Horizon Scan Report 0010 **6 January 2010**

Diagnostic Technology: Point of care urine albumin:creatinine ratio test for the early detection and management of renal disease and as a risk factor for cardiovascular disease

Clinical Question:

In patients at risk of developing impaired renal function, does a point of care urine albumin:creatinine ratio test accurately detect albuminuria compared to standard laboratory testing?

Advantages over Existing Technology:

Increased excretion of urinary albumin (albuminuria) is an indicator of the early stages of renal disease and is a risk factor for cardiovascular disease. The gold standard for albuminuria is the measurement of albumin excretion rate on a 24 hour urine specimen [1]. However collection of 24 hour urine samples is a burden for patients and known to be unreliable in about 20% of cases, due to incomplete collection. The urinary excretion of albumin is known to vary throughout the day, but this can be reduced by using the albumin to creatinine ratio (ACR) [2]. The quantitative measurement of a random urine ACR has been shown to correlate well with the 24 hour collection (Spearman's $r_s > 0.87$, $P < 0.0001$) [3], and is now used in routine clinical practice. The ACR is currently performed on a sample of urine in hospital laboratories, however points of care tests for ACR can now be performed on random urine samples collected at the time of consultation. A semi-quantitative point of care ACR test could be used to rule out significant albuminuria and reduce the number of laboratory tests. A quantitative point-of-care test could be used as a substitute to the laboratory assay.

Details of Technology:

Several point of care tests for albuminuria are available:

Quantitative devices:

1. DCA Vantage (upgraded from DCA 2000) (Siemens Healthcare Diagnostics, UK)*. Desktop device with disposable cartridges. Sample volume: 40 µl; analysis time: 7 min.
2. Afinion (Axis-Shield, UK)*. Desktop device with disposable cartridges. Sample volume: 3.5 µl (1 drop); analysis time: 5.5 min.

Semi-quantitative devices:

3. Clinitek Microalbumin (used with Clinitek 50 or Clinitek Status analyser) (Siemens Healthcare Diagnostics, UK). Desktop device used with reagent strips. Sample volume: 8-10 ml; analysis time: 1.25 min.
4. Microalbustix (Siemens Healthcare Diagnostics, UK). Reagent strip analysed by colour comparison with reference colours. Sample volume: 8-10ml; analysis time: 1.25 min.
5. Aution Eleven (Arkray Inc., Kyoto, Japan). Desktop device used with urine dipstick. Analysis time: 1 min.

**Note: DCA Vantage and Afinion also measure HbA1c on blood samples, refer to Horizon Scanning Report 0007.*

The devices are reviewed by the same buyers' guide as the HbA1c devices (Buyer's Guide: Point of care devices for the measurement of HbA1c and low concentration albumin in urine. CEP 08057. June 2009).

Patient Group and Use:

- Screening for albuminuria in patients with diabetes mellitus
- Identification of patients at high risk of cardiovascular disease
- Monitoring of patients with renal disease

Importance:

Microalbuminuria is a significant risk factor for the development of diabetic nephropathy in both non-insulin- and insulin-dependent diabetics and is also recognised as a non-specific marker of both systemic and local inflammation [4-6]. Proteinuria (a measure of total protein including albumin) is a risk factor for hypertension [7, 8], as well as pre-eclampsia

in pregnant women [9]. The use of ACR is increasingly advocated over urinary albumin excretion rate as it demonstrates less analytical method variability.

Diabetes UK reports 2.5 million people diagnosed with diabetes in the UK in 2008 (3.8% prevalence) [10]. Data reported by the British Heart Foundation from a survey conducted in 2006 estimates that around 3.4 million adults in the UK report angina and/or a heart attack and that cardiovascular disease was the second most commonly reported longstanding illness in the UK [11].
Risk assessment for cardiovascular disease, hypertension, diabetes and chronic kidney disease form part of the NHS Health Check Programme initiated in 2008, which offers preventative checks to everyone aged 40-74 (http://www.improvement.nhs.uk/nhshealthcheck/).

Previous Research:
Accuracy compared to existing technology
In patients with chronic kidney disease, a study comparing the Clinitek and DCA 2000 systems with 24-hour urinary albumin measurement showed that both systems reliably ruled out increased urinary albumin excretion at the cut-off rate of 30 mg/24h (ACR ≈ 30 mg/g), the threshold for microalbuminuria (Clinitek test: negative likelihood ratios < 0.05; DCA 2000 system: negative likelihood ratios < 0.02) [12]. A comparison of Clinitek with laboratory ACR analysis on samples from 252 patients attending a diabetic clinic and 40 patients admitted to intensive care showed that at an ACR of 3.4 mg/mmol (32 mg/g) the Clinitek analysis had a sensitivity and specificity of 75% and 94%, respectively (positive predictive value 76%; negative predictive value 94%) at a prevalence of 20% [13]. A comparison of the DCA 2000 measurements with laboratory measurements of diabetic patients reported sensitivity, specificity, negative and positive predictive values of 92%, 100%, 93% and 100%, respectively at an albumin concentration cut-off of 20 mg/L [14]. Another study comparing DCA 2000 ACR measurements with laboratory measurements reported 92% sensitivity, 100% specificity and a positive predictive value of 100% at a cut-off of 20 mg/L for albumin [15].

A study evaluating the diagnostic performance of the Clinitek Microalbumin strip test for measuring ACR in the general population (201 subjects) and diabetic patients (259 type 2 diabetic patients) showed that the strip test had an overall 90% sensitivity and 91% specificity compared to laboratory ACR assay [16]. The authors proposed that the strip test could be used for screening in the general population, ruling out the presence of increased albumin excretion, and reducing the number of samples sent to the laboratory.

A study comparing the Clinitek strip test with a standard laboratory test in a random community and a pregnant cohort, showed sensitivity and specificity ranges of 19-59% and 45-84%, respectively in the pregnant cohort; and a sensitivity and specificity of 52% and 97% in the community cohort [17]. The low sensitivity would limit the usefulness of this as a screening test. A study comparing DCA 2000 ACR measurements to laboratory measurements in pregnant populations showed that the DCA 2000 was accurate for the measurement of ACRs in an uncomplicated pregnant population, where the mean difference in ACR between the DCA 2000 and the laboratory assay was 0.08 mg/mmol (SD 0.28; 95% limits of agreement, −0.47, 0.63). However mean differences between assays in a hypertensive group had broader 95% limits of agreement due to greater variability in the samples with high albumin concentrations (>40 mg/L) [18].

Only one study was identified comparing the Arkray Aution reflectometer with a standard laboratory procedure [19]. Albumin/creatinine ratios agreed in 86% of cases with those obtained from laboratory analysis and at the 3.4g/mol limit the reflectometer had specificity of 95% and a sensitivity of 88%.

A recent report from the NHS Centre for Evidence-based Purchasing ranked the DCA Vantage to be the best quantitative device for ACR measurement and the Clinitek Status to be the most accurate compared to the other non-quantitative urine albumin analysers [20].

Impact compared to existing technology
A systematic review of studies comparing ACR on random urine samples to an overnight and 24 hour timed sample in diabetic patients concluded that the random sample ACR was effective as an initial test in screening diabetics for

microalbuminuria, saving the inconvenience of collecting a timed sample with negligible loss of case detection [1]. A recent study also showed that ACR can be used in patients with kidney disease to rule in or rule out abnormal 24 hour excretion of albumin, and that random samples can be used instead of 24 hour urine samples [3]. A multicentre, cluster randomised controlled trial in general practice in Australia comparing the clinical effectiveness of point-of-care testing (POCT) to laboratory testing studied several point-of-care tests, including ACR. It found the influence of POCT ACR on therapeutic control was found to be the same or better than pathology laboratory testing [21]. An Aboriginal community-based renal disease management study using the DCA 2000 analyser to measure ACR reported that POC ACR testing could be effectively utilised for patient management [22]. A study of POC ACR testing in Australian general practices found that it was associated with patient satisfaction and acceptability [21].

A systematic review of spot protein:creatinine ratio and albumin:creatinine ratio as diagnostic tests for significant proteinuria in hypertensive pregnant women concluded that the spot protein:creatinine ratio is a reasonable "rule-out" test for detecting proteinuria of 0.3 g/day or more in hypertensive pregnancy, but that information on use of the albumin:creatinine ratio in these women is insufficient [9].

Cost-effectiveness and Economic Impact:
Currently limited evidence exists on the cost-effectiveness of ACR testing compared to standard laboratory testing for albuminuria in patients at risk of developing impaired renal function. There is only one cost-effectiveness analysis of POCT for ACR in general practice compared to laboratory testing, based on a RCT with 4,698 patients in 53 general practices across Australia [23]. POCT led to cost savings for both direct costs and patient and family costs related to travel and time incurred seeking healthcare. The main contributors to the costs were the reduced hospital admissions and increased test costs. POCT for ACR dominated the comparator of standard laboratory testing in terms of its incremental cost-effectiveness , being both less costly and more effective (with a significant level of related uncertainty in this base case point estimate). The study is limited by the fact that it reports its measure of effectiveness in terms of 'proportion of patients within the therapeutic range', rather than life-years or QALY's hence limiting the application of the results to decision makers – the implementation of this type of testing would be dependent on the value society would place on maintaining a patient within the therapeutic range.

Two further studies have hinted at the potential for cost-effectiveness in its implementation without conducting any formal cost-effectiveness analyses [14, 19]. The authors argue that POCT for urine ACR could prove to be cost-effective due to the low cost of the test (£3.50-£4.50), the enabling of immediate action upon abnormal results, the removal of the requirement for refrigerated storage and laboratory analysis of samples [14]. One important factor that may impact on the cost-effectiveness of the POC ACR test is the sensitivity/specificity cut-off values, in clinical practice specificity may be considered important in order to avoid false-positive diagnostics and increased costs due to excessive confirmatory investigations [19]. However with a semi-quantitative strip test it could be used to rule out albuminuria, especially in a screening situation in primary care – the argument then being that you would rule out the majority of patients and therefore not requiring as many samples having to be sent to the laboratory i.e. sensitivity is important. If a fully quantitative urine ACR was use this could be used to rule in and rule out, as both sensitivity and specificity are good.

Guidance:
NICE guidelines recommend use of the ACR test to identify low levels of protein in the urine indicative of chronic kidney disease, and use of ACR for people with diabetes:

National Institute for Health and Clinical Excellence. Chronic kidney disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. Clinical Guideline 73. September 2008. www.nice.org.uk/Guidance/CG73

National Institute for Health and Clinical Excellence. Type 2 diabetes: The management of type 2 diabetes (update). Clinical Guideline 66. May 2008. www.nice.org.uk/Guidance/CG66

The NICE guideline on hypertension recommends testing protein in patients' urine as an estimate of cardiovascular risk:

National Institute for Health and Clinical Excellence. Hypertension: Management of hypertension in adults in primary care. Clinical Guideline 34. June 2006. http://www.nice.org.uk/Guidance/CG34

The NICE guideline on routine care for healthy pregnant women recommends when evaluating the risk for pre-eclampsia at first contact, a urine sample should be tested for proteinuria:
National Institute for Health and Clinical Excellence. Antenatal care: Routine care for the healthy pregnant woman. Clinical Guideline 62. March 2008.
http://www.nice.org.uk/Guidance/CG62

There is a difference in the cut-off values recommended for ACR. The American Diabetes Association (ADA) quote <3.4 mg/mmol, while the UK NICE quote <2.5 mg/mmol for males and <3.5 mg/mmol for females.

Research Questions:

1. What is the accuracy of POCT ACR compared to laboratory ACR for screening and monitoring all populations of interest in primary care (cardiovascular disease, diabetes, pre-eclampsia, renal dysfunction)?
2. Is urine ACR a better screening test for cardiovascular risk compared to serum creatinine, other random urine dipstick tests, or other measure of renal impairment?
3. What is the impact of POCT ACR compared to laboratory testing for improving clinical outcomes and patient satisfaction, and what is the optimal combination/package of POC tests it should it be included in?
4. Is the use of ACR POCT cost-effective compared to laboratory testing?
5. What is the basis for the different cut-off values provided by the American Diabetes Association and NICE?
6. What is the impact of the performance of the semi-quantitative POCT assays using the different cut-off values?

Suggested next steps:

Economic assessment of semi-quantitative and fully quantitative POCT tests in primary care.
Evaluation of accuracy of PCT ACR in various populations of interest in primary care.
Determine the optimal cut-off values for ACR using best available evidence.

Expected outcomes:

Tests performed at time of consultation reduce the workload of laboratory testing and provide more efficient management of patients in primary care.

References:

1. Ewald, B. and J. Attia, *Which test to detect microalbuminuria in diabetic patients? A systematic review.* Aust Fam Physician, 2004. **33**(7): p. 565-7, 571.
2. Newman, D.J., et al., *Urinary protein and albumin excretion corrected by creatinine and specific gravity.* Clin Chim Acta, 2000. **294**(1-2): p. 139-55.
3. Guy, M., et al., *Protein and albumin-to-creatinine ratios in random urines accurately predict 24 h protein and albumin loss in patients with kidney disease.* Ann Clin Biochem, 2009. **46**(Pt 6): p. 468-76.
4. Gosling, P., *Microalbuminuria: a marker of systemic disease.* Br J Hosp Med, 1995. **54**(6): p. 285-90.
5. Krolewski, A.S., et al., *Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus.* N Engl J Med, 1995. **332**(19): p. 1251-5.
6. Mogensen, C.E., *Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes.* N Engl J Med, 1984. **310**(6): p. 356-60.
7. Hillege, H.L., et al., *Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population.* Circulation, 2002. **106**(14): p. 1777-82.
8. Pedrinelli, R., et al., *Microalbuminuria, an integrated marker of cardiovascular risk in essential hypertension.* J Hum Hypertens, 2002. **16**(2): p. 79-89.
9. Cote, A.M., et al., *Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review.* BMJ, 2008. **336**(7651): p. 1003-6.
10. Diabetes, U.K. *http://www.diabetes.org.uk*. 2010 [cited; Available from: http://www.diabetes.org.uk.

11. *British Heart Foundation: Prevalence of coronary heart disease*. 2010 [cited; Available from: http://www.heartstats.org/datapage.asp?id=1584.
12. Guy, M., et al., *Diagnostic accuracy of the urinary albumin: creatinine ratio determined by the CLINITEK Microalbumin and DCA 2000+ for the rule-out of albuminuria in chronic kidney disease.* Clinica Chimica Acta, 2009. **399**(1-2): p. 54-8.
13. Croal, B.L., et al., *The clinical application of a urine albumin:creatinine ratio point-of-care device.* Clinica Chimica Acta, 2001. **307**(1-2): p. 15-21.
14. Collins, A.C., et al., *An aid to the early detection and management of diabetic nephropathy: assessment of a new point of care microalbuminuria system in the diabetic clinic.* Diabetic Medicine, 2001. **18**(11): p. 928-32.
15. Parsons, M.P., et al., *Validation of a point-of-care assay for the urinary albumin:creatinine ratio.* Clinical Chemistry, 1999. **45**(3): p. 414-7.
16. Graziani, M.S., et al., *Diagnostic accuracy of a reagent strip for assessing urinary albumin excretion in the general population.* Nephrol Dial Transplant, 2009. **24**(5): p. 1490-4.
17. Wilde, H.M., et al., *Evaluation of the Bayer microalbumin/creatinine urinalysis dipstick.* Clin Chim Acta, 2008. **393**(2): p. 110-3.
18. Waugh, J., et al., *Validation of the DCA 2000 microalbumin:creatinine ratio urinanalyzer for its use in pregnancy and preeclampsia.* Hypertens Pregnancy, 2003. **22**(1): p. 77-92.
19. Kouri, T., et al., *Evaluation of the ARKRAY AUTION Eleven reflectometer in detecting microalbuminuria with AUTION Screen test strips and proteinuria with AUTION Sticks 10PA strips.* Scandinavian Journal of Clinical and Laboratory Investigation, 2009. **69**(1): p. 52-64.
20. *Point of care devices for the measurement of HbA1c and low concentration albumin in urine*, in *NHS Purchasing and Supply Agency Buyers' Guide CEP08057*. June 2009.
21. Bubner, T.K., et al., *Effectiveness of point-of-care testing for therapeutic control of chronic conditions: results from the PoCT in General Practice Trial.* Medical Journal of Australia, 2009. **190**(11): p. 624-6.
22. Shephard, M.D.S., et al., *Results of an Aboriginal community-based renal disease management program incorporating point of care testing for urine albumin:creatinine ratio.* Rural & Remote Health, 2006. **6**(4): p. 591.
23. Laurence, C.O., et al., *The cost-effectiveness of point of care testing in a general practice setting: results from a randomised controlled trial.* BMC Health Serv Res. **10**: p. 165.

This report was prepared by the Primary Care Diagnostic Horizon Scanning Centre Oxford
Contact details: Dr. Annette Plüddemann; Email: horizonscanning@dphpc.ox.ac.uk