

**Please read this bit first**

This CPD/ CEU exercise is designed to take approximately two hours as a small group exercise within your laboratory. The Thistle QA CPD No is: **MT00025**.

Please keep a register of those taking part in the exercise. When the exercise is completed, please ask using the above email address, and we will send you a sheet showing the correct responses to each question.

Each attendee should claim two CPD points for completing the questions correctly, by retaining a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

## **Tests used to diagnose and monitor prostatic cancer: are they good enough?**

### **Introduction**

The "traditional" tests used to diagnose and monitor prostatic cancer are Total and Prostatic Acid Phosphatase. Their performance on Thistle EQA will be considered in the light of a recent paper on the bias and molarity of commercial assays for PSA (Prostatic Specific Antigen), a more recently introduced test (Roddam AW et al, *Ann Clin Biochem* 2006; **43**: 35-48).

### **Acid Phosphatase – Performance**

A recent review of the performances of all analytes assessed on the Thistle QA Chemistry EQA showed that several analytes were consistently performed poorly.

Prostatic and Total Acid Phosphatase were both poorly performed. The table below shows the Average CV of all labs sending in results, compared to the % CV used by Thistle QA to determine whether a lab result is acceptable (a % from the mean lower than this figure) or poor (a % above this figure). The database number of results collected over a cycle is also shown, and indicates a reduction of the number of labs either sending in results or, more likely, performing this test. For illustration, calcium over the same period of six months had a database of over twenty thousand results.

<b>Analyte</b>	<b>% Acceptable CV</b>	<b>% Average CV</b>	<b>Database</b>
Acid Phosphatase - Prostatic	12	25.3	1566
Acid Phosphatase – Total	12	19.4	1984

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This table shows that the average laboratory sending in results fails to achieve a result within the required percentage of the mean. For both enzymes, this is 12%, a figure derived from a careful scrutiny of standards such as BV (Biological Variation) and CLIA'88, the USA standards for performance on EQAs. In fact approximately 61% of results received by Thistle QA are classified as poor for Prostatic Acid Phosphatase; while 58% of Total Acid Phosphatase results are classified as poor.

The various reasons for this are as follows:

- Unsatisfactory sample from Thistle QA
- Poor laboratory performance
- Problems with commercial kits
- Methodology problems in general.

The first two of these possibilities is unlikely in view of the performance of all other enzymes on the Chemistry EQA. The percentage of poor results ranges from about 15% (lipase) to less than 5% (many enzymes). It is difficult to imagine a sample that would be selectively poor for two enzymes only. The labs sending in poor results for these tests are perfectly able to satisfactorily perform other enzyme assays, therefore it is difficult to place the "blame" for this performance on the labs *per se*.

The possibility of problems with certain commercial kits does not apply either, as a survey did not find any significant difference in performance between any of the kits currently being used. All show similar performances.

We are left with the likelihood that the methodology itself is the problem, either because of some inherent difficulties or some technical issues related to the substrate specificity or calibration.

In conclusion, we are faced with two poorly performed tests, showing a marked decrease in 'popularity', both showing a high degree of either/ or imprecision or bias, rendering them suspect as tests suitable for either diagnosis or monitoring of prostatic cancer.

### **PSA – performance**

It has been recommended that assays for PSA should be equimolar in their response to free and complexed PSA, and be calibrated to the WHO (World Health Organisation) First International Standard.

To test this, the authors of the paper sent 15 samples with varying mixtures of free and complexed PSA to 223 labs in England. The results were converted to recovery percentages and analysed statistically for significance. In total 11 methods were used by the labs involved, from Abbott (2 methods), DPC (2), Bayer (2), Beckman, Ortho, Perkin-Elmer, Roche and Tosoh.

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No method was found to be both unbiased and equimolar. Estimates of bias varied with concentration for many methods, ranging from -5% to + 22%, while estimates of non-equimolarity ranged from -0.18% to +0.28%. These variations, according to the authors, are a result of epitope recognition differences between kits, affecting both the accuracy (bias) and the ability to recognise both free and complexed PSA.

The authors conclude that the recommended aims of PSA assays have not yet been achieved. While it is reasonable to expect a degree of variation between commercial kits, performance limits need to be set to ensure that no one method can have a detrimental impact of clinical outcomes. In other words, the needs of the patient must be paramount, and tests for prostatic cancer need to be improved.

**NB:** The difference between kits and methods for PSA would not be seen on your Thistle QA report if we only reported your INSTRUMENT stats. A biased method can only be seen when compared to OTHER methods.

### **Conclusion**

We are fast moving away from the “traditional” tests for prostatic cancer, with obvious technical limitations. Unfortunately the PSA test also has limitations that hopefully will be addressed urgently, with the needs of concerned patients in mind.

### **CPD Questions**

1. Discuss the reasons given here for poor performance of the Acid Phosphatase tests. Is the list complete or do you think there are other reasons? Do you agree with the conclusions presented here?
2. If you measure any of the three tests mentioned above in your laboratory look at your performance on EQA. Do you agree with the conclusions presented above? Now look at your Internal (Daily) QC. Calculate your own CV for the tests you perform and compare with the conclusions above? Any difference? Why? *PS: If you are unsure how to calculate your CV, it is your SD as a percentage of the mean? Still confused? Call us for advice.*
3. Why is it important for assays for PSA to be “equimolar”?
4. If you perform PSA on Thistle QA’s Chemistry EQA, please look at the graphs on your report. Are you given different information on the “Method Graph” compared to the “Instrument Graph”? What are the implications of relying on the “Instrument Graph” if your method has an inherent bias?

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