The current 'gold' standard of care for prostate cancer lacks specificity and additional biomarkers are needed to supplement or potentially replace serum PSA testing.

New potential multiplex biomarker test for detecting prostate cancer

Researchers at the University of Michigan, MI, USA, have developed a new, experimental biomarker assay that could potentially detect prostate cancer more accurately than any other test currently used by physicians.

In their recently published study, the researchers describe a 'simple urine test' that screens for the presence of four specific RNA molecules that accurately identified 80% of prostate cancer positive patients in the study as well as being effective in ruling out 61% of study participants who did not have cancer.

"Relative to what is out there, this is the best test so far", commented the study's lead author, Arul Chinnaiyan, director of the Michigan Center for Translational Pathology at the University of Michigan. "We want to develop a test to allow physicians to predict whether their patients have prostate cancer that is so accurate a biopsy won't be needed to rule cancer out", explained Chinnaiyan. "No test can do that now".

The current standard test for prostate cancer is the prostate-specific antigen (PSA) blood test that is used worldwide and accurately detects prostate cancer in men with the disease. However, it also identifies many men with enlarged prostate glands who do not develop cancer. Even the new *PCA3* test, which screens for a molecule specific to prostate cancer and is in use both in the USA and Europe, has been shown to be less precise than PSA.

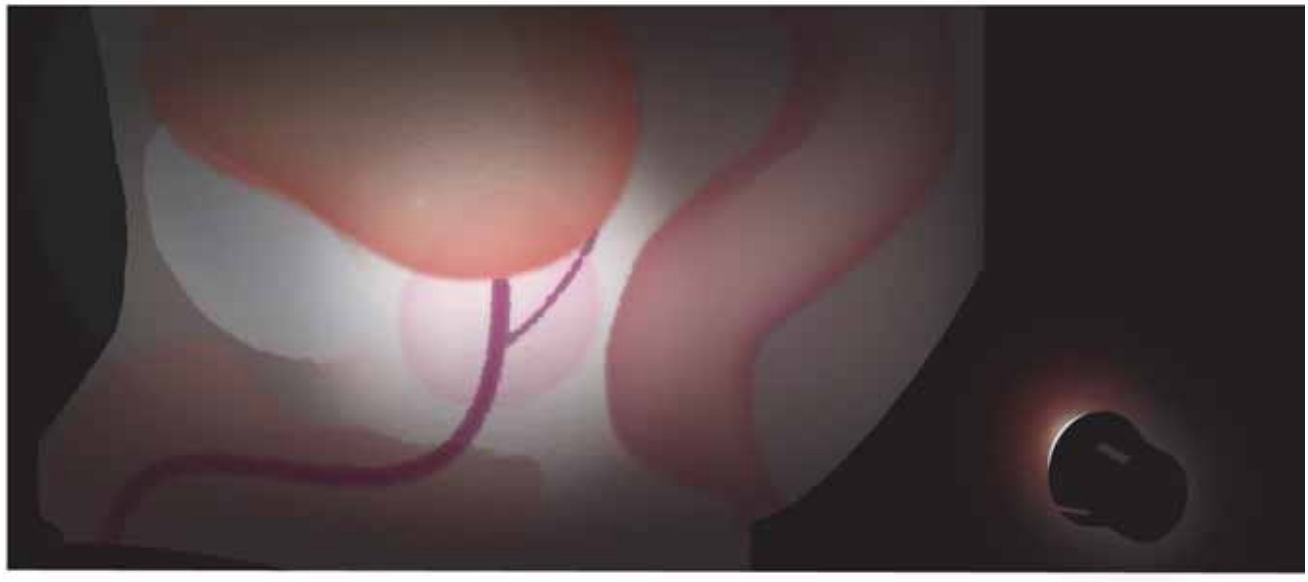
In this study, the researchers collected urine samples from 234 men with elevated PSA levels before they had prostate biopsies at the University of Michigan's urology clinic. The biopsy results confirmed a positive diagnosis of prostate cancer in 138 patients, while the remaining 96 patients did not have cancer.

The researchers used the current *PCA3* test as a starting point for designing their new multiplex assay by screening for six additional biomarkers, including *TMPRSS2:ERG* as well as some molecules that have been generally shown to be involved with prostate cancer. The expression of the seven putative prostate cancer biomarkers, including *PCA3*, was measured in the sedimented urine samples from the patient cohort using quantitative PCR. They found, by correlating the urine biomarker test results with the biopsy data, that increased *GOLPH2, SPINK1*, and *PCA3* transcript expression and *TMPRSS2:ERG* fusion status were significant predictors of prostate cancer. The sensitivity and specificity for the multiplexed model were 65.9 and 76.0%, respectively, and the positive and negative predictive values were 79.8 and 60.8%, respectively.

"PSA was not predictive at all", explained Chinnaiyan. "You might as well have flipped a coin". When tested as individual biomarkers, *GOLPH2*, *PCA3* and *SPINK1* were all shown to outperform PSA, which had identified all of the men in the study as potentially positive for prostate cancer.

The researchers concluded that taken together, these results provide the framework for the development of highly optimized, multiplex urine biomarker tests for more accurate detection of prostate cancer.

Source: Laxman B, Morris DS, Yu J *et al.*: A first-generation multiplex biomarker analysis of urine for the early detection of prostate cancer. *Cancer Res.* 68(3), 645–649 (2008).



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in brief…

Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2 (HER-2) in advanced inflammatory breast cancer with lapatinib monotherapy.

Johnston SS, Trudeau MM, Kaufman BB *et al.: J. Clin. Oncol.* 26(7), 1066–1072 (2008).

In a previous Phase I trial, lapatinib demonstrated clinical activity in four of five IBC patients. In this study, the authors conducted a Phase II trial to confirm the sensitivity of IBC to lapatinib, to determine whether the response depended on either EGF receptor (EGFR) or HER-2 and to elucidate a biomarker that is predictive of sensitivity to lapatinib. They conducted an open-label multicenter Phase II trial to assess the clinical activity and safety of lapatinib monotherapy in patients with recurrent or anthracycline-refractory IBC. The patients were assigned to either cohort A (HER-2-overexpressing [HER-2$^+$]) or B (HER-2$^-$/EGFR$^+$) and fresh pretreatment tumor biopsies were collected. The results showed that lapatinib is well tolerated with clinical activity in heavily pretreated HER-2$^+$, but not EGFR$^+$/HER-2$^-$, IBC. They also found that coexpression of pHER-2 and pHER-3 in tumors seems to predict for a favorable response to lapatinib. The authors concluded that their findings warrant further investigation of lapatinib monotherapy or combination therapy in HER-2$^+$ IBC.

Serum biomarker profiling by solid-phase extraction with particle-embedded micro tips and matrix-assisted laser desorption/ionization mass spectrometry.

Navare A, Zhou M, McDonald J, Noriega FG, Sullards MC, Fernandez FM: *Rapid Commun. Mass Spectrom.* 22(7), 997–1008 (2008).

The development of proteome fractionation approaches that can allow for the acquisition of reproducible profiles with a maximum number of spectral features and minimum interferences from biological matrices remains one of the main challenges of high-throughput serum profiling by MALDI-TOF MS. This study evaluated a new class of solid-phase extraction (SPE) pipette tips that were embedded with different chromatographic media for the fractionation of model protein digests and serum samples. The researchers showed that different types of particle-embedded SPE micro tips provided complementary information in terms of the spectral features detected for control human serum samples and β-casein digests. The results of their study demonstrated the usefulness of how the simple SPE tips combined with offline MALDI-TOF MS obtained information-rich serum profiles that resulted in a robust, versatile and reproducible open-source platform for serum biomarker discovery.

Interferon-γ: a possible predictive biomarker for the clearance of human papillomavirus in women

Recent research conducted by investigators at the Korea University, Seoul, Korea, have identified a cytokine that might predict high-risk human papillomavirus (HPV) clearance or persistence in untreated patients with mild dysplasia or less of the uterine cerix. The investigators hypothesized that since IFN-γ concentrations are detectable during HPV infections it may act as a valuable clearance biomarker.

To test their hypothesis, they performed a prospective analysis on 57 patients who had developed high-risk HPV and were histologically verified to have mild dysplasia or less as well. The researchers assessed cell-mediated immunity among the patient cohort of women infected with HPV who had not received any treatment. All the patients underwent a follow-up evaluation after 1 year. To quantify the levels of different cytokines, real-time PCR was used to detect IFN-γ, IL-10, IL-6 and TNF-α transcripts.

The results of their analysis demonstrated that among the 57 patients who were untreated with mild dysplasia or less, 46 (80.7%) had no detectable HPV after 1 year of follow-up.

This meant that the women were significantly more likely to be HPV infection-free at follow-up if they had tested positive for the presence of IFN-γ, at 93.3 versus 66.7% for women who tested negative for IFN-γ. They also studied the influence of other biological and lifestyle factors such as age, lesion grade in the colposcopic biopsy, IL-10, IL-6, TNF-α, day of menstrual cycle, smoking and use of oral contraceptives. They found that none of these factors were significantly associated with high-risk HPV negative or positive results after 1 year of follow-up in patients with untreated mild dysplasia or less.

> '…intralesional IFN-γ may be a prognostic marker for clearance of high-risk HPV.'

The investigators of the study concluded that their results suggested that intralesional IFN-γ may be a prognostic marker for clearance of high-risk HPV.

Source: Song SH, Lee JK, Lee NW, Saw HS, Kang JS, Lee KW: Interferon-γ (IFN-γ): a possible prognostic marker for clearance of high-risk human papillomavirus (HPV). *Gynecol. Oncol.* 108(3), 543–548 (2008).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and launches in the application of biomarkers in medicine. The editorial team welcomes suggestions for timely, relevant items. If you have newsworthy information, please contact:

Laura Dormer, Head of Commissioning
Future Medicine Ltd, Unitec House,
2 Albert Place, London N3 1QB, UK
Tel.: +44 (0)20 8371 6090; Fax: +44 (0)20 8343 2313
E-mail: l.dormer@futuremedicine.com

Functional genomics may have identified blood biomarkers for mood disorders

A breakthrough in the way that mood disorders and biopolar illness are diagnosed and treated has been made by researchers at the Indiana University (IU) School of Medicine, IN, USA. In their report, they propose and provide evidence of proof of principle for an approach to help identify blood biomarkers for mood state. There are currently no objective clinical laboratory blood tests for mood disorders. Thus, the reliance on patient self-report of symptom severity and on the clinicians' impression is restrictive towards new drug development and effective treatment.

"Although psychiatrists have been aware that bipolar illness and other psychiatric conditions produced molecular changes in the brain, there was no way to measure those changes while the patient was living," commented Alexander B Niculescu 3rd, lead author and Assistant Professor of Psychiatry, Medical Neurobiology and Neuroscience at the IU School of Medicine Institute of Psychiatric Research. "Blood now can be used as a surrogate tissue to diagnose and assess the severity of the illness".

> "This discovery is a major step towards bringing psychiatry on par with other medical specialties that have diagnostic tools to measure disease states and the effectiveness of treatments..."

In the study, the researchers measured the differences in the whole-genome gene expression from blood samples taken from subjects with bipolar disorder who had low mood versus those that had high mood at the time of the blood draw, as well as separately monitoring the changes in gene expression in the brain and blood of a mouse pharmacogenomic model. They integrated the human blood gene-expression data with animal model gene-expression data, human genetic linkage/association data and human postmortem brain data. From this, a list of candidate blood biomarker genes included five genes involved in myelination (*Mbp, Edg2, Mag, Pmp22* and *Ugt8*), and six genes involved in growth factor signaling (*Fgfr1, Fzd3, Erbb3, Igfbp4, Igfbp6* and *Ptprm*).

"This discovery is a major step towards bringing psychiatry on par with other medical specialties that have diagnostic tools to measure disease states and the effectiveness of treatments," explained Niculescu. Their studies suggest that blood biomarkers may offer an informative window into brain functioning and disease state.

Source: Le-Niculescu H, Kurian SM, Yehyawi N *et al.*: Identifying blood biomarkers for mood disorders using convergent functional genomics. *Mol. Psychiatry* (2008) (Epub ahead of print).

Status of *KRAS* is required for Vectibix™ efficacy in cancer

Recent data generated from the biomarker analysis of a Phase III, randomized, controlled clinical trial indicated that in metastatic colorectal cancer (mCRC) patients who had failed all other chemotherapeutic regimens, the efficacy of Vectibix™ (panitumumab) monotherapy was related to the status of *KRAS* in patients. The trial (known as the '408' study) was conducted by Amgen and collaborators in Belgium and Italy.

KRAS has been extensively studied over the past 20 years. It has been found to play an important role in cell growth regulation and oncogenesis. The KRAS protein is always turned 'on' regardless of whether EGF receptor (EGFR) has been activated or therapeutically inhibited in patients with tumors that have a mutated or activated KRAS. Thus, signaling continues despite anti-EGFR therapy. Mutated *KRAS* is detected in approximately 40% of CRC tumors.

In this trial, it was found that, specifically in patients who were positive for the nonmutated (wild-type) *KRAS* tumors, Vectibix significantly increased progression-free survival. It was also shown to have an impact on quality of life and disease-related symptoms, compared with the best supportive care alone.

> "We are hopeful that the use of biomarkers like *KRAS* will enable improved treatment outcomes for colorectal cancer patients."

A total of 463 randomized patients were included in the trial. KRAS data were available for 427 patients and 57% of patients had tumors with normal, nonmutated KRAS. In the group of patients with nonmutated KRAS who received Vectibix, 34% reported stable disease and 17% were found to respond to treatment. However, there were no responders found in the group of patients treated with Vectibix who had mutated KRAS, and stable disease was only reported in 12% of these patients.

"These data have substantially advanced our thinking about individualized treatment of colorectal cancers," commented Roger M Perlmutter, executive vice president of Research and Development at Amgen. "We are hopeful that the use of biomarkers like *KRAS* will enable improved treatment outcomes for colorectal cancer patients".

The researchers also suggest that *KRAS* and other biomarker analyses must continue to be integrated into the ongoing clinical program studying Vectibix in the earlier lines of mCRC therapy in combination with chemotherapy, as well as in other tumor types. The conclusion of the trial was that *KRAS* status should be considered when selecting patients with mCRC as candidates for Vectibix monotherapy.

Source: Amado RG, Wolf M, Peeters M *et al.*: Wild-type *KRAS* is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J. Clin Oncol.* (2008) (Epub ahead of print).