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The Performance of the Point of Care Test (POCT) I-CHROMA™ PSA Method Using Internal and External Quality Assessment Schemes: United Kingdom External Quality Assessment Service (UKNEQAS) And Randox International Quality Assessment Service (RIQAS)

John Bolodeoku[1*], Olu Coker[1], Suman Bains[1], Chidi Anyaeche[2], Kyum Kim[3], Frank Chinegwundoh[4]

[1]JB Consulting (MDP) Limited, Cherwell Innovation Centre, 77 Heyford Park, Upper Heyford, Oxfordshire, OX25 5HD, UK.

[2]Pathaway Services Limited, Headlands House, 1 Kings Court, Kettering, NN15 6WJ

[3]Boditech Med Inc, 43, Geodudanji 1-gil, Dongnae-myeon, Chuncheon-si, Gangwon-do 24398, Korea

[4]Department of Urology, Barts Health NHS Trust, Royal London Hospital, Whitechapel, London & School of Health Sciences, University of London, London

[*]**Corresponding author:** Dr John Bolodeoku, JB Consulting (MDP) Limited, 1 Bell Street, Maidenhead, Berkshire SL6 1BU, UK. Tel: +4407765401135 Email: john.bolodeoku@jbconsultingmdp.com

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Abstract

Objective: We set out to address and widen the knowledge about the i-CHROMA™ PSA method in its performance using the (Internal Quality Control) IQC and with a wide range of PSA methods enrolled in the United Kingdom National External Assessment Scheme (UKNEQAS) and Randox International Quality Assessment Scheme (RIQAS).

Design and Methods: Thirty-three Internal Quality Controls (IQC), and distributions of the UKNEQAS PSA scheme between February 2013 and December 2014 and samples from the RIQAS scheme were analysed for PSA using the i-CHROMA™ PSA method. The PSA results obtained from samples of the NEQAS and RIQAS were compared with the other PSA methods included in the schemes.

Results: The PSA estimations for IQC material were 2.48 - 4.13 ng/ml, with an average of 3.5 ng/ml. All estimations apart from the first one of 2.48 ng/ml, fell within the lower and higher values of 2.6 ng/ml and 4.33 ng/ml, respectively. The i-CHROMA™ PSA method's results correlated very well with the PSA estimations of the methods enrolled in the external quality schemes (RIQAS and UKNEQAS). The bias ranged between -2.99 ng/ml and +6.8 ng/ml with an average of +0.88 ng/ml with the methods in the RIQAS and +0.53 ng/ml and + 2.65 ng/ml with an average of +1.46 ng/ml with the methods in the UKNEQAS.

Conclusion: The i-CHROMA™ PSA method performed quite well with the IQC with almost all the values falling within the central, lower and higher values. The i-CHROMA™ PSA method also showed a very good correlation with the other PSA methods enrolled in the EQA schemes: RIQAS and UKNEQAS, showing a positive bias greater than 1.0 ng/ml in over 50% of the methods. Therefore, it is important to take these positive biased into consideration when using the i-CHROMA™ PSA method and adjust the reference ranges accordingly.

Keywords: I-CHROMA™; Point of Care; POCT; Prostate Specific Antigen; PSA Assay Method

Introduction

The estimation of PSA levels in the blood is the most important biomarker in the diagnosis of prostate cancer [1] and at present, there are several laboratory PSA assay systems from different manufacturers in the market. The NHS Centre for Evidence-Based Purchasing (CEP) recently evaluated three quantitative methods, the Qualigen™ FastPack®, VEDALAB PSA-CHECK-1, Mediwatch PSAwatch™ and Bioscan™ systems, and one semi-quantitative method, Sure Screen PSA test [2]. These methods did not compare favourably with assays currently used routinely in the laboratory and all of the systems demonstrated poor precision, with the exception of the FastPack® and the VEDALAB PSA-CHECK-1. Furthermore, none of these POCT PSA tests satisfied the acceptable performance criteria for use when testing asymptomatic men as part of the NHS Prostate Cancer Risk Management Programme [3]. Therefore, in view of the poor performance of the POCT PSA assays and the incomparability between laboratory and POCT PSA methods, the report concluded that it was doubtful that the introduction of a POCT PSA testing service could offer any significant improvement in the diagnosis and monitoring of prostate cancer.

Recently, more quantitative Point of Care Testing (POCT) PSA methods have been developed such as the PSAWatch [4], the FREND™ PSA Plus [5], the OPKO 4Kscore® Test [6] and the i-CHROMA™ PSA method [7]. With most of these POCT PSA assays, their comparative performance has been with a few other PSA methods: the PSAwatch method correlated well with the Roche Elecsys total PSA method (r^2=0.88), the OPKO 4Kscore® test using a finger stick of whole blood correlated extremely well with laboratory assays over the clinically relevant range of PSA, including at very low PSA concentrations [5] ; and the i-CHROMA™ PSA system showed a good correlation when compared with the Abbott AxSYM and Centaur PSA methods, r^2= 0.993 and r^2= 0.992, respectively [7]. In addition, we demonstrated that the i-CHROMA™ PSA method correlated well with the Roche COBAS® e602 [8] and Abbott Architect [9] PSA method with values of r^2=0.9841 and r^2=0.90845 respectively, with a positive bias. However, the performance of these POCT PSA methods have not been thoroughly undertaken and demonstrated using Internal Quality Assessment (IQA) and External Quality Assessment (EQA), which is a mandatory laboratory practice. We set out to address and widen the knowledge about the i-CHROMA™ PSA method in its performance using the (Internal Quality Control) IQC and with a wide range of PSA methods enrolled in the United Kingdom National External Assessment Scheme (UKNEQAS) and Randox International Quality Assessment Scheme (RIQAS).

Methods

I-CHROMA™ Materials

i-CHROMA™ uses a sandwich immuno-detection principle, such that the fluorescence-labelled detector antibody binds to the target protein in the sample. The sample is then applied onto a test strip (Figure 1) and the fluorescence labelled antigen-antibody complex is captured by a second antibody embedded in the solid phase. The signal intensity of fluorescence of the captured complex is directly proportional to the amount of PSA present and thus allows for the calculation of sample PSA concentration and the result is displayed on the reader (Figure 2) as nanograms per millilitre (ng/mL). A fluorescence-labelled control protein is included in the reaction and the intensity of the control line is measured as a quality check.

Figure 1: PSA test strip and detection buffer containing fluorescence-labelled anti-PSA monoclonal antibodies and anti-rabbit IgG.

Figure 2: i-CHROMA™ reader.

The assay was performed following the manufacturer's instructions. In brief, 75µL of serum was mixed with a pre-measured volume of detection buffer containing fluorescence-labelled anti-PSA monoclonal antibodies and anti-rabbit IgG, then 75µL of the mixture was then loaded into the sample well of the test strip and the cartridge was incubated at room temperature for 15 minutes (Figure 2). The intensity of the captured fluorescence-labelled PSA-antibody complexes was measured using the supplied meter, and the concentration of PSA in the sample was calculated.

Method

PSA Concentration estimations

For measurement of the PSA concentration, a sandwich immune chromatography technology is used. 75 µL is mixed with detection buffer containing fluorescence labelled anti-PSA mono-

clonal antibodies and anti-rabbit IgG. The mixture is loaded onto the well of the test strip and will stop the PSA complexes immobilised on the matrix by anti-PSA bound to the matrix and after 15 minutes of immune reaction, the test and control lines are scanned for fluorescence intensity. The fluorescence intensities converted into a P - PSA concentration calculated by pre-programmed calibration process. The result of the tests is displayed on the reader as micrograms per litre (ng/ml).

Test procedure

1. Collect 75 µL of serum or control using a pipette
2. Add the sample into the tube containing detection buffer
3. Shake the tube up and down 10 times or more
4. Collect 75 ul of the mixture
5. Transfer the mixture onto the sample well of the test device
6. Wait 15 minutes
7. Place the test device on the test device holder of the i-CHROMA™ device
8. Press "select"
9. Read the results on the display screen

Materials

Internal Quality Control (IQC)

Thirty-three internal quality control solutions were analysed during the assays for the EQA quantification. The internal control provided by the manufacturer was i-CHROMA™ UNIVERSAL Control I made up of 1ml of sterilized water and analysed during each UKNEQAS quantification, the PSA expected values were 2.60-4.33 ng/ml with a mean of 3.46 ng/ml (2.48 - 4.13 ng/ml).

UKNEQAS

Forty-three distributions of the UKNEQAS PSA scheme between February 2013 and December 2014 were analysed for PSA using the i-CHROMA™ PSA method as described in PSA concentration estimations. There were 9 methods registered with the scheme: Abbott Architect (n=43), Beckman Access standardised to WHO (n=43), Beckman DXI standardised to Hybritech (n=43), Ortho Vitros (n=43), Roche Modular E-170 (n=43), Roche Elecsys, (n=43), Siemens Advia Centaur (n=43), Siemens Immulite 1000 (n=43), Roche COBAS® (n=43).

RIQAS

Samples 2-12 of Cycle 41 from the RIQAS scheme were analysed for PSA using the i-CHROMA™ PSA method as described in PSA concentration estimations. There were 21 methods registered with the scheme: Abbott Architect (n=12), Beckman Access standardised to WHO (n=12), Beckman DXI standardised to Hybritech (n=12), Ortho Vitros (n=12), Roche Modular E-170 (n=12), Roche Elecsys (n=12), Siemens Advia Centaur (n=9), Siemens Immulite 1000 (n=12), Roche COBAS® (n=12), Abbott Axsym Monoclonal (n=12), Abbott Axsym polyclonal (n=11), BioMerieux Vidas (n=12), Siemens Centaur XP/XPT/Classic (n=12), Siemens/Dade Dimension (n=8), Siemens Immulite 2000/2500 (n=12), Siemens Immulite 1000 3rd generation (n=12), DiaSorin, Liaison (n=12), Monobind Inc ELISA/CLIA (n=12), Roche COBAS® 4000/e411 (n=12), Beckman DXI standardised to WHO IRP96/670 (n=12).

Results

Internal Quality Control (IQC)

The PSA estimations for IQC material for the (i-CHROMA™ UNIVERSAL Control I) were 2.48 - 4.13 ng/ml, with an average of 3.5 ng/ml. The figure below shows that all estimations apart from the first one of 2.48 ng/ml, fell within the lower and higher values of 2.6 ng/ml and 4.33 ng/ml, respectively.

Figure 3: Internal quality control values.

External Quality Control (RIQAS and UKNEQAS) - Correlations

The results of the i-CHROMA™ PSA method correlated very well with the Abbott Architect, Beckman Access standardised to WHO, Beckman DXI standardised to Hybritech, Ortho Vitros, Roche Modular E-170, Roche Elecsys, Siemens Advia Centaur, Siemens Immulite 1000, Roche Cobas, Abbott Axsym Monoclonal, Abbott Axsym polyclonal, BioMerieux Vidas, Siemens Centaur XP/XPT/Classic, Siemens/Dade Dimension, Siemens Immulite 2000/2500, Siemens Immulite 1000, Siemens Immulite 2000 /2500 3rd generation, DiaSorin, Liaison, Monobind Inc. ELISA/CLIA, Roche COBAS® 4000/e411, Beckman DXI standardised to WHO IRP96/670 (Table 1). The best correlation was with the Roche Elecsys (r^2=0.9938) in the RIQAS and Siemens Advia Centaur (r^2=0.9909) in the UKNEQAS. The method with the worst correlation was the Siemens Advia Centaur (r^2=0.1753) in the RIQAS. Upon further investigation of the poor correlation between the i-CHROMA™ and the Siemens Advia Centaur methods, we found

that about a third of the results were discordant compared to the i-CHROMA™ PSA methods and other methods in the scheme. For example, the correlation between The Roche Elecsys method, when compared with the Siemens Advia centaur result, produced a similar poor correlation (r^2=0.029), as seen with the i-CHROMA™ and Siemens Advia centaur results.

Method	RIQAS	UKNEQAS
Abbott Architect	0.9917	0.9834
Beckman Access (Who)	0.9904	0.9902
Beckman DXI	0.9927	0.991
Ortho Vitros	0.959	0.9892
Roche Modular E-170	0.9908	0.9889
Roche Elecsys	0.9938	0.9895
Siemens Advia Centaur	0.1753	0.9909
Siemens Immulite 1000	0.9841	0.9718
Roche Cobas	0.7511	0.99
Abbott Axsym	0.9887	
Abbott Axsym Polyclonal	0.9492	
Biomerieux Vidas	0.9836	
Siemens Centaur	0.9925	
Siemens/Dade Dimension	0.9891	
Siemens Immulite 2000/2500	0.9801	
Siemens Immulite 1000	0.9899	
Siemens Immulite 200 3rd Generation	0.9859	
Diasorin Liaison	0.9854	
Monobind Inc. ELISA/CLIA Method	0.9789	
Roche C 4000/E411	0.9909	
Beckman DXI Standardised To WHO IRP	0.9903	

Table 1: Correlation values for the RIQAS and UKNEQAS PSA samples.

External Quality Control (RIQAS and UKNEQAS) - Bias

The Bland-Altman plots show that over 95% of all data points lie within the two standard deviations proving that the i-CHROMA™ PSA method and all other laboratory PSA methods yield similar results. Most of the data points are evenly distributed below and above that of the mean, which demonstrates that the i-CHROMA™ PSA values are sometimes higher than those seen with other laboratory PSA methods, but also sometimes lower. The bias results of the i-CHROMA™ PSA method to the other PSA methods are shown in (Table 2). The bias ranged between -2.99 and +6.8 with an average of +0.88 with the methods in the RIQAS and +0.53 and + 2.65 with an average of +1.46 with the methods in the UKNEQAS. Twelve out of the 21 (57%) methods in the RIQAS had a positive bias. 3 methods (Abbott Architect, Siemens/Dade Dimension and Siemens Immulite 2000 3rd generation) had a positive bias of between +1 and +2 whilst 7 methods (Ortho Vitros, Siemens Immulite 1000, Abbott Axsym, Abbott Axsym polyclonal, Siemens Immulite 2000/2500, Siemens Immulite 1000 and Diasorin Liaison) had a positive bias of greater than +2. Nine of the 21 (43%) methods in the RIQAS had a negative bias. 5 methods (Beckman DXI, Roche Modular E-170, Roche Elecsys, BioMerieux Vidas and Roche C 4000/e411) had a negative bias of between -1 and -2 whilst 2 methods (Siemens Advia Centaur and Monobind Inc ELISA/CLIA method) had a negative bias of greater than -2. 9 out of the 9 (100%) methods in the UKNEQAS.

Method	RIQAS ng/ml	UKNEQAS ng/ml
Abbott Architect	1.24	1.69
Beckman Access (Who)	-0.22	2.65
Beckman DXI	-1.14	0.53
Ortho Vitros	6.8	1.56
Roche Modular E-170	-1.25	1.38
Roche Elecsys	-1.48	1.38
Siemens Advia Centaur	-2.1	1.71
Siemens Immulite 1000	2.65	0.89
Roche Cobas	-0.73	1.39
Abbott Axsym	2.23	
Abbott Axsym Polyclonal	2.89	
Biomerieux Vidas	-1.26	
Siemens Centaur	0.69	
Siemens/Dade Dimension	1.17	
Siemens Immulite 2000/2500	2.68	
Siemens Immulite 1000	2.84	
Siemens Immulite 2000 3rd Generation	1.76	
Diasorin Liaison	5.71	
Monobind Inc. ELISA/CLIA Method	-2.99	
Roche C 4000/E411	-1.6	
Beckman DXI Standardised To WHO IRP	0.59	

Table 2: Bias values for the RIQAS and UKNEQAS PSA samples.

Discussion

The PSA estimations for IQC material for the (i-CHROMA™ UNIVERSAL Control I) were 2.48 - 4.13 ng/ml, with an average of 3.5 ng/ml. All the estimations apart from the first one of

2.48 ng/ml, fell within the lower and higher values of 2.6 ng/ml and 4.33 ng/ml, respectively. The average mean value of the IQC estimations was 3.5 ng/ml, which was comparable and consistent with the expected mean of the IQC of 3.46 ng/ml. This was a very good performance of the i-CHROMA™ PSA method with the IQC provided by the manufacturer.

In this study, the performance of the i-CHROMA™ PSA method with all the PSA methods (Abbott Architect, Beckman Access standardised to WHO, Beckman DXI standardised to Hybritech, Ortho Vitros, Roche Modular E-170, Roche Elecsys, Siemens Advia Centaur, Siemens Immulite 1000, Roche Cobas, Abbott Axsym Monoclonal, Abbott Axsym polyclonal, BioMerieux Vidas, Siemens Centaur XP/XPT/Classic, Siemens/Dade Dimension, Siemens Immulite 2000/2500, Siemens Immulite 1000, Siemens Immulite 2000 /2500 3rd generation, DiaSorin, Liaison, Monobind Inc. ELISA/CLIA, Roche COBAS® 4000/e411, Beckman DXI standardised to WHO IRP96/670) enrolled in both the RIQAS and UKNEQAS was very good. The estimated correlations of the following methods in this study: Abbott Architect (0.9917 and 0.9834), Abbott AxSYM (0.9887) and Centaur (0.9909) were consistent with previous findings from independent studies where the i-CHROMA™ PSA method correlated well with the Abbott Architect (0.90845), Abbott AxSYM (0.993) and Centaur (0.992) methods [1,2,9].

In this study, using the Bland-Altman plots, we observe the level of bias ranged between -2.99 ng/ml and +6.8 ng/ml with an average of +0.88 ng/ml with the methods in the RIQAS and +0.53 ng/ml and +2.65 ng/ml with an average of +1.46 ng/ml with the methods in the UKNEQAS. Twelve out of the 21 (57%) methods in the RIQAS had a positive bias, while 9 out of the 9 (100%) methods in the UKNEQAS had a positive bias. The following methods: Ortho Vitros, Siemens Immulite 1000, Abbott Axsym, Abbott Axsym polyclonal, Siemens Immulite 2000/2500, Siemens Immulite 1000 and Diasorin Liaison had a positive bias of greater than +2. Nine of the 21 (43%) methods in the RIQAS had a negative bias with Siemens Advia Centaur and Monobind Inc ELISA/CLIA method) having a negative bias of greater than -2. This observation is comparable and consistent with another independent study that also found the i-CHROMA™ PSA method to have a positive bias [1]. When interpreting PSA values especially in screening programmes, it is important to be aware that even a difference of 0.5ng/ml could make a difference between being grouped as having a slightly abnormal PSA when the individual has a normal PSA or abnormal PSA when the individual has a slightly abnormal PSA. Therefore, it would be very important to take this positive bias into consideration when comparing the i-CHROMA™ PSA method results with the aforementioned methods.

In summary, the i-CHROMA™ PSA method performed quite well with the IQC with almost all the values falling within the central, lower and higher values. The i-CHROMA™ PSA method also showed a very good correlation with the other PSA methods enrolled in the EQA schemes: RIQAS and UKNEQAS, showing a positive bias greater than 1.0 ng/ml in over 50% of the methods. Therefore, it is important to take these positive biases into consideration when using the i-CHROMA™ PSA method and adjust the reference ranges accordingly.

Declaration of Interests

JB Consulting (MDP) is the UK distributor for Boditech Med Inc., the manufacturer of the i-CHROMA™ system.

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