Ontario Prostate Specific Antigen (PSA) Clinical Guidelines: The PSA Clinical Guideline Expert Committee for the Laboratory Proficiency Testing Program (LPTP), 97.09.30

Physician Reference Document

The information in this booklet is based on the recommendations of the Ontario Prostate Specific Antigen (PSA) Clinical Guidelines (97.09.30). These guidelines reflect the opinions of and were developed by the PSA Clinical Guideline Expert Committee for the Laboratory Proficiency Testing Program (LPTP), chaired by Dr. Harold Richardson. The Ontario Ministry of Health is providing this information to all Ontario physicians. The Ministry acknowledges the contribution of the Institute for Clinical Evaluative Sciences (ICES) in the preparation of the educational materials on its behalf.

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The educational materials contained herein are believed to be valid as of 1998.12.16.

Information for Physicians on the New Clinical Guidelines in Ontario For Prostate Specific Antigen (PSA) Testing

The purpose of this booklet is to inform physicians about the new Ontario Prostate Specific Antigen (PSA) Clinical Guidelines for Testing released in September 1997. An expert panel of specialists from laboratory medicine, oncology, urology, family medicine and radiology, as well as prostate cancer survivors, participated in developing guidelines for the use of the PSA test in four areas:

I. Screening - *using the PSA test for the early detection of prostate cancer in asymptomatic men;*

II. Diagnosis/Investigation - *using the PSA test in combination with Digital Rectal Examination in patients in whom prostate cancer is suspected;*

III. Monitoring - *using the PSA test to monitor patients with prostate cancer; and,*

IV. Laboratory Quality Assessment for PSA Testing - *standardizing assay of PSA so that determinations are reliable and useful.*

I. *PSA TESTING: Screening*

The purpose of this section is to help you in discussing the PSA test with your male patients. The term "screening" is defined here as performing a stand-alone PSA test to look for prostate cancer in **asymptomatic** men who have no physical abnormality suggesting the presence of prostate cancer (or who have only mild symptoms of prostatism, which are present in virtually all men over the age of 50).

Routine screening for prostate cancer is controversial for a number of reasons.

Much of the disagreement involving quality of life issues. Those *against* routine screening argue that given the possibility of unnecessary significant morbidity associated with the diagnosis and treatment of prostatic cancer lesions, careful evaluation of screening is imperative; those *in favour* argue that early detection strategies may be found to save lives.

Ideally, a screening test should be capable of distinguishing between cancers or precancerous lesions that, when left undetected, result in morbidity and mortality—and cancers that do not. The problem with the PSA test is that it is not perfectly accurate; it lacks sensitivity[1] and specificity[2]. In the context of screening, it can be difficult to interpret exactly what an elevated PSA means: it can be elevated in benign

[1] The proportion of truly diseased persons in the screened population who are identified as diseased by the screening test.

[2] The proportion of truly non-diseased persons who are identified correctly by the screening test.

prostatic hyperplasia (BPH), in less aggressive-appearing, low-grade tumours, as well as in rapidly-growing tumours, or because of day-to-day variation (see Section IV).

Prostate cancer differs from other types of cancer in that its clinical course can vary widely. In some men, prostate cancers can be slow-growing, non-life-threatening, may not become clinically apparent during their lifetime, and may never require treatment. However, in others the diagnosis is made only when the cancer is too advanced to cure. The difficulty comes in differentiating between relatively benign disease and a course that may prove fatal, which reflects the diversity of the natural history of the disease. Usually the treatment of advanced prostate cancers is beneficial, but the current treatments have not yet been adequately or completely evaluated to demonstrate whether they can extend life in men with *early stage* or *low grade* prostate cancer (see Appendix A). Furthermore, these treatments have the potential for significant adverse events, and patients with early-stage prostate cancer who are treated with surgery or radiation are exposed to the same risk of significant side effects as are patients with later-stage disease: incontinence, erectile dysfunction (impotence), rectal injury and operative mortality. Whether or not prostate cancer is diagnosed early, the majority of men who have the disease will not experience significant symptoms and will in fact die from another cause. Autopsy studies have shown that by the age of 90, most men have latent or microscopic prostate cancer, which has not been the cause of death.

All these statements obviously are of concern to physicians trying to help men decide about the uncertain benefits of undergoing prostate cancer screening. They also highlight why family doctors should assist men to understand and evaluate the potential risks and harms, as well as the potential benefits, that may result from the process that is put into motion by screening. This process may continue on through diagnosis and treatment with its resulting side effects. Long-term randomized controlled trials (RCTs) providing the evidence to determine whether screening and treatment of early stage disease are beneficial but will take about 15 years to complete.

In order for doctors to be able to help their male patients make a decision about whether or not they should have a PSA test for screening, both doctor and patient need to be well informed. The role of the family doctor here is twofold: to help men gain the information they need to understand the implications of PSA testing; and, for those who choose to be tested, to exercise clinical judgement and to assist with proper interpretation of the results, given the test limitations.

Men between the ages of 50 and 75 years who have a life expectancy of at least ten years (meaning the absence of severe chronic health conditions) should be offered a brochure that discusses the potential benefits *and* risks of screening with PSA testing (available from the Canadian Cancer Society). For men who have a family history of prostate cancer or other factors that put them at high risk (e.g., black race), this information should be provided after the age of 40.

The Ontario Ministry of Health supports the expert committee's recommendation that men be informed of the risks and benefits of PSA testing *before* they decide whether they should undergo it. Men should be able to make an informed decision, with the help of their family physician, as to what is best for them as individuals.

Some Commonly Asked Questions

What causes prostate cancer and what are its symptoms?

We still do not know what causes prostate cancer. Factors associated with higher rates are increasing age (especially over 50), family history of the disease (one or two first-degree relatives, such as a father or brother), and black race. We are not yet sure how much other factors, such as a diet low in fibre or high in fat, or low levels of physical activity, play a role.

The symptoms of early-stage prostate cancer are similar to other common prostate problems associated with aging, such as benign prostatic hyperplasia (BPH). They include the following: urinating more frequently, especially at night; having difficulty in starting the urine stream, or feeling a need to push or strain to start urinating; having a weak or interrupted urine stream; or feeling that the bladder is not completely empty. Urinary symptoms are particularly likely if the cancer is located near the bladder or the urethra. Pain or discomfort is not a typical early presenting symptom in prostate cancer; however, it is a common symptom of bone metastases, when the disease is no longer curable.

How common is prostate cancer?

Of every 100 asymptomatic men, about 10 will be diagnosed with prostate cancer during their lifetime, and 3 of the 100 will die from the disease. These numbers *may* increase as therapies for other illnesses in the elderly improve. It is important to understand that some men with prostate cancer who do not die of the disease will nonetheless have disease progression whether or not they are treated initially, and may have a lower quality of life as a result.

It is important to distinguish *clinically significant* prostate cancer from cancer that is slow-growing and non-life-threatening. "Clinically significant" means that leaving the cancer untreated would result in symptoms requiring treatment or would lead to mortality.

What is the PSA blood test, and how is it used to screen for prostate cancer?

Prostate-specific antigen (PSA) is a protein produced by prostate tissue. An elevated PSA level in the blood *may* identify the presence of cancerous abnormalities of the prostate gland before symptoms are reported, and thus has been used as a screening test. The limitation of PSA as a diagnostic test is that PSA levels can be elevated in benign diseases of the prostate as well as in malignancies.

What is the "normal" PSA level?

A PSA value of >4.0 ug/L has often been defined in the literature as abnormal and is frequently used as a cut-point. However, a man's PSA level increases steadily as he ages, and some—not all—urologists advocate the use of age-related "normal" PSA cut-points, rather than using >4 ug/L for all. The table below shows suggested age-specific ranges.

Table Ia. Age-related "normal" PSA cut-points

Age Range (years)	Serum PSA Concentration (ug/L)
40 – 49	<2.5
50 – 59	<3.5
60 – 69	<4.5
70 - 79	<6.5

Source: Oesterling JE et al. *JAMA* 1993; 270:860

What happens if the PSA test is abnormal?

If a PSA test is close to the cut-off value, you may decide to repeat it to make sure it is not a laboratory error. You might immediately investigate your patient for prostatic enlargement, infection or cancer yourself if the PSA is above the cut-off value.

What is the accuracy of the PSA test?

For every 100 men over the age of 50 who have the PSA test:

(INSERT 100 man diagram here from pilot project version.)

- X About 90 will have a normal PSA level, and about 10 will have a higher than normal level.
- X These 10 men will then need to go through other tests and examinations. At the end of these tests:
  - X Three men (3/10) will be found to have significant prostate cancer after the first biopsy; i.e., seven men (7/10) will be found *not* to have prostate cancer at this time (false positives);
  - X Over the next several years, another two of these men will have significant prostate cancer detected during follow-up;
  - X Over an extended period of time, five of the ten men will be found *not* to have prostate cancer despite further investigation (false positives).
- X One or two of the 90 men who had a normal PSA test will actually have prostate cancer that is clinically significant and will cause symptoms at a later date (false negatives).

Most abnormal PSA results are caused by BPH. Very high PSA levels *usually* occur in men with advanced or metastatic prostate cancer, but such high levels are *rarely* seen in men with early disease.

What factors might have a misleading impact on the test result?

Any of the following can cause PSA levels to fluctuate modestly: prostate manipulation during digital rectal examination, transrectal ultrasound (TRUS), biopsy, presence of infection, strenuous exercise, ejaculation and normal day-to-day variation, to mention a few. See Table IVa in Section IV for a more comprehensive list.

The way that the blood is drawn and stored for testing may also affect the PSA level. See Table IVb in Section IV showing important factors in blood collection characteristics.

Are there other screening tests for prostate cancer?

Another test used is the **digital rectal examination (DRE)**, which is considered part of routine medical care. However, certain factors limit its sensitivity for prostate screening. The examiner can palpate only the posterior and lateral aspects of the prostate—and up to 40% of tumours occur anterior to the prostate midline, so they can't be felt. Moreover, stage A (early) tumours *are not palpable by definition*. Various studies have reported a wide range for the sensitivity of DRE, from a low of 18%–22% up to 55%–68%; limited specificity is also reported, producing a considerable number of false-positive results. These facts provided the platform for the Canadian Task Force on the Periodic Health Examination "Category D" recommendation for DRE. The recommendation may be revisited when considered in combination with PSA testing. Finally, there is as yet no evidence that screening with isolated DRE in asymptomatic men reduces prostate cancer mortality.

Transrectal ultrasound (TRUS) has also been proposed as a screening test. This technology documents prostate volume and detects areas of the prostate that are suspicious for cancer, as cancerous tissue is frequently hypoechoic. However, it is not an alternative to DRE, and a normal TRUS does not eliminate the possibility of cancer. It is most useful for further prostate evaluation, and provides guidance for the urologist or radiologist when performing a prostatic biopsy. The combination of PSA and DRE is as sensitive as TRUS for establishing a *suspicion* of cancer.

What do I need to consider in determining if PSA screening is appropriate for a patient?

The whole issue of the benefit of screening must involve consideration of the success of treatment of early-stage prostate cancer. There are three generally accepted treatments for prostate cancer, however detected: **"watchful waiting"** (also called "delayed therapy" or "expectant management"), and **prostatectomy** (surgery), **radiation therapy**.

X In "watchful waiting," the patient is not treated immediately but is followed carefully and treated only if the disease progresses. This approach is most appropriate for older men with small amounts of less aggressive-appearing, low-grade, slow-growing cancers, who are likely to die from other illnesses before needing treatment for their cancer. Men managed with this approach have to be selected carefully, because there is a risk that the cancer will progress and become incurable. Patients have to understand that risk and be willing to take it;

X Prostate surgery is favoured for younger men without major co-morbid conditions;

X Radiation therapy is more often considered for older men who are at greater risk for complications from a major operation.

All three treatments have their associated risks, and all have significant potential effect on quality of life (QOL) issues. Data on treatments and outcomes are reviewed in Appendix A.

Are there specific circumstances where screening PSA tests are definitely not recommended?

Since PSA testing for screening purposes in asymptomatic men is of uncertain benefit, performing it on men whose life expectancy is less than ten years is potentially inappropriate, as it is likely that most of their morbidity and mortality will be related to disease processes other than prostate cancer. However, there is no consensus on an upper age limit. In asymptomatic men, PSA testing for screening purposes is of uncertain benefit.

Should I advise my patients to be screened with the PSA test—or not? What do the experts say?

There are no general statements about screening that are applicable to all men. Even the experts disagree. Canadian and American organisations that have a policy on using the PSA test to screen asymptomatic men do not recommend population-wide screening rather they endorse endorse the importance of informed choice.

As mentioned earlier, much of the disagreement over routine screening involves quality of life issues. It seems that the most difficult part of the screening question boils down to two issues: one philosophical, one definitional. Philosophically, some physicians (and members of the public) believe that despite the lack of accuracy of the PSA test and the attendant morbidity of potentially unnecessary treatment, *all* men over the age of 50, and those at high risk (first-degree relatives with prostate cancer and/or black race) over the age of 40, should be tested for prostate cancer.

But then there is the definitional issue. At about age 50, most men start having at least some symptoms of prostatism: it's a normal part of the aging process for males. Most men who attend their family physicians regularly will have a DRE as part of a check-up. When there are no findings on the DRE and the patient has no symptoms, doing a PSA test is not recommended. But if the examining physician feels a change in the prostate—thickening, asymmetry, nodule, and/or focal lesions—then combining DRE with a PSA test moves from being a screening test to being an *investigative manoeuvre*. PSA testing as a stand-alone, isolated screening test in asymptomatic males **is not the same** as coupling it with suspicious DRE findings to investigate or rule out disease, be it BPH or prostate cancer. Simply put, *screening* is not the same as *investigation and diagnosis* (see Section II)—a distinction that needs to be underscored.

All the information you have just read is pertinent when helping your individual male patients with their screening decisions. It is essential for all men to be fully informed and aware of the potential consequences of their decision to be screened or not screened. The evidence to support PSA testing as a screening tool is limited. The spectre of lifelong urinary incontinence and/or erectile dysfunction following prostatic surgery and/or radiation makes the decision very difficult for many men, particularly when they take into consideration that some prostate cancers are slow-growing or never become life-threatening.

What do I tell my patients if they say, "Isn't finding cancer early supposed to improve my chances of cure?"

Generally, this is true with respect to people who have symptoms of cancer, but it is not always the case when tests are applied to people *who do not have symptoms*. We know that the screening of asymptomatic women for cervical cancer by PAP smears and the screening of asymptomatic women aged 50 and over for breast cancer by mammography save lives. However, screening younger women for breast cancer and screening for lung cancer have not been shown to reduce cancer mortality. These experiences have taught us that not all screening tests necessarily result in decreased deaths from a particular cancer.

There is some reason to hope that PSA screening for prostate cancer may save lives. DRE, coupled with PSA measurement, may increase early detection and may improve quantity and quality of life. However, until we *know* definitively, men should be made aware of the potential risks and benefits of early detection so that they can make an informed decision about being screened. They need to understand that screening is a *process*, and that this process may continue through to having to make decisions about treatment and experiencing side effects as a result of that treatment.

Is PSA testing for screening purposes insured?

No. Although the Ontario Ministry of Health endorses the PSA Clinical Guideline Expert Committee's recommendation that men be well-informed and understand the ramifications of PSA testing, and supports development and dissemination of educational materials for both physicians and their patients, PSA testing for screening purposes in asymptomatic males is not insured in Ontario. Asymptomatic men who, with the help of their family physician, make an informed decision to be tested and who feel it is important to their well-being must understand that they will have to pay for the test themselves.

What's the bottom line on using the PSA test for screening for prostate cancer in asymptomatic males?

According to the Ontario Prostate Specific Antigen (PSA) Clinical Guidelines,

PSA determination should not be used as a population-wide mass screening test for the early detection of prostate cancer in asymptomatic males.

II. PSA TESTING: *Investigation/Diagnosis*

This section discusses testing *men with symptoms*, in whom there is suspicion of prostate cancer.

Whom should I test?

There are two groups of men who should undergo PSA testing.

First, experts recommend that PSA testing be performed in patients in whom there is increased suspicion of prostate cancer based on either suspicious DRE findings (prostate nodule or focal lesion, abnormal-feeling prostate, discrete change in the texture, fullness or symmetry of prostate) or the presence of a secondary carcinoma of unknown origin. In patients whose life expectancy is less than ten years (i.e., those for whom morbidity and mortality will likely be related to factors other than prostate cancer), PSA testing is recommended *only* when searching for a source of metastatic carcinoma.

Second, for men with benign prostatic hyperplasia (BPH), PSA testing is recommended in those with *moderate to severe symptoms,* since as mentioned in the previous section it can be difficult to differentiate the symptoms of BPH from early-stage prostate cancer. Often it is difficult to quantify how severe the symptoms of BPH are in an individual. To help determine this, a symptom index has been developed by the American Urological Association (AUA) and has been validated and tested for reliability. Many physicians are now using this simple scoring system to determine a baseline symptom score for patients complaining of symptoms associated with prostatism, and using the score in each follow-up visit to quantify changes in symptom severity. This system also makes it easier for patients, who cannot always easily recall shifts in urinary patterns.

The index includes seven questions covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency. The symptoms are graded on a six-point scale (0-5), with a maximum score of 35. The questions and the accompanying scale are shown in the following table.

Table IIa. The AUA Symptom Index

1. During the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating? 9
2. During the last month or so, how often have you had to urinate again less than 2 hours after you finished urinating? 9
3. During the last month or so, how often have you found you stopped and started again several times when you urinated? 9
4. During the last month or so, how often have you found it difficult to postpone urination? 9
5. During the last month or so, how often have you had a weak urinary system? 9
6. During the last month or so, how often have you had to push or strain to begin urination? 9

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
0	1	2	3	4	5

7. During the last month or so, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

None	1 time	2 times	3 times	4 times	5 or more times
0	1	2	3	4	5

SUM OF QUESTIONS 1-7 ☐

Source: Barry MJ. *J Urol* 1992;148:1549-57

The table below shows how to score the symptom index (International Prostatic Symptom Score [IPSS]):

Table IIb. The AUA Symptom Index Score

Symptom	Total Score	Guidelines recommend:
mild symptoms	0-7	PSA *not* recommended for diagnosis
moderate symptoms	8-19	PSA recommended for diagnosis
severe symptoms	19-35	

Adapted from: Barry MJ. *J Urol* 1992;148:1549-57

PSA testing is not recommended in patients with BPH who have only mild symptoms; however, those patients with moderate or severe symptoms (scores of 8–35 using the AUA symptom index) *should* have a PSA test done. It is important to remember that BPH will itself cause an increase in PSA level and decreases the diagnostic specificity of the test.

It is also important to note that there are no data to support the concern that men with BPH may have an increased risk of developing prostate cancer. Prostatitis is also not a risk factor for prostate cancer

What's the bottom line on using the PSA test for the investigation/diagnosis of prostate cancer?

According to the Ontario Prostate Specific Antigen (PSA) Clinical Guidelines,

A PSA determination is recommended for any man, with a life expectancy of ten years or more, found to have a prostatic nodule on DRE.

A PSA determination is recommended for any man, with a life expectancy of ten years or more, where there is an increased suspicion of prostate cancer. Within the context of a suspicion of prostate cancer is an abnormal-feeling prostate, focal lesion, discrete change either in texture, fullness or symmetry, or secondary carcinoma of unknown origin.

The use of a PSA test is also recommended for men with moderate or severe symptoms of prostatism in whom treatment is contemplated. Severe and moderate symptoms are defined according to the International Prostatic Symptom Score (IPSS).

III. PSA TESTING*: Monitoring*

The PSA test is recommended for use in monitoring patients with diagnosed prostate cancer (based on positive biopsy), in order to look for recurrence. It should be repeated, in combination with DRE, at 3–6 month intervals for patients who are being monitored with "watchful waiting," at 3–6 months for patients who are being treated with hormonal therapy, and at 3–12 months for patients who have undergone radical treatment (prostatectomy or radiation therapy). The test should not be repeated more often than once a month. See Appendix A for information options on treatment.

What's the bottom line for using the PSA test to monitor patients with prostate cancer?

According to the Ontario Prostate Specific Antigen (PSA) Clinical Guidelines,

The use of the PSA test is recommended to monitor patients with established cancer. The PSA test should not be repeated more often than once a month.

IV. PSA Testing: *Assessment of Laboratory Quality*

Are PSA tests done the same way everywhere in Ontario?

Unfortunately, current methods of measuring PSA levels in the province of Ontario are not comparable. The standardization of ranges and results across assay systems has been recommended, and laboratory standards and quality assurance programs are being put into effect. As a minimum, the reference range for the method utilized must be made available to physicians and included on all PSA test reports to help your interpretation of the test results.

What external factors can have an impact on the serum PSA level?

The following external factors can all cause PSA levels to fluctuate modestly: prostate manipulation during DRE, biopsy, presence of infection and normal day-to-day variation.

Table IVa. Factors Related to Fluctuation in PSA Level

Factors	Effect on PSA levels	Comment
Prostate Disease		
BPH Prostatitis Prostate Ischemia	May be elevated	False positive when used to diagnose prostate cancer
Other disease		
Acute Renal Failure Bypass Surgery	May be elevated	
Clinical Manipulation		
Digital Rectal Exam Trans-rectal ultrasound	May be elevated	May be elevated 6%
Prostate biopsy TURP	Result elevated	Do not test until 4-6 weeks afterwards
Treatment		
Radiation treatment (transient)	May be temporarily elevated	
Radiation treatment	Result decreased	Nadir has prognostic significance. Lowest level expected in 3-9 months
Antiandrogen drug therapy: nafarelin, buserelin, goserelin (Zoladex), leuprolide, flutamide, finasteride (Proscar)	Result decreased	Nadir has prognostic significance. Do not test until 3-6 months after treatment. Lowest level expected in 3-12 months
Prostatectomy	Result should be undetectable unless residual disease	Do not test until one month after surgery
Other Patient Characteristics		
Prolonged exercise	May be increased	
Patient age and prostate size	May lead to increase	Age-adjusted reference ranges may be helpful
Ejaculation	May be increased or decreased (studies vary)	

Adapted from: Bunting PS. *Clin Biochem* 1995;28:221-241

The way that the blood specimen is drawn, handled and stored for testing can also affect the PSA level. The following table shows important blood collection characteristics.

Table IVb. Blood Collection Characteristics

Characteristic	Comment
Specimen container	Blood sample must be a clotted specimen
Specimen handling	Specimens should be centrifuged and serum separated from the red cells within a few hours
Storage: Stability of serum	
at room temperature	1-2 days
at 4^0C	1 week
at -20^0C	Several weeks

Source: Laboratory Proficiency Testing Program of Ontario 97.09.15

The variation in PSA levels within an individual patient (coefficient of variation) has been reported in the literature as ranging between 5% and 40% (mean: 16%), which means that the 95% confidence limits of a given PSA result are approximately 32%. The laboratory coefficient of variation on an individual PSA specimen is only about 5%, and contributes very little to test variability, provided the same method is used each time.

Can we expect to see more sensitive assays that will differentiate between elevated PSA levels in BPH and in prostate cancer?

A test that would successfully distinguish PSA results that were abnormal due to prostate cancer from those that were abnormal due to BPH would decrease the need for biopsy, with its attendant patient morbidity.

Researchers are investigating the potential usefulness of *Free to Total PSA Ratio* (F/T PSA) testing to help make this distinction. Current evidence suggests that the specificity of the PSA test may be enhanced by the use of this measurement. In general, the proportion of free PSA to PSA-ACT (alpha $_1$-antichymotrypsin) is lower in prostate cancer patients than in normal subjects or in men with non-cancerous disease, such as BPH.

Patients with a Total PSA of 3–10 ug/L are the most difficult to diagnose, and constitute the group most frequently biopsied to rule out or confirm cancer. If the DRE and TRUS are negative and there is an isolated elevation of PSA, many of the biopsies in this group prove to be negative (yet have attendant morbidity). Patients do not require a biopsy if the F/T ratio is >0.25, as the risk of prostate cancer in that case is only five per cent, and the type of cancer found in that five per cent is “usually indolent.”

Table IVc.
Probability of Prostate Cancer Based on Free to Total PSA Ratio

F/T PSA	Probability	Footnote
<0.10	>90%	probabilities change depending on age, race, and family history
>0.20	<10%	

Source: *Urology* 1996;48(6a): entire issue.

It has been suggested that 30%–40% of negative biopsies could be avoided by the use of this assay in those patients with abnormal Total PSA. To date, the Free-to-Total PSA assay is not widely available in Ontario, and until there is better evidence and the variability of different assay systems improved, it will not be recommended. However, the procedure is exciting because of its potential for reducing unnecessary biopsy procedures, and it will be revisited as new evidence is published.

What is free PSA?

An abnormal PSA result has often been defined as >4.0 ug/L and is frequently used as a cut-point in the prostate cancer literature. Generally, experts do not recommend biopsying men younger than 60 years of age whose PSA levels are <4.0 ug/L, unless there is a concomitant abnormal DRE. However, more than 20% of men with diagnosed prostate cancer have PSA levels lower than this. Research has shown that prostate cancer can be detected within 3–5 years in 13%–20% of men whose PSA levels are between 2.6 and 4.0 ug/L. Importantly, about 30% of men with PSA levels between 4.0–10.0 ug/L have cancers that have extruded beyond the prostatic capsule at the time of diagnosis with concomitant poorer prognosis.

A strategy for reducing unnecessary biopsies may be to measure free-to-total PSA levels, enhancing specificity.

In one study, Catalona and colleagues looked at the prevalence and clinicopathological features of prostate cancer in men with PSA levels of 2.6–4.0 ug/L and benign DRE to see if measuring the per centage of free PSA could reduce the number of additional biopsies needed. Of 14,193 men who had PSA and DRE, 914 volunteers aged 50 and over had PSA levels of 2.6–4.0 ug/L with BPH and no prior suspicious screening tests. Of these, 332 (36%) underwent ultrasound-guided-sextant needle biopsy. Cancer was detected in 73 (22%). Fifty-two of these cases were surgically staged; of these, 42 (81%) were organ-confined. Ten per cent had clinically low-volume or low-grade tumours; and 17% were low-volume or low-moderate grade (possibly harmless). Using a free PSA cut-off of $\leq$ 27% as the criterion for doing biopsy would have detected 90% of cancers, avoided 18% of benign biopsies (false positives), and produced a positive predictive value of 24% in men who had a biopsy performed. By reducing the lower PSA cut-off, it may be possible to reduce the number of additional biopsies required.

Is there any way to tell quickly (i.e., before clinical suspicion) if the cancer is recurring?

New, more sensitive assays have been developed to detect PSA at levels of 0.1 ug/L, 0.01 ug/L and lower, resulting in the potential to demonstrate incomplete resection postoperatively or to detect early recurrence of tumour. One recent study demonstrated that increases in serum PSA at levels of 0.001–0.1 ug/L after radical prostatectomy are associated with clinicopathological features of poor prognosis. This highly sensitive assay may potentially serve as an effective way to monitor biochemical relapse early after radical prostatectomy. However, evidence to support its use is limited and not recommended at this time. A change in this recommendation is anticipated once further evidence becomes available.

What's the bottom line on quality assessment?

According to the Ontario Prostate Specific Antigen (PSA) Clinical Guidelines, a quality assessment program to monitor the testing of PSA to ensure a province-wide standard will be implemented.

The lowest detection limit for the PSA assay used must be made available by reporting laboratories to assist the physician in the monitoring of patients treated for prostate cancer.

The current methods for the measurement of a PSA level are not comparable; therefore, as a minimum, the reference range for the method must be available. The reference ranges must be included in all PSA test reports. Standardisation of ranges and results across assay systems is desirable and recommended.

Determination of the Free to Total PSA ratio has potential to reduce the number of negative prostatic biopsies but is not recommended until there is more evidence to substantiate its utility and the problems of the inter-assay variability have been clarified.

The potential use of an ultra-sensitive PSA test for the monitoring of residual disease or relapse of prostate cancer is recognised but no recommendation for its use is made at this time. The scientific evidence to support the use of the ultra-sensitive test is not available and the accessibility is limited. A change in this recommendation is anticipated once further evidence is available.

Appendix A: Background Information

For quick reference when reviewing the tables in the appendix two general information tables have been included–one with stage definitions and one with ten-year survival rates

Table A.1: Standard Treatment Offered Based on Stage of the Disease

Stage	Definition	Treatment
A1 or T1a	Presence of cancer cells in *less than 5%* of fragments from a transurethral resection of the prostate	Observation
A2 or T1b	Presence of cancer cells in *more than 5%* of fragments from a transurethral resection of the prostate; no nodule detected on rectal exam	Prostatectomy or radiotherapy
B0 or T1c	Cancer detected by biopsy after finding high PSA levels; rectal examination and transrectal ultrasound normal	Prostatectomy or radiotherapy
B1 or T2a	Cancerous nodule occupying *less than half* of one prostate lobe	Prostatectomy or radiotherapy
B2 or T2b	Cancerous nodule occupying *more than half* of one prostate lobe	Prostatectomy or radiotherapy
B3 or T2c	Tumour involving both prostate lobes	Prostatectomy or radiotherapy
C or T3	Tumour not confined to prostate capsule, invading seminal vesicles or the pelvis	Radiotherapy Prostatectomy in certain cases
D1 or N+	Involvement of pelvic lymph nodes	Early or late hormone therapy
D2 or M1	Distant metastases	Hormone therapy
D3	Relapse following hormone therapy	Palliative care Chemotherapy in certain cases
The options include watchful waiting in all cases, based on grade, stage of the disease, age, comorbidity and patient's preference		

Source: Adapted by the Collège des médecins du Québec, *The PSA Test and Screening for Prostate Cancer*, February 1998 from Gaudet R et al in Le Clinicien 1996; II:134.

Table A.2: Ten-year Survival Rates*

Extent of Cancer	**Rate** (%)
Cancer confined to prostate	75
Regional extension of cancer	55
Cancer with distant metastases	15

* Survival rates are affected by tumour grade, patient age and comorbidity
Source: Woolf SH. *N Engl J Med* 1997; 333:1401-5.

Localized Prostate Cancer - Disease Control Rates

The data available on localized prostate cancer is observational, since randomized trial data are not yet available. This remains a significant limitation.

Regardless of how prostate cancer is detected, there are three generally accepted treatments for prostate cancer that is confined to the prostate gland at the time of diagnosis. These include: "watchful waiting" (also called "delayed therapy" or "expectant management"); prostatectomy; radiation. Please refer to the accompanying tables for disease control rates as reported in observational studies.

Unfortunately, terms and groupings are not used consistently in the research literature. Disease-specific (also called cause-specific) survival data are presented when available. For example, in the tables shown below, the radiation therapy article did not provide information on disease-specific survival, nor did it provide survival data related to histologic grade. The categorization of histologic grade in the Chodak and Zinke articles is similar but not identical. Finally, both Chodak and Zinke refer to metastasis-free survival, while Perez refers to disease-free survival. The latter includes progression of disease locally and/or at metastatic sites. We have added some tables from other centres with large sample sizes showing their experience, but these suffer from the same problems. Comparisons between surgical and radiation series have also been confounded by issues of age and co-morbidity.

Table A.3: Patient Characteristics and Outcomes of Treatment for Localized Prostate Cancer

	Watchful Waiting		**Radiation Therapy**		**Radical Prostatectomy**	
	Median (CI) *	n*	Median (CI)	n	Median (CI)	n
Patient characteristics:						
Age	71 (69-73)	27	66 (64-66)	49	63 (61-64)	33
% of cancers poorly differentiated	7 (6-11)	19	21 (13-24)	45	11 (6-25)	22
Outcomes:						
Annual mortality rate						
All causes	.060 (.050-.04)	27	.045 (.040-.052)	45	.032 (.020-.044)	27
Cancer-specific	.009(.006-.012)	23	.023 (.010-.030)	22	.009 (.007-.013)	23
Metastatic Rate	.017 (.011-.043)	15	.050 (.030-.095)	17	.023 (.014-.025)	18

* CI = confidence interval; n=number of studies

Source: US Congress, Office of Technology Assessment. *Costs and Effectiveness of Prostate Cancer Screening in Elderly Men*. OTA-BP-H-145. Washington DC; US Government Printing Office, May 1995 from data reported in Wasson JH et al. *Arch Int Med* 1993; 2:487-93.

Table A.4: Disease Control for Patients Managed by Watchful Waiting

Histologic Grade	10-year Disease-specific Survival (%)	10-year Metastasis-free Survival (%)
Grade 1 (favourable histology)	87	81
Grade 2 (intermediate histology)	87	58
Grade 3 (unfavourable histology)	34	26

Source: Chodak et al. *N Engl J Med* 1994; 330:242-48.

There are no unambiguous randomized controlled trials comparing radiation therapy to surgery in the curative treatment for prostate cancer. All that is presently available are survival rates following the respective treatments.

Table A.5: Survival Following Radical Prostatectomy without Adjuvant Therapy

Stage	Patients (N)	10-year Cause-specific Survival (%)	10-year Metastasis-free Survival (%)
T1	74	93	93
T2a	360	91	86
T2b + T2c	512	90	78
Histologic (Gleason) Grade			
2-3	156	94	95
4-6	667	91	93
7-10	123	86	67

Source: Zinke et al. *J Clin Oncology* 1994; 12:2254-63.

Table A.6: Multi-institutional Pooled Analysis of 2758 men Following Radical Prostatectomy

Category	**10-year Disease-specific Survival** % (95% Confidence Interval)	**10-year Metastasis-free Survival** % (95% Confidence Interval)
All patients	85 (81-87)	70 (66-74)
Grade 1	94 (87-98)	87 (78-92)
Grade 2	80 (74-85)	68 (62-73)
Grade 3	77 (65-86)	52 (38-64)
Clinical stage T1	90 (82-94)	80 (72-86)
Stage T1, grade 1	100 …	99 (95-99)
Stage T1, grade 2	82 (64-91)	75 (62-84)
Stage T1, grade 3	75 (37-92)	43 (9-74)
Clinical stage T2	83 (79-86)	67 (62-71)
Stage T2, grade 1	92 (82-97)	81 (68-90)
Stage T2, grade 2	79 (72-84)	66 (59-72)
Stage T2, grade 3	78 (64-87)	55 (40-67)
Organ confined	91 (87-94)	83 (78-87)
Not organ confined	77 971-83)	59 (53-65)

Source: Gerber G et al. *JAMA* 1997; 276(8):615-9.

Table A.7: Survival Following External Beam Radiotherapy

Clinical Stage	**10-year Overall Survival** (%)	**10-year Disease-free Survival** (%)
T1b	60 – 66	45 – 70
T2	43 – 86	45 – 85

Source: Perez CA et al. *Cancer* 1993; 72: 3156-73.

Table A.8: Definitive Irradiation in 963 Patients (65-71Gy in 6.5 - 7 weeks)

Clinical Stage	**10-year Disease-Free Survival** (%)	**Initial PSA Level Correlated With Freedom From Chemical Failure (Post-Radiation PSA-Level Elevation)**	
A1 or T1a	100	PSA<10ug/L	PSA>10ug/L
A2 or T1b,c	69	96%	75%
B or T2	57	89%	65%
C or T3	41	not reported	not reported

Source: Perez CA et al. *Mo Med* 1995; 92(11):696-704.

Risks And Side Effects Associated With Treatment

As with any condition, there are risks. With "watchful waiting", the risk is that the disease may progress to a point where intervention will not prevent the spread of disease.

There are risks to radical therapy as well. The risks associated with prostatectomy include those of any major surgical procedure in an elderly population (a small risk of death, and postoperative complications, such as infections or thromboembolic disease), as well as risks particularly associated with prostate surgery, primarily urinary incontinence and erectile dysfunction. With radiation therapy, although deaths are rare, it too has significant morbidity from urinary incontinence and erectile dysfunction. Rates of reported side effects vary widely. Variations in death rates may be due to differences in patient selection among those included in the reports. For other side effects, it may be a matter of who is asked about them (i.e., the patient or the physician) and how the problem is defined, as well as issues of patient selection.

Complications of urinary incontinence and erectile dysfunction resulting from radical prostatectomy and radical radiation therapy for prostate cancer are shown in the tables below. These tables reflect the latest information available to date.

Table A.10: Symptoms Of Urinary Incontinence, Stratified By Age

			Responding Men with Complaint (%)		
Complaint	**Age (years)**	**Treatment***	**Baseline**	**3-months**	**12-months**
No. of patients responding⊥	64 or less	P	91	83	77
		R	31	27	25
	65 or more	P	34	33	33
		R	104	98	88
Leak or dribble	64 or less	P	2	24§	9
		R	0	0	0
	65 or more	P	3	24§	15
		R	1	2	2
Use of pads required	64 or less	P	2	57§	35§
		R	0	0	0
	65 or more	P	3	61§	36§
		R	2	0	0

* P=prostatectomy, R=radiotherapy;

⊥ Incidence of incontinence was <3% pretreatment in both groups. Due to omitted responses, denominators for individual items vary by up to 2%.

§ $p<0.005$ comparing prostatectomy with radiotherapy patients.

Source: Talcott JA. *J Clin Oncol* 1998; 16:275-83.

Table A.11: Symptoms Of Sexual Dysfunction Among Patients Who Received Radical Prostatectomy or Radical Radiotherapy as Initial Therapy for Early Prostate Cancer, Stratified By Age

			Responding Men with Complaint (%)		
Complaint	**Age (years)**	**Treatment***	**Baseline**	**3-month**	**12-month**
No erections in the last 4 weeks	64 or less	P	6	86**	69**
		R	12	13	20
	65 or more	P	29	82**	91**
		R	19	29	37
Usual erections inadequate for sex					
	64 or less	P	26	96**	91**
		R	32	39	52
	65 or more	P	53	95**	97**
		R	49	63	71

* P=prostatectomy, R=radiotherapy;

** p<0.005 comparing prostatectomy patients with radiotherapy patients. Complete sexual impotence (including absence of morning erections) was reported by 11% of surgery patients and 18% of radiotherapy patients before surgery (p=0.09). Pretreatment surgery patients were younger.

Source: Talcott JA. *J Clin Oncol* 1998;16:275-83.

Table A.12: Risk of Complications Following Prostatectomy or Radiotherapy

Risk	**Surgery** (%)	**Radiotherapy** (%)
Death	0.1 - 2.0	<1
Erectile dysfunction (impotence)	25 - 85	25 - 40
Any incontinence*	20 - 63	5 - 10
Complete incontinence**	1 - 7	<1
Uretheral Stricture***	10 - 20	5

* Requiring the use of pads or clamps to control urinary dripping.

** Continuous urinary dripping.

*** Requiring at least one procedure to dilate the urethra.

Note that some of the complications reported in Table A.12 (e.g., erectile dysfunction) have very wide ranges and may seem less than useful, but in fact they are included to help reveal the controversies, as using averages would be misleading. The lower complication rates tend to be reported in series where patients are younger and healthier and from medical centres with a special interest in prostate cancer.

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