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Urine Based Laboratory Diagnosis

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ABSTRACT

Medical Laboratory diagnosis begins with qualitative urine analysis using a random voided urine for micro, sugar and albumin to diagnose symptoms associated with infection, diabetes and renal failure. Quantitative analysis using blood is the method of choice and once autoanalyser evolved, laboratories started using urine for quantitative analysis. Biochemistry plays a significant role in the quantitative measurements of metabolites and its end products excreted in urine to correlate their levels in blood. The other body fluid used for laboratory diagnostic purpose are saliva and sweat. Saliva and urine based biochemical tests are emerging as latest trends in laboratory diagnosis. The diagnostically useful tests using urine as specimen are TB-LAM to confirm TB, Fibrinopeptide A for ovarian and Gastric Cancer and Apo A1,A2, E and α1 antitrypsin for bladder cancer. This paper is an attempt to bring out the latest research findings in the use of urine for quantitative measurement of various analytes and its clinical usefulness.

Keywords: Urine, TB-LAM, Apolipoproteins, Bladder Cancer

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INTRODUCTION

The worldwide dissemination of infectious agents have created a demand for simple diagnostic tests. Urine-based testing makes use of non-invasive collection of specimens, and there is no need for expensive facilities and equipment, or for highly trained personnel. As urine antibodies retain activity under normal conditions of transport and storage, such tests appear to have widespread application. Urine-based antibody tests have also indicated a compartmentalized antibody response to HIV-1 infection. Quantitative urine analysis indicates that antibodies to the products of endogenous viral genes may be involved in the pathogenesis of chronic diseases of suspected viral etiology.[1]The conventional rapid detection method for AIDS is testing HIV-1 antibody in blood. Urine HIV-1 antibody testing is a new approach with great potential for development, because of its safe, convenient and low cost.[2] Detection of antigen in urine also could provide diagnostic information that could be useful in directing early therapeutic intervention. The detection of antigen in urine by the monoclonal antibody-based dot-ELISA has high potential for rapid, sensitive, and specific diagnosis of leptospirosis at a low cost.[3] Detection of urinary anti-Rubella Virus (RV)IgG could be a useful test for screening previous RV infection, and measurement of urinary anti-RV IgA/IgG ratio might be useful for diagnosing recent infection.[4] The assay for detection of amplified T cells vaginal is DNA in first-catch urine which showed a sensitivity of 92.7%, a specificity of 88.6%, and an adjusted specificity of 95.2% compared to culture of urethral swabs or urine sediment. For clinical research settings in which urethral swabs are not available and culture is not feasible, the urine-based PCR-ELISA may be useful for detection of trichomonias in men.[5]

TB in HIV patients could be easily tested using Alere Determine TB-LAM rapid screening test and this test is found to be better than finding out cluster of Differentiation 4 cells (CD-4) by Flow-cytometer. However, to confirm it, sputum smear microscopy should be done.[6]When patients CD-4 cell counts fall below 100 cells/μL, the TB-LAM test was found to be superior to sputum microscopy. The TB-LAM test could reduce the diagnosis time to 3 weeks. Further urinary LAM test will also predict the development of immune reconstitution diseases.[7]Effective TB control in HIV-prevalent settings is hindered by lack of accurate, rapid TB screening tests. The accuracy of a urine LAM test for TB diagnosis has been established in South Africa. The urine LAM test detected a subset of HIV-infected patients with severe TB in whom sputum smear microscopy had suboptimal sensitivity. The combination of urine LAM testing and sputum smear microscopy is attractive for use in settings with high HIV burden.[8]The most

commonly observed Western blot reactivity pattern in urine samples included bands against three groups of HIV structural proteins such as envelop, polymerase and groups specific antigens. The results indicate that urine could be used in screening for HIV antibodies in epidemiological studies of high-prevalence populations, though it is not recommended for individualized diagnostic purpose.[9]

Western Blot test for urine HIV-1 antibody shows a 98.73% sensitivity confirming that neither serum nor urine results alone are sensitive for HIV-1 antibody detection compared to combined results using both samples.[10] Urine also is a valuable source of candidate cancer biomarkers. A wide variety of pre analytical issues concerning patient selection and sample handling should be considered since it could affect the quality of the results by introducing bias and artifacts. Optimization of both the analytical strategies and the processing of bioinformatics data is also essential to minimize the false-discovery rate. Peptidomics-based studies of urine and other body fluids have yielded a number of biomolecules and peptide panels with potential for diagnosing different types of cancer, especially of the ovary, prostate, and bladder. Large-scale studies are needed to validate these molecules as cancer biomarkers.[11]

Cytologic analysis of voided urine, though attractive due to its noninvasive nature, has been found to have neither the sensitivity, cost-effectiveness, nor the ease of administration necessary to replacemore invasive diagnostics in the evaluation of microscopic hematuria.[12] Urine cytology is useful for the diagnosis of high-grade tumor recurrence. Molecular medicine holds the promise that clinical outcomes will be improved by directing therapy towards the mechanisms and targets associated with the growth of an individual patient's tumor. The challenge remains to optimize measurement of these targets, evaluate the impact of such targets for therapeutic drug development, and translate molecular markers into improved clinical management of bladder cancer patients. Physicians and researchers eventually will have a robust set of molecular markers to guide prevention, diagnosis, and treatment decisions for bladder cancer.[13]

Urine Fibrinopeptide A is a useful and highly specific marker for ovarian and bladder cancer, and this has been confirmed in a study using a large number of patients suspected of having such cancers.[14] The levels of apolipoprotein A-I (APOA1), apolipoprotein A-II, heparin cofactor 2 precursor and peroxiredoxin-2 were analyzed by western blot method. APOA1, a principal bladder cancer marker was further confirmed by ELISA technique.[15]

Another study has confirmed that α1-antitrypsin and apo-E were also found to be significantly increased in bladder cancer patients.[16] Increased levels of urinary Alpha-1-antitrypsin (A1AT) glycoprotein were indicative of the presence of bladder cancer and correlate with augmented

voided urine cytology results. A1AT detection classified bladder cancer patients with a sensitivity of 74% and specificity of 80%.This strategy will enable higher resolution profiling of the proteome in biological fluids by reducing complexity. Application of glycoprotein enrichment will provide a novel candidate for further investigation as a biomarker for noninvasive detection of bladder cancer.[17]

A multivariate urine-based assay can markedly improve the accuracy of non-invasive Bianchoninic acid (BCa) detection. Further validation studies are under way to investigate the clinical utility of this panel of biomarkers for BCa diagnosis and disease monitoring.[18]No statistically significant differences were observed between the concentrations of A Disintegrin and Metalloproteinase Domain 12 (ADAM 12) in the urine of breast cancer patients prior to treatment and that of their age-matched controls; however the concentration of ADAM 12, both alone and as a function of urine total protein, are significantly elevated following surgery. Patients who underwent a mastectomy have significantly higher urinary ADAM 12 concentrations than those who underwent a lumpectomy. These findings suggest that urinary ADAM 12 may not correlate directly with the status and stage of breast cancer as previously thought; rather these increases may be a result of tissue injury and inflammation from biopsy and surgical resection, suggesting a need for biomarkers to be evaluated carefully in the context of tissue damage.[19]A number of recent reports have demonstrated the utility of urine in the identification of novel cancer biomarkers and also the improved performance of biomarkers previously evaluated in serum. In a study, findings regarding the identification of specific urine biomarkers for each disease are highlighted along with comparative analyses of urine and serum biomarkers as diagnostic tools.[20] In 78% of the samples with mono microbial infections, the assay contained probes to detect the bacteria present in the urine specimens and 99% of these uropathogens was correctly identified and this proof-of-concept approach demonstrates that the assay can distinguish bacteriuria from no bacteriuria as well as detect the involved uropathogen within 4 hours after sampling, allowing adequate therapy decisions within the same day as well as drastically reducing consequent urine culturing.[21]The use of paired serum and urine samples provided higher sensitivities of antibody detection than either single specimen, and anti-GlcB antibodies were present in the serum and/or urine in 90% of smear-positive patients with TB. Although, with the current methods and antigens, the level of sensitivity is insufficient to design a urinary antibody diagnostic test and may provide the foundation for further studies on the development of a urine antibody-based immunoassay for TB.[22]

Micro RNA and use of non-invasive laboratory test such as Cxbladder showed improved sensitivity for the detection of urothelial carcinoma compared to the Nuclear Matrix Protein 22 assay. Stratification with Cxbladder provides a potential method to prioritize patients for the management of waiting lists.[23] The expression levels of the micro RNA were significantly lower in urine collected after surgery. MiR-183, miR-96 and miR-183 in urine are promising tumor markers for ulcerative colitis (UC). In particular, miR-96 may be a good diagnostic marker in combination with urinary cytology.[24]An improved antigen detection assay based on L. infant umproteins present in the urine of patients with Visceral Leishmanias (VL) may represent an important new strategy for the development of a specific and accurate diagnostic test that has the potential to both distinguish active VL from asymptomatic infection and serve as an important tool to monitor therapy efficacy.[25]In many clinical settings, the posterior probability of urinary tract infection given a negative dipstick is too high to exclude it. Within most clinically relevant ranges of true- and false-positive rates, a negative urine dipstick test could exclude the diagnosis of urinary tract infection in patients with high prior probabilities of contracting this infection. For lower prior probabilities, the clinical efficacy of these rapid tests would best be determined by decision analysis, for which these receiver-operating characteristic functions would serve as valuable analytical tools.[26]The biomarker demonstrating the highest diagnostic performance was a protein of 8860 Da that predicted Coronary Artery Diseases (CAD) with a sensitivity of 93% and a specificity of 65%. Moreover, combination of these biomarkers in two multivariate analyses improved the diagnostic potential of CAD. Relevance of these individual biomarkers and a decisional algorithm constituted of 3 proteins was confirmed in an independent cohort of patients with undetermined CAD status one year post-transplant.[27]

Immunological markers are superior to cytological evaluation and image analysis for detecting low grade transitional cell carcinoma but they have low specificity and sensitivity in grade 3 transitional cell carcinoma. Urine bound diagnostic tools cannot replace cystoscopy.[28]Several urinary markers have higher but still insufficient sensitivity compared with cytology. Urinary cytology or markers cannot safely replace cystoscopy in this setting. To identify an optimal marker that could delay cystoscopy in the diagnosis of bladder cancer, large prospective and standardized studies are needed.[29]Urinary amanitin analysis is a valuable diagnostic tool and may significantly contribute to the management of suspected mushroom poisoning. At present, the best diagnostic accuracy can be obtained taking advantage of both the high sensitivity and negative predictive value of the clinical assessment performed by an experienced toxicologist,

and the high specificity and positive predictive value that characterize urinary amanitin analysis.[30]With a multivariate approach and using the method of Partial Least Squares Discriminant Analysis (PLS-DA). Extremely Low Birth Weight (ELBW) metabolic profiles could be correlated with Urinary Neutrophil Gelatinase Lipocalin (uNGAL) concentration. Conversely, uNGAL could not be correlated to Appropriate for Gestational Age (AGA), suggesting the relevance of the metabolomic technique as a predictive tool for the metabolic status of ELBW. This could be confirmed by the use of uNGAL as a biomarker which may predict a subclinical pathological process in the kidney such as chronic kidney disease.[31]

Rapid diagnosis from sputum and/or urine samples was possible in >80% of patients in sub-groups with poor prognosis as defined by either CD4 counts <100 cells/μL, in advanced symptoms, CRP concentrations >200 mg/L or hemoglobin<8.0 g/dL. Urinary Kidney Injury Marker (UKIM) may be a promising biomarker for early detection of Acute Kidney Injury with considerable predictive value, especially for cardiac surgery patients, and its potential value needs to be validated in large studies and across a broader scope of clinical settings. Retrospective testing of urine samples with Determine TB-LAM assay correctly identified all those with TB who died. The sensitivities of Xpert MTB/RIF and Determine TB-LAM for HIV-associated TB were highest among HIV-infected patients with the most advanced disease and poor prognostic characteristics. These observations provide strong justification for large-scale intervention studies that assess the impact on survival of screening using these new sputum-based and urine-based diagnostic approaches.[32]The appropriate treatment for Urinary Tract Infection (UTI) has been controversial and has become more complex with the emergence of resistance to commonly used antibiotics. The anatomic evaluation and long-term management of a child after a UTI have been based on limited evidence, and newer studies question some of the tenets of prior recommendations.[33]

All urinary markers have a higher sensitivity as compared with cytology but they score lower in specificity. Many soluble and cell based markers have been developed. Only two of the soluble and cell based markers have obtained the Food and Drug Administration approval and some new urine markers used have also been highlighted.[34]Trovagene has prioritized the development of the Braf Gene (BRAF) assay to address the clinical need to monitor patient response to therapies. BRAF mutations are prevalent in many different cancers. Trovagene'scf-BRAF mutation assay is being validated across a range of solid tumors, confirming that urine-based mutation detection is applicable across many cancer types.[35]Clinical validation of Trovagene's ultra-sensitive assay procedure has been confirmed for the detection of BRAF mutation from cell-free (cf) DNA in

urine. The cf-BRAF test will be available as a laboratory developed test (LDT) this quarter, and offered through the company's Clinical Laboratory Improvement Amendment Lab (CLIA).The ability to detect and quantify oncogenic mutations in the urine of cancer patients represents a significant step towards better patient monitoring," said Mark Erlander, Ph.D., chief scientific officer for Trovagene. "The analytic performance levels required to achieve this are made possible through the large sample volumes available from urine, combined with state-of-the-art digital PCR and sequencing platforms".[36]

Bladder Cancer (BC) is a common cancer but diagnostic modalities, such as cystoscopy and urinary cytology have limitations. High-performance Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometry (HPLC-QTOFMS) was used to profile urine metabolites in patients with BC and control subjects. Multivariate statistical analysis revealed that the cancer group could be clearly distinguished from the control groups on the basis of their metabolomic profiles, even when the hematuric control group was included. Patients with muscle-invasive BC could also be distinguished from patients with non-muscle-invasive BC on the basis of their metabolomic profiles. Successive analysis identified 12 differential metabolites that contributed to the distinction between the BC and control groups, and many of them turned out to be involved in glycolysis and beta oxidation. The association of these metabolites with cancer was corroborated by microarray results showing that carnitine transferase and pyruvate dehydrogenase complex expressions are significantly altered in cancer groups. In terms of clinical applicability, the differentiation model diagnosed BC with a sensitivity and specificity of 91.3% and 92.5%, respectively, and comparable results were obtained by receiver operating characteristic analysis. Multivariate regression also suggested that the metabolomic profile correlates with cancer-specific survival time. The excellent performance and simplicity of this metabolomics-based approach suggests that it has the potential to augment or even replace the current modalities for BC diagnosis.[37]

CONCLUSION

This review article has highlighted the various research findings during the last two decades using urine for identification and quantitative measurement of various analytes. Random voided urine is an excellent specimen of choice for the detection of HIV-antibody, screening for TB, Cytology for high grade tumors, apolipoprotiens, kidney injury markers, bladder cancer markers and many other biomarkers. As specimen used is non-invasive, urine screening tests for special markers will be very useful and will serve as good as serum markers for a wide range of

diagnostic purposes. The contents of this review article will certainly help the research community to establish reliable methods for urine based screening and quantitative biomarkers for routine use in clinical laboratories.

Conflicts of Interest: The authors have no conflict of interest.

REFERENCE

1. Urnovitz HB, Murphy WH, Gottfried TD, Friedman-Kien AE. Urine-based diagnostic technologies. Trends Biotechnol. 1996 Oct;14(10):361-4.
2. Ji Q, He X, Luo Z. Urine HIV-1 antibody testing technology. Wei Sheng Yan Jiu. 2008 Jul;37(4):511-4.
3. Patcharin Saengjaruk, Wanpen Chaicumpa, George Watt, Gaysorn Bunyaraksyotin, Vanaporn Wuthiekanun, Pramuan Tapchaisri, Chuanpit Sittinont, Thanachai Panaphut, Kanchana Tomanakan, Yuwaporn Sakolvaree, Manas Chongsa-Nguan, YuvadeeMahakunkijcharoen, Thareerat Kalambaheti, PimjaiNaigowit, Michael Angelo L. Wambangco, Hisao Kurazono, and Hideo Hayashi Diagnosis of Human Leptospirosis by Monoclonal Antibody-Based Antigen Detection in Urine. J ClinMicrobiol. Feb 2002; 40(2): 480–489.
4. Shigeo Takahashi, Fusaichi Machikawa, Atsunari Noda, Tetsuya Oda, and Tetsuya Tachikawa. Detection of Immunoglobulin G and A Antibodies to Rubella Virus in Urine and Antibody Responses to Vaccine-Induced Infection. ClinDiagn Lab Immunol. Jan 1998; 5(1): 24–27.
5. Kaydos-Daniels SC, Miller WC, Hoffman I, et al. Validation of a urine-based PCR-ELISA for use in clinical research settings to detect *Trichomonasvaginalis* in men. J ClinMicrobiol 2003;41:318-23.
6. Stephen D Lawn, Andrew D Kerkhoff, Monica Vogt, and Robin Wood.Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. Lancet Infect Dis. Mar 2012; 12(3): 201–209.
7. Lawn SD, Edwards DJ, Kranzer K, Vogt M, Bekker LG, Wood R. Urine lipoarabinomannan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease. AIDS. 2009;23:1875–1880.

8. Shah M, Variava E, Holmes CB. Diagnostic accuracy of a urine lipoarabinomannan test for tuberculosis in hospitalized patients in a High HIV prevalence setting. J Acquir Immune DeficSyndr. 2009;52:145–151.
9. Martinez P, Ortiz de Lejarazu R, Eiros J M, De Benito J, Rodriguez-Torres A. Urine samples as a possible alternative to serum for human immunodeficiency virus antibody screening. Eur J ClinMicrobiol Infect Dis.1996;15:810–813.
10. Howard B. Urnovitz, Jerrilyn C. Sturge & Toby D. Gottfried. Increased sensitivity of HIV-1 antibody detection. Nature Medicine.1997; 3 : 1258.
11. Josep Miquel Bauça ,Eduardo Martínez-Morillo and Eleftherios P. Diamandis. Peptidomics of Urine and Other Biofluids for Cancer Diagnostics. Clinical Chemistry August 2014 ; 60(8): 1052-1061.
12. Trivedi D, Messing EM. Commentary: the role of cytologic analysis of voided urine in the workup of asymptomatic microhematuria. BMC Urol. 2009;9:13.
13. Kamat AM, Hegarty PK, Gee JR, Clark PE, Svatek RS, Hegarty N, et al. ICUD-EAU International consultation on bladder cancer 2012: screening, diagnosis, and molecular markers. Eur Urol. 2012 Oct; 4:S0302–S2838.
14. Theodorescu D, Wittke S, Ross MM, Walden M, Conaway M, Just I, et al. Discovery and validation of new protein biomarkers for urothelial cancer: a prospective analysis. Lancet Oncol. 2006 Mar;7(3):230–240.
15. Chen YT, Chen CL, Chen HW, Chung T, Wu CC, Chen CD. Discovery of novel bladder cancer biomarkers by comparative urine proteomics using iTRAQ technology. J Proteome Res. 2010 Nov 5;9(11):5803–5815.
16. Urquidi V, Goodison S, Ross S, Chang M, Dai Y, Rosser CJ. Diagnostic potential of urinary alpha1-antitrypsin and apolipoprotein E in the detection of bladder cancer. J Urol. 2012 Dec;188(6):2377–2383.
17. Yang N, Feng S, Shedden K, Xie X, Liu Y, Rosser CJ, et al. Urinary glycoprotein biomarker discovery for bladder cancer detection using LC/MS-MS and label-free quantification. Clin Cancer Res. 2011 May 15;17(10):3349–3359.
18. Goodison S, Chang M, Dai Y, Urquidi V, Rosser CJ. A multi-analyte assay for the non-invasive detection of bladder cancer. PLoS One. 2012;7(10):e47469.
19. Erin K Nyren-Erickson**,** Michael Bouton**,** Mihir Raval**,** Jessica Totzauer**,** SankuMallik and Neville Alberto. Urinary concentrations of ADAM 12 from breast cancer patients pre- and

post-surgery vs. cancer-free controls: a clinical study for biomarker validation. Journal of Negative Results in BioMedicine 2014, 13:5.

20. Nolen BM, Lokshin AE: The advancement of biomarker-based diagnostic tools for ovarian, breast, and pancreatic cancer through the use of urine as an analytical biofluid. Int J Biol Markers 2011, 26(3):141-152.
21. Wendy L. J. Hansen,Christina F. M. van der Donk, Cathrien A. Bruggeman, Ellen E. Stobberingh, Petra F. G. Wolffs. A Real-Time PCR-Based Semi-Quantitative Breakpoint to Aid in Molecular Identification of Urinary Tract Infections. PLOS. April 23, 2013.
22. Krishna K. Singh, Yuxin Dong, Laura Hinds, Marc A. Keen, John T. Belisle, Susan Zolla-Pazner, Jacqueline M. Achkar, Nadas Arthur J, Vijay K. Aroraand SumanLaal. Combined Use of Serum and Urinary Antibody for Diagnosis of Tuberculosis. J Infect Dis. 2003; 188 (3): 371-377.
23. O'Sullivan P, Sharples K, Dalphin M, Davidson P, Gilling P, Cambridge L, A multigene urine test for the detection and stratification of bladder cancer in patients presenting with hematuria. J Urol.2012 Sep;188(3):741–747.
24. Yamada Y, Enokida H, Kojima S, Kawakami K, Chiyomaru T, Tatarano S, et al. MiR-96 and miR-183 detection in urine serve as potential tumor markers of urothelial carcinoma: correlation with stage and grade, and comparison with urinary cytology. Cancer Sci. 2011 Mar;102(3):522–529.
25. Beijon C, Kashino SS, Silva FO, Costa DL, Fujiwara RT, et al. Identification and diagnostic utility of Leishmaniainfantum proteins found in urine samples from patients with visceral leishmaniasis. Clin Vaccine Immunol.2012; 19: 935–943.
26. Hurlbut TA, Littenberg B. The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. Am J ClinPathol. 1991 Nov;96(5):582-8.
27. Tetaz R, Trocmé C, Roustit M, Pinel N, Bayle F, Toussaint B, Zaoui P. Predictive diagnostic of chronic allograft dysfunction using urinary proteomics analysis. Ann Transplant. 2012 Jul-Sep;17(3):52-60.
28. Wiener HG, Mian C, Haitel A, Pycha A, Schatzl G, Marberger M. Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer? J Urol. 1998 Jun;159(6):1876-80.
29. Tilki D, Burger M, Dalbagni G, Grossman HB, Hakenberg OW, Palou J, Reich O, Rouprêt M, Shariat SF, ZlottaAR.Urine markers for detection and surveillance of non-muscle-invasive bladder cancer. Eur Urol. 2011 Sep;60(3):484-92.

30. Butera R, Locatelli C, Coccini T, ManzoL. Diagnostic accuracy of urinary amanitin in suspected mushroom poisoning: a pilot study. J ToxicolClinToxicol. 2004;42(6):901-12.
31. Atzori L, Mussap M, Noto A, Barberini L, Puddu M, Coni E, Murgia F, Lussu M, FanosV.Clinical metabolomics and urinary NGAL for the early prediction of chronic kidney disease in healthy adults born ELBW. J MaternFetal Neonatal Med. 2011 Oct;24Suppl 2:40-3.
32. Stephen D Lawn, Andrew D Kerkhoff, Monica Vogt, Robin Wood. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. BMC Medicine.2013; 11(1):231.
33. XinghuaShao, LeiTian, WeijiaXu, Zhen Zhang, hunlin Wang, Chaojun Qi, Zhaohui Ni, Shan Mou .Diagnostic Value of Urinary Kidney Injury Molecule 1 for Acute Kidney Injury: A Meta-Analysis.PLOS. January 03, 2014.
34. Joseph J. Zorc, Darcie A. Kiddoo and Kathy N. Shaw.Diagnosis and Management of Pediatric Urinary Tract Infections. Clin. Microbiol. Rev. April 2005vol. 18 no. 2 417-422.
35. NehaWadhwa, Suresh Kumar Jatawa, Archana Tiwari. Non-invasive urine based tests for the detection of bladder cancer. Postgrad Med J 2013;89:352-357.
36. Urine-based Cancer Detection Technology Validated. Trovagene, Inc. SAN DIEGO, July 22, 2013.
37. Xing Jin, SeokJoong Yun, Pildu Jeong, Isaac Yi Kim, Wun-Jae Kim, and Sunghyouk Park. Diagnosis of bladder cancer and prediction of survival by urinary metabolomics. Oncotarget. Mar 2014; 5(6): 1635–1645.