The Association for Clinical Biochemistry & Laboratory Medicine
Better Science, Better Testing, Better Care

The Royal College of Pathologists
Pathology: the science behind the cure

Audit Template

Audit Title: A regional audit of PSA practice in Scotland

Lead Auditor: Dr Harriet Hale	**Audit date(s):** Nov-Dec 2023
Please indicate if: Regional Audit Please indicate which hospital & location or region: Scotland	**Report Author:** Name: Dr Harriet Hale Email: Harriet.hale@nhslothian.scot.nhs.uk

Aims of the Audit:

Prostate cancer is the second most common cancer in males. A variety of guidelines and studies have been published relating to diagnosis, monitoring and treatment of prostate cancer e.g. NICE Prostate Cancer Guidelines NG131 (last updated December 2021), Prostate Cancer Guidelines from the European Association of Urology (last updated 2019) and the STAMPEDE RCT which began in 2005. Prostate specific antigen plays a significant role in the clinical diagnosis and monitoring of patients, as well as guiding treatment options. PSA practice across Scotland was last audited in 2004 although unfortunately there is no longer a record of this audit. In collaboration with the ACB Scotland Audit Group, we audited PSA practice in Clinical Biochemistry laboratories in NHS Scotland. The audit aims to better understand the requesting, analysis and reporting of PSA, to see if reporting of results adheres with published guidance and to determine whether any recommendations can be shared with Scottish laboratories to improve the way we provide this essential service.

Audit Method:

A 19 question survey was designed by ACB Scotland Clinical Audit Group and was sent to all 14 regional health boards in Scotland. The questionnaire remained open from 3rd November 2022 to the 24th December 2022.

Audit Outcomes:

Ten responses to the Questionnaire were received. All 10 labs who responded performed PSA analysis within their Lab.

Prostate Specific Antigen and Prostate Cancer

Prostate cancer is the second most common cause of cancer deaths in the UK for people with prostates, resulting in 12,000 deaths per year from the disease. It is a rare disease in people below the age of 50 and risk increases with age.

Prostate specific antigen (PSA) is a serine protease glycoprotein produced mainly in the prostate gland, where its function is to liquefy semen and allow spermatozoa to move more

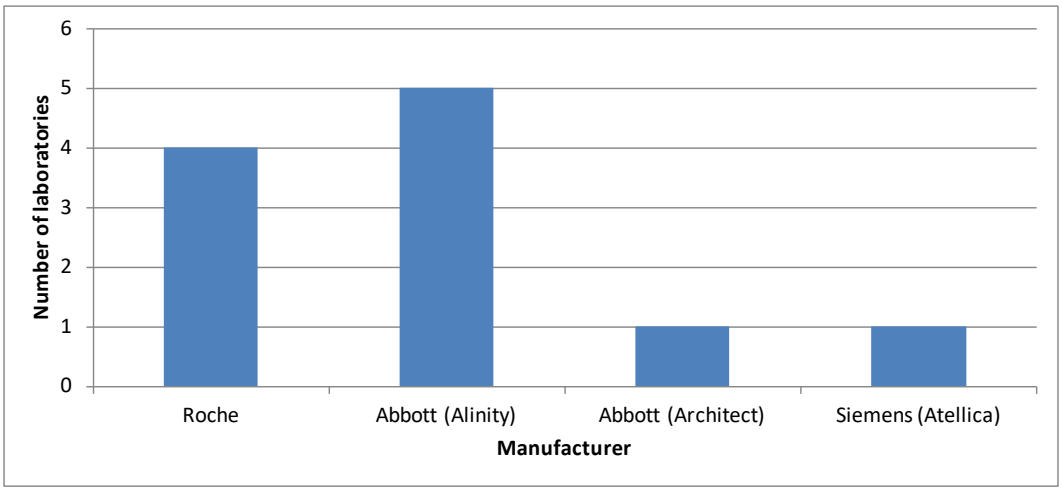
freely. Elevated concentrations of PSA in serum can be indicative of a pathological condition of the prostate, such as prostatitis, benign hyperplasia, urinary tract infection or carcinoma. However, an inflammation or trauma of the prostate (e.g. in cases of urinary retention or following rectal examination, cytoscopy, coloscopy, transurethral biopsy etc) can also lead to a rise in PSA levels. Despite not being a very specific marker for prostate cancer, PSA measurement can be combined with other information such as prostate size, digital rectal examination (DRE) findings, age, ethnicity, family history of prostate cancer, body weight, co-morbidities, history of any previous negative biopsy or any previous PSA history. This information can be used to determine which patients are referred to specialist care.

PSA results also contribute to risk stratification for people with localised or locally advanced prostate cancer. A combination of the Gleason score (grade of cancer cells), PSA level and the T stage (the size and area of the cancer) are used to determine which prognostic group a patient belongs to. Measuring PSA levels is particularly useful in monitoring the progress and efficiency of therapy in patients with known prostate cancer or receiving hormonal therapy. Finally, PSA levels are a useful indicator of disease recurrence, particularly after radical prostatectomy where the majority of prostate and lymph tissue has been removed.

Analysis

Manufacturer

All laboratories included in this audit measure PSA on their main biochemistry analysers. The manufacturer used by the majority of laboratories is Abbott (Alinity) with one laboratory also using an Abbott (Architect) machine. Roche was the second most popular manufacturer used by Scottish laboratories for PSA measurement and Siemens (Atellica) was used by one laboratory.



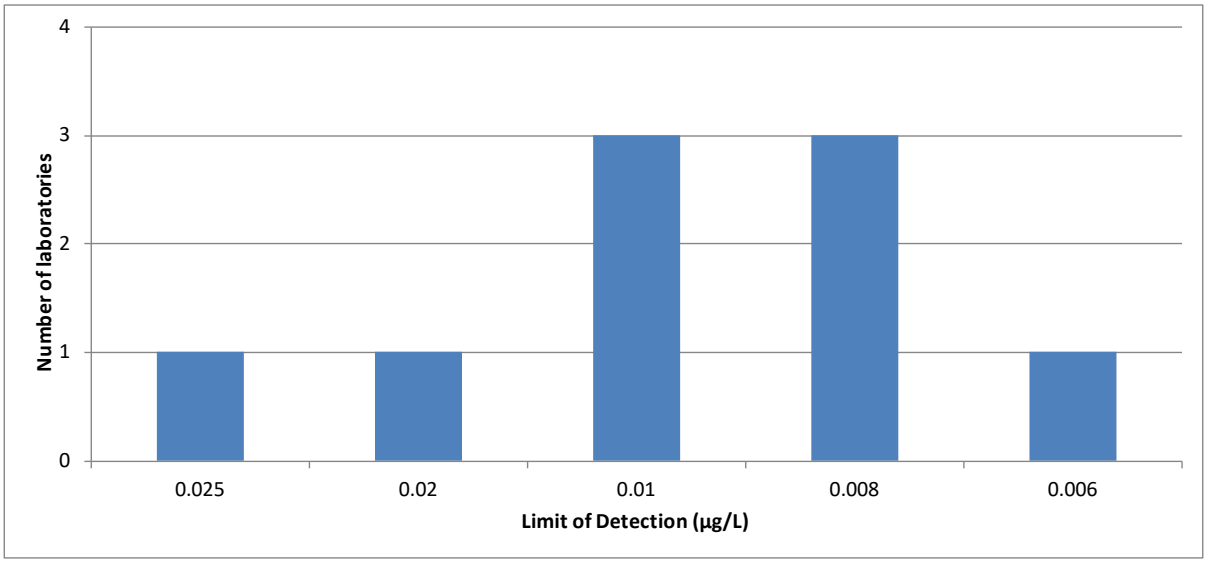
What is being measured

The free PSA test measures the percentage of the total PSA that is not bound to proteins in the patient's blood. A study conducted in 2003 (Ito *et al*) suggests that the free PSA ratio can help predict the probability of cancer, particularly in those patients with total PSA levels between 2.0 to 10.0 µg/L. Findings suggested a free-PSA result above 25% indicates a lower risk of cancer, whereas a lower percentage indicates a higher probability of disease. It is

possible that this information can reduce the number of unnecessary biopsies, although current NICE guidelines do not mention the use of free PSA ratio in diagnosis of prostate cancer. All laboratories included in this audit report total PSA (free and complexed) and none measured free PSA. All laboratories in Scotland use the SI units µg/L, although NICE guidelines use conventional units of ng/ml.

Limit of Detection

Limit of detection is determined based on the limit of blank and the standard deviation of low concentration samples and corresponds to the lowest analyte concentration which can be detected by the analyser with statistical significance. There were differences in limit of detection reported by laboratories which is probably reflected in the different analyser manufacturers. The majority of laboratories use a limit of detection of 0.01 or 0.008µg/L. These are all below a cut off point that could help guide clinical decisions for the patient. It is not known whether the laboratories reporting at very low concentrations of PSA are using ultrasensitive PSA methods and whether they use IQC samples at concentrations low enough to give assurance that reporting at such low levels is analytically sensible.



Upper limit of linearity

The upper limit of linearity of the PSA assay was 100µg/L for every laboratory included in this audit. Some responders included information about reportable ranges based on diluted samples, with one laboratory reporting up to 1000µg/L on a 1 in 10 diluted sample and two laboratories reporting up to 5000µg/L (1 in 50 dilution).

Requesting

Questions asked at point of request

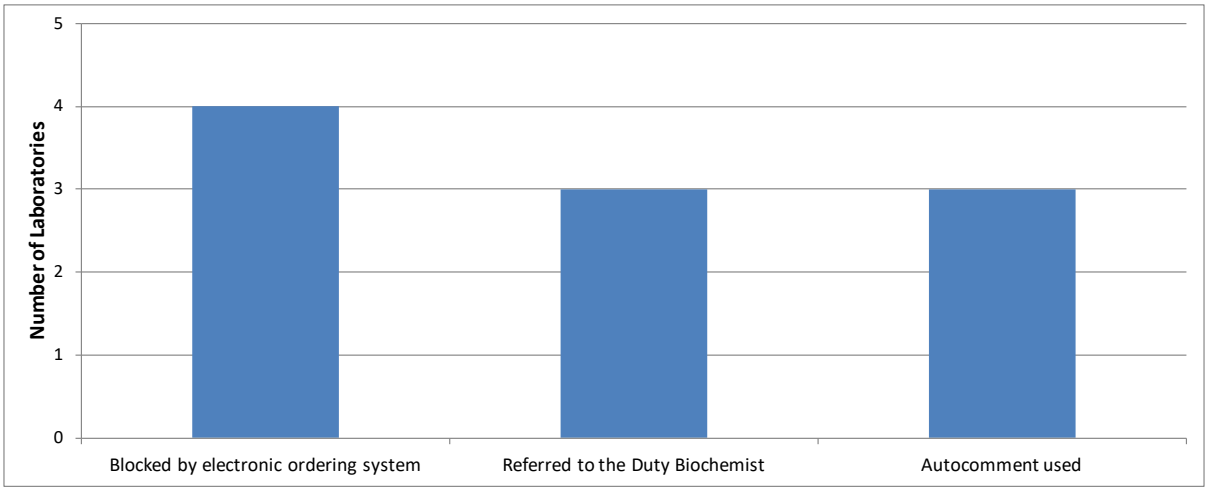
All 10 laboratories included in this audit responded that electronic ordering was in place for PSA at their hospital. However, only two sites replied that specific questions that can help with reporting and appropriate automatic commenting were asked at the point of request. These questions were:

1. Is the patient taking finasteride?

2. Has this patient had a radical prostatectomy?
3. Is this patient known to have prostatic cancer?

Protocol with respect to requests in women

PSA requests in women are not appropriate unless the patient has transitioned from male to female and have a prostate. A question in this audit asked how the different sites deal with PSA requests in women. Almost half of laboratories reported that requests were blocked in women by the electronic reporting system and their LIMS system, with an error message appearing. One laboratory indicated that whilst this was the case for requests from primary care, requests from secondary care were not restricted in women. The protocol for three laboratories in Scotland is that PSA requests in women would be taken to the Duty Biochemist or a consultant clinical scientist to investigate and make a decision on whether this is appropriate for this patient (i.e. they are a transgender female). The other three laboratories applied an autocomment to PSA results in women with similar wording, for example 'For women with a prostate PSA level of 1 µg/L and above may be associated with an increased risk of prostate cancer'. One laboratory which utilises this autocomment also mentioned that these results are held for review prior to authorisation.



Reporting

Age-related reference intervals

Data taken from NICE guidelines (Last updated 2021) and outlined in Clinical Knowledge Summaries provides age specific PSA thresholds for people with possible symptoms of prostate cancer, as shown below.

Age (years)	PSA level (µg/L)
<40	Use clinical judgement
40-49	>2.5
50-59	>3.5
60-69	>4.5
70-79	>6.5
>79	Use clinical judgement

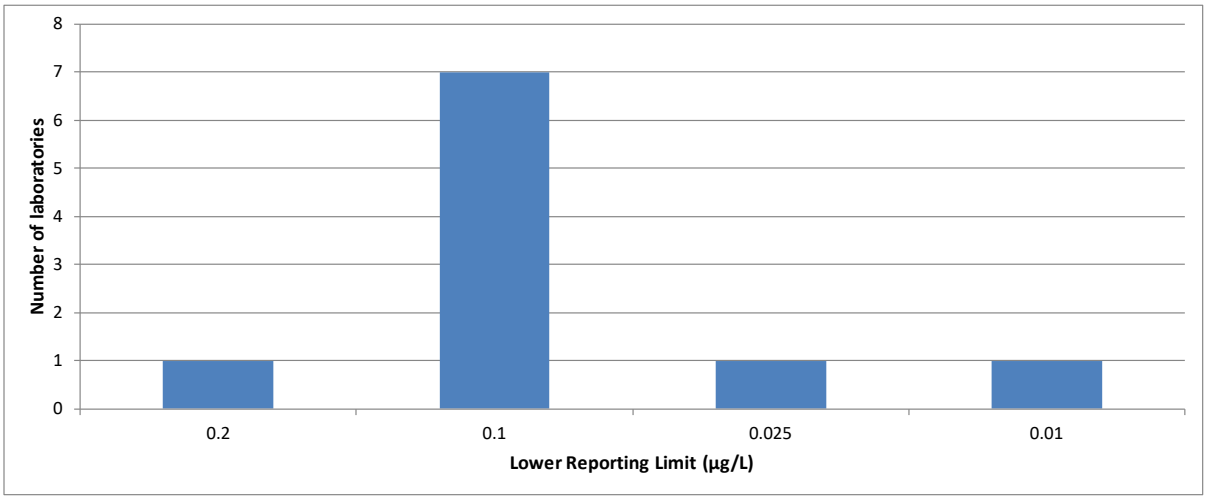
Seven laboratories audited here have adopted the age-related reference intervals outlined below, which differ slightly to the recommended thresholds in the guidelines. One health board reported that urologists were initially using more cut-off levels based on these guidelines but pragmatically it was decided to reduce these to three.

Age (years)	**PSA level**
0 – 60	<3µg/L
≥60-69	<4µg/L
≥70	<5 µg/L

Two laboratories implement a lower age-related cut-off of 40 and 50 years old (i.e. 40 or 50 to 60 years old, PSA <3µg/L) and results in patients younger than this are held for review by the duty biochemist. For one laboratory, the reference intervals are simplified with a single cut-off of 70 years old used; younger than 70 has a reference interval of <3µg/L and older than 70 is <5µg/L.

Lower reporting limit and decimal places

Only one laboratory differed to the rest, reporting PSA results to three decimal places. The remaining laboratories report to one decimal place. Instances where it would be useful to see results to more than one decimal place include subtle changes in PSA levels post radical prostatectomy. However, a cut-off of 0.2µg/L is widely used as an indicator of prostate cancer recurrence and few labs have adopted using a PSA velocity of >0.75µg/L/year, which would require reporting to more than one decimal place. One laboratory has a lower reporting limit of 0.2µg/L.



Surgical radical prostatectomy

Radical prostatectomy aims to remove the entire prostate gland and lymph nodes in order to remove the cancerous tissue. Changes in PSA levels after radical treatment are an effective way of indicating relapse in patients. A study by Freedland *et al* in 2003 carried out a retrospective survey of 358 men undergoing radical prostatectomy. The 3-year and 5-year risk of PSA recurrence using various cut offs (>0.1, >0.2, >0.3, >0.4 and >0.5µg/L) were investigated. This study concluded that patients with a postoperative PSA value greater than 0.2µg/L are at very high risk of developing an additional rise in PSA. The European Association of Urology 2022 guidelines have adopted this cut-off, as have American

Urological Association. Only one manufacturer, Siemens, recommended a level of ≥0.02µg/L for recurrence of prostate cancer post radical prostatectomy. However, the lower reporting limit used by this laboratory is 0.2µg/L and the laboratory reports results to one decimal place and so this recommendation cannot be used in practice.

Only one laboratory uses a different reference range for those patients who have had a surgical radical prostatectomy (<0.2µg/L) and any results above this level are highlighted in bold. This information is gathered at the point of request, with the specific question asking if the patient has had a radical prostatectomy. An autocomment stating 'when this PSA level was requested it was indicated that this patient had a radical prostatectomy for prostate cancer. If this is the case a PSA level of 0.2µg/L or above may indicate disease recurrence and urgent urology review' is input by the laboratories LIMS system. Another laboratory holds all PSA results <1µg/L in a reporting queue and the duty biochemist adds a discretionary comment as appropriate such as 'May indicate recurrence if PSA increases to >0.2µg/L'.

Monitoring change in PSA levels

PSA velocity is the rate of change of a person's PSA level over time. According to NICE guidelines, a PSA velocity of >0.75µg/L/year can help in the assessment and diagnosis of patients when they have had a negative MRI scan or biopsy but there is still a strong suspicion of prostate cancer. For those patients who are discharged to primary care if the level of suspicion is low, a PSA velocity of >0.75µg/L/year is a cut-off for primary care at which they can re-refer. No laboratory reported having an IT solution for determining PSA velocity but two laboratories replied saying the duty biochemist will look at previous results and determine if there is a significant change in a certain time frame, although that change was not defined by one laboratory and the other laboratory would comment on a doubling time of <2 years to primary care. Delta checks define the allowable difference between consecutive results within a certain time interval. One laboratory has implemented a delta check for PSA results in their LIMS system, based on a change of 7µg/L or 15% change over 600 days.

Criteria for holding PSA results for DB review

There was quite a lot of variation in practice for which PSA results are held for review and which results are autoauthorised. One laboratory held all PSA results from primary and secondary care for review by a clinical scientist whereas another laboratory only held results from primary care. In contrast, another laboratory autoauthorised all results and none were held for review. Three laboratories only hold results which are outwith the age-related reference intervals. Another laboratory would also trap results if they are requested in females. Four other laboratories hold PSA results if they are greater than 8, 10, 40 or 500µg/L. Therefore, the majority of labs would hold results for review by a clinical scientist if the results were considered very high, outwith an age-related reference interval or requested in a woman.

Finasteride treatment

Finasteride is a specific inhibitor of the enzyme 5α-reducatase, which metabolises testosterone into the more active metabolite, dihydrotestosterone. It is administered to men with benign prostatic enlargement as they can improve lower urinary tract symptoms, such as difficulty passing urine, urinary retention and poor urinary flow by reducing the size

of the prostate. As a consequence of this, PSA levels will also be reduced and could mask underlying prostate cancer. Several studies, including the Prostate Cancer Prevention Trial (2005) have investigated the affect of taking finasteride on PSA levels and these have shown that finasteride decreases PSA by ~50% during the first 12 months of use. This particular study concluded that the adjustment factor required to preserve median PSA increased from 2 at 24 months to 2.5 at 7 years after initiation of finasteride. One laboratory asks an automatic question at the point of request about finasteride treatment and an autocomment is provided by the LIMS system saying that the PSA result should be doubled. This depends on the clinician reading this comment and doubling the PSA result themselves to interpret the PSA result appropriately.

PSA results in Transgender Patients

Four laboratories have a protocol in place for how to process PSA results in female transgender patients. These are:

1. Requests for PSA in female patients are brought to the attention of the Duty Biochemist who will try to determine if request is appropriate. PSA can be added by DB in LIMS if request deemed appropriate.
2. Requests will be passed to Duty Biochemist for review.
3. All gender blocks removed and autocomment appended
4. No specific protocol. An auto-comment is sent with the result when there is a PSA request for a female. “For women with a prostate PSA level of 1 μg/L and above may be associated with an increased risk of prostate cancer”. This is the same autocomment appended to requests in PSA requests for women.

Reporting results directly to patients

None of the 10 laboratories involved in this audit were aware of any current plans for reporting PSA results directly to patients however, this question was asked as there has been interest from certain groups. There is currently one funded project underway in Scotland that we are aware of where PSA results are being taken directly from SCI store rather than the laboratory LIMS system and are sent directly to the cancer patient who is being monitored. It is not clear if all results are being sent to patients or just patients with known prostate cancer and unfortunately this particular laboratory did not respond to this audit questionnaire.

Another laboratory has been approached by a the WoSCAN Prostate Cancer Digital PSA group who have shown interest in introducing reporting PSA results directly to patients however there are no immediate plans to do so. This indicates that there is interest out there, although it is not clear if this is driven by patients or clinicians.

Audit Recommendations / Standards:

This audit results highlight areas where current practice differs across sites.

Suggested areas which should be focused on in review of local practice:

1. Gather important information at the point of request which can enable different reference ranges to be applied to those patients who have had a radical prostatectomy or are taking finasteride.

2. Consider introducing a protocol with respect to PSA requests in women that does not automatically block requests as this may prevent measurement of PSA in a transgender woman. Instead, consider an autocomment that is applied to all PSA levels in women that refers to people with a prostate.

3. Consider implementing an IT solution that allows calculation of PSA velocity. As recommended by NICE Guidelines, this can be useful for clinicians for diagnosis of prostate cancer in patients who have had a negative MRI scan or biopsy, but for which there is still a strong suspicion of prostate cancer or for those patients discharged to primary care but require re-referral to a specialist.

4. Engage with Labs IT to introduce rules that hold PSA results for review by a clinical scientist if outwith age-related reference intervals or have breached a cut-off such as 0.2µg/L in a patient who has had a radical prostatectomy or the PSA level has failed a delta check.

5. Consider liaising with eHealth colleagues to discuss if there is drive for reporting results straight back to patients with known prostate cancer.

Please indicate to whom and when audit presented &/or circulated &/or published:
Poster presentation at UK MedLab23

Audit recommendations / standards ratified by … and when:

Audit documents for upload to http://www.acb.org.uk/whatwedo/science/audit.aspx
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