressed envelope which were delivered to you earlier.

Please do not hesitate to call me collect, or leave a message on our answer tape, if you have any questions regarding the study. Similarly, if you require a replacement questionnaire, or envelope, we can fax one to you if you leave us a fax number on our answer tape, or mail one to you again if you prefer. I can be reached at 416-480-5854, and our secretary can be reached at 416-480-4646; my pager number is 416-582-9807. Alternatively, we can be reached by fax (416-480-4651) or by e-mail, as follows:

peter.bunting@sunnybrook.on.ca.

Yours sincerely,

Peter Bunting, PhD DCC FCACB

Project Coordinator
1. Canadian Cancer Statistics 1995; National Cancer Institute of Canada. Table 1, p 13.


35. Schroder FH Bangma CH: The European randomised study of screening for prostate cancer (ERSPC). Br J Urol 1997; (Suppl 1);68-71


64. Laboratory Proficiency Testing Program, Ontario Medical Association, Endocrinology Committee, November 1995.


70. Ontario Regulation 856/93 under the Medicine Act of 1991, Section (2).


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