Urine Markers

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Urology Times, Oct. '05: MUST READ article:

Markers in bladder cancer: Their role continues to evolve

Interview with Michael O'Donnell

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On this page:

Cytology, BTA stat test/BTA TRAK assays, NMP22-BladderChek, FISH, Vysis®Urovysion Immunocyt™, FDP, Telomerase, Hyaluronic Acid, BLCA-4

separate pages for; VYSIS®; NMP22® BladderChek® ; DiagnoCure’s ImmunoCyt™

Cystoscopy remains the "gold standard" for identifying bladder cancer, but has it's drawbacks: it is expensive, invasive and many people find it uncomfortable. A urine test is far easier to get patients to readily comply to.

Urine cytology, the most commonly used test for bladder cancer, microscopically identifies the presence of abnormal, malignant cells, which are shed into the urine in patients with bladder cancer. The method has high specificity (ie, few false-positives). However, it has low sensitivity (ie, many false-negatives, especially in superficial and low-grade tumors), results are not immediately available and are interpreter-dependent [subjective]. While quite accurate in detecting high-grade bladder cancer and carcinoma in situ, its ability to detect low-grade cancer is limited.

Therefore, urine-based marker tests are being developed to fill some of the remaining needs. These newer tests are more accurate in detecting low-grade bladder cancer, so they are especially useful in monitoring for recurrence, may significantly improve and simplify workup, diagnosis, and follow-up, and hopefully allow for detection of disease at an earlier stage, thus improving the chances of curative therapy.

The urine marker assays discussed here have shown enhanced sensitivity in detecting bladder cancers. However, each still requires further validation and testing in clinical trials to determine how best to apply these tools for in individual patients. In recent years several of the newer tests are being used by urologists as another weapon in the arsenal. Although immunological markers are superior to standard urine cytology, at the present time urine bound tests are not specific enough to completely replace cystoscopy as a definite diagnostic tool.

In order to understand what these tests are about it's helpful to have an understanding of Sensitivity vs. Specificity:

A diagnostic test is one that predicts the presence of a disease. An ideal diagnostic test would always give the right answer, with a positive result in everyone with the disease and a negative result in everyone else - and would be quick, safe, simple, painless, reliable, and inexpensive, as well. Since no current diagnostic test is ideal, we need to evaluate each of them for their clinical usefulness. In practice, for any diagnostic test there is a trade-off between sensitivity and specificity. In cancer diagnosis, the need for this trade-off is rooted in the fact that cancer arises from our own tissues. It is not completely "foreign" to our systems like a virus or bacterium is.

It's important to remember that there are four possible results when a diagnostic test is run:

True positive - when the test is positive and the patient does have the disease

False positive - when the test is positive but the patient does not have the disease

True negative - when the test is negative and the patient does not have the disease

False negative - when the test is negative but the patient does have the disease

Here's another way of looking at this (often referred to as a "truth table"):

Test Result	The disease being tested for is present	The disease being tested for is not prestent
"Postitive"	True positive	

False positive

"Negative"

False negative

True negative

Calculating the disease sensitivity and specificity are ways of evaluating diagnostic tests, using the four possible results.

Sensitivity - is the ability of a test to correctly identify a positive specimen, and it tells you how good the test is at identifying the disease. Statistically, it's the proportion of patients with the disease who have a positive result, that is, the number of "true positives" out of all the situations where the disease is present.

For example, 100 patients with cancer are tested using a test that detects tumors. There are 80 positive results and 20 negative results. This means the test has a sensitivity of 80% - it correctly identified 80 of the 100 cancers - and it gave 20 false negative results.

Specificity - is the ability of a test to correctly identify a negative specimen, and it tells you how good the test is at identifying when the disease is absent. The statistical way of looking at this is the proportion of patients without the disease who have a negative test, that is, the number of "true negatives" out of all the situations where the disease is not present.

For example, 100 normal, healthy individuals are tested using a test that detects tumors. There are 80 positives and 20 negatives. This means the test has a specificity of 20% - it correctly identified 20 of the 100 negative specimens - and it gave 80 false positive results.

Both sensitivity and specificity are very important, and they can both be influenced by various factors, such as the

characteristics of the population tested or the value used as a cut-off for the test (above which the test is positive and below which it is negative). A test with low sensitivity and many false negative results will fail to detect the tumor in a large portion of the patients being tested, while a test with low specificity with many false positive results may lead to unnecessary invasive or expensive procedures and cause undue alarm.

Many, but not all, patients report they would rather be "scared for nothing" than miss a tumor, and are therefore most interested in tests with high sensitivity.1

BTA stat Test and the BTA TRAK Assay

The original Bard BTA Test, which continues to be referred to in the literature from time to time, was a latex agglutination test detecting bladder tumor-associated analytes and is no longer distributed in the US. It is important to note that it has been replaced by two newer tests based on significantly improved technology with much better sensitivity and specificity.

Both of the new tests detect a human complement factor H-related protein (hCFHrp) which has been shown to be produced by several human bladder cancer cell lines, and by human bladder cancers, but not by other epithelial cell lines (Kinders, Clin Cancer Res 4:2511, 1998). It is thought that factor H acts to protect the tumor cell from the body's natural immune system (Corey, J Biol Chem 275:12917, 2000). Both the BTA stat and BTA TRAK tests can provide valuable but slightly different information for the bladder cancer patient and her doctor.

The BTA stat Test is a qualitative (positive or negative) test provided in a disposable format similar to a home pregnancy test. It uses five drops of urine and can be read in five minutes by the appearance of a colored line in the patient window, while a colored line appears in a "check" window to indicate the test is working properly. This test is cleared in the US for use by clinical laboratories, the physician or his staff right in the office, or even by the bladder cancer patient at home (with a physician's prescription). To date, it is the only tumor marker in the United States with this status. Besides being highly sensitive, fast, and easy to use, with a unique availability to be run by the physician and/or the patient, this test is significantly less costly than other diagnostic tests or cytology.

The BTA TRAK Assay is a quantitative immunoassay test and provides a numerical result of the hCFHrp level. Like the NMP22 test, urine must be sent to a reference laboratory where the test is performed by professional technologists. In addition to knowledge of the specific level, an advantage of the BTA TRAK test is the ability to monitor the rise or fall of hCFHrp.

Numerous clinical studies have been conducted with the new BTA tests. Most reports state findings in terms of "sensitivity" and "specificity." Briefly, sensitivity is the ability of the test to correctly identify a positive specimen, and specificity is the ability of the test to correctly identify a negative specimen.

BTA stat Test Studies

In the most recent study (June 2000) and the largest of its kind to date, Raitanen reported the overall sensitivity of BTA stat as 82%, and cytology as 30% (Raitanen, J Urol 163:1689, 2000). In another study, Pode reported 100% BTA stat

sensitivity in tumors of stage T2 or higher, grade III, and all tumors greater than 2cm (Pode, J Urol 161:443, 1999). Specificity of the BTA stat Test has been reported as 72-95% (Sarosdy, Urology 50:349, 1997) and 98% in healthy individuals (Raitanen, Scand J Urol Nephrol 33:234, 1999).

BTA TRAK Assay Studies

In one study, the overall sensitivity of the BTA TRAK Assay was reported as 72% with a specificity of 75-97% (Ellis, Urology 50:882, 1997). Heicappell again reported an overall sensitivity of 72%, with 97% specificity in healthy individuals. He also reported that BTA TRAK levels reflect tumor stage and grade, with levels in superficial bladder cancer at high risk of tumor progression significantly higher compared to low and intermediate grade superficial cancers (Heicappell, Eur Urol 35:81, 1999).

Comparison Studies

In a study conducted at the Mayo Clinic, several urine tumor markers were evaluated, including urine cytology, BTA stat, NMP22, fibrin/fibrinogen degradation products (FDP), telomerase, chemiluminescent hemoglobin and hemoglobin dipstick. The telomerase test presented the highest combination of sensitivity and specificity for screening. However, other researchers have had difficulty reproducing the telomerase results of this study, possibly due to the technical difficulties of running the test. It's also important to note that telomerase is a "Research Use Only" test, and has not received FDA clearance for marketing in the US. In the same study, the BTA stat Test was shown to have the best overall sensitivity (74%), and the best sensitivity for T1-T3 and primary tumor detection (Ramakumar, J Urol 161:388, 1999).

Another comparison study (Giannopoulos, Urology 55:871, 2000) published this year showed that the BTA stat Test was more sensitive than cytology in all stages and grades except G3, while NMP22 was more sensitive than cytology only in stage Ta and Grade 1 and 2. The BTA stat Test also had higher sensitivity than NMP22 in all stages and grades.

It is also important to note that in both of the BTA tests, and with NMP22 as well, results can be compromised if there is a urinary tract infection, inflammation, or kidney stones present, if there has been recent trauma to the bladder, or if the specimen is collected by catheter. The paper by Sharma, for example, shows the dramatic increase in specificity when these conditions are excluded from testing (Sharma, J Urol 162:53, 1999). As with any test, for the results to be most useful they should be interpreted in light of all the medical and clinical information available.

Clinical trials in both the US and Europe are continuing to broaden our understanding of the optimal use of the BTA products, and we await the publications of these results.1

The preceding information was provided by the Manager of Clinical Affairs at http://www.alidexinc.com [formerly known as Bion Diagnostic Sciences (BDS)] in Redmond Washington, USA, the manufacturer of the BTA stat Test and the BTA TRAK Assay: Alidexinc is a subsidiary of Polymedco, Inc.

More information about the BTA stat test can be found here: http://www.btastat.com

The BTA stat® Test is available for purchase with a prescription http://www.btastat.com/how_to_get_test.html

NMP22 'BladderChek'

During the American Urological Ass.’s Western Section 2003 annual meeting, a study headed by Kevin M. Tomera, MD and Alaska Urological Associates concluded that Matritech’s Bladderchek is significantly more sensitive than cytology at detecting the disease in high-risk patients, as well as effective at determining risk of recurrence.

The study compared cystoscopy, cytology, and BladderChek; the NMP22/Bladderchek test had a considerably higher detection rate than cytology (67% vs. 20%). Cystoscopy detected 86% of bladder cancers.

More cost effective than cytology, the Bladderchek test could also be a good adjunct to cystoscopy. The test costs in the range of $20 to $25, which Medicare reimburses for both bladder cancer monitoring and detection. It is a waived test under the Clinical Laboratory Improvement Amendments (CLIA).

While the test showed a high negative predictive value, it produced a false-positive result in 19 of the 194 patients without bladder cancer. Dr. Tomera advised that such patients need to be watched closely. Earlier data by Mark Soloway, MD, has shown that bladder cancer will be found in 70% of these individuals during the following 3 to 6 months (J Urol 1996; 156:363-7).

Please see the complete power point presentation discussing these findings presented at the 2003 ASCO meeting; Performance of a New Office Test NMP-22 BladderChek for Urothelial Cancers in a Community Practice AUA Show Powerpoint Presentation. Kevin M. Tomera; William R Clark; Lawrence R. Strawbridge; Raymond S. Lance. Anchorage, Ak

NMP22's core technology is based on the level of nuclear matrix proteins (NMPs) that are detected in body fluids. These levels are correlated to the presence of early-stage cancerous abnormalities, which have been validated in multiple clinical studies. The technology was discovered at the Massachusetts Institute of Technology and licensed to Matritech.

FISH - also on WebCafe: an expert P.F. Bassi, MD, reviews FISH

Florescence in situ hybridization (FISH) is an assay which uses a mixture of fluorescent labeled probes to assess urinary cells for chromosomal abnormalities associated with malignancy.

The FISH method detected cancerous cells in the urine of 81 percent of the patients with bladder cancer,” said Kevin Halling, M.D., a Mayo Clinic pathologist and lead researcher on the study. “By comparison, urine cytology detected cancerous cells in only 57 percent of the patients with bladder cancer. “Most importantly, the FISH test picked up more than 95 percent of the high grade cancers, which are the most dangerous and important group of bladder cancers because they have a high probability of progressing to potentially incurable muscle-invasive bladder cancer,” says Dr. Halling. “With only one exception, the only cancers the test missed were low-grade tumors, which are less dangerous and have only a 3 to 5 percent chance of progressing to a higher stage tumor over five years.” The FISH test also detected recurrence of the cancer three to six months earlier than by the cytology, says Dr. Halling. This earlier detection capability should allow treatment to be initiated earlier and possibly give the patient a greater chance for survival, he said.

From the website of MD. Anderson Cancer Center

http://mdaisd1.mdacc.tmc.edu/depts/pathology/fish/urovysion.html

Fluorescence-in-situ-hybridization (FISH) for multiple centromeric probes has previously been shown to be a very sensitive test for diagnosing UC, however the test was limited by the requirement of multiple cytospins to evaluate 4 or more probe sets. Recently a new commercial test (VYSIS) for evaluating urinary cytology became available in which 4 probes are simultaneously evaluated on a per cell basis on a single cytospin. We performed a pilot study to test the efficacy of the new FISH test compared to standard urine cytology. This study showed that the multi-color FISH probe test was more sensitive than cytology, easily performed and yielded a high number of cells with numerical chromosomal aberrations.

UroVysion FISH Test -New Multiprobe FISH Test on Urologic Specimens is Highly Sensitive in the Diagnosis of Urothelial Carcinoma Abha Khanna, Aazam Alizadeh, Jun Gu, Feng Jiang, Hua-Zhong Zhang, Arnout Ruifrok, Nancy Caraway, Dennis Johnston, Ruth L Katz. University of Texas, M.D.Anderson Cancer Center, Houston, TX; University of Texas, M. D.Anderson Cancer Center, Houston, TX.

VYSIS® - UroVysion FISH Test For info about clinical studies, sensitivity and specificity of the Vysis kit, please click here

Vysis® UroVysion Bladder Cancer Recurrence Kit (UroVysion Kit), takes a Cellular Genomics approach to disease management by detecting genomic changes (chromosome abnormalities) in bladder cells that are indicative of cancer. As few as four abnormal cells identified with the UroVysion Kit indicate the presence of cancer. For info about clinical studies, sensitivity and specificity of the Vysis kit, please click here

DiagnoCure’s ImmunoCyt™ Bladder Cancer Monitoring Test

DiagnoCure’s ImmunoCyt™, the most sensitive 510(k) cleared by FDA, noninvasive, assay for monitoring recurrence of bladder cancer; for take home messages on the major publications about the test, click here

ImmunoCyt™ is a 510(k) cleared, by the FDA, qualitative direct immuno-cytofluorescence assay, intended for use in conjunction with cytology to increase the overall sensitivity for the detection of tumor cells exfoliated in the urine of patients previously diagnosed with bladder cancer.

ImmunoCyt™ contains a cocktail of three monoclonal antibodies labeled with fluorescent markers. The cocktail of antibodies have been shown to react with a mucin glycoprotein as well as to be specific to a glycoform of CEA. The test detects cellular markers specific for bladder cancer in exfoliated cells isolated from urine sample. This non-invasive test, when coupled with urine cytology proves to be more sensitive than urine cytology alone or other currently available tumor markers.

The current standard method for non-invasive detection of bladder cancer is urinary cytology, which consists of

identifying the presence of cancer cells in urine. Urinary cytology has high specificity but poor sensitivity, typically no greater than 30% to 45%. This sensitivity varies according to the stage and grade of the tumor.

ImmunoCytT™is carried out in parallel with cytology to improve cytology's sensitivity at detecting tumor cells in the urine of patients, especially those with low stage, low grade tumors. The concomitant use of classical cytology and ImmunoCytTM can substantially improve the detection of bladder cancer. As shown in the ImmunoCytTM performance analysis (cumulative data from eleven publications and presentations from 3,203 cases), a sensitivity of 88% has been obtained when both cytology and ImmunoCyt™ were used together
http://www.diagnocure.com/anglais/section4/sec4.htm - DiagnoCure Inc. website, manufacturers of ImmunoCyt™.

A multicenter study in the United States, published in the Journal of Urology, concluded: ImmunoCyt™ enhances the sensitivity of cytology, which is a specific but not a sensitive method for detecting bladder cancer. The ability of this immunocytochemical test to detect low grade, superficial, small tumors makes it the most suitable available marker to test for monitoring strategies in patients with low risk bladder cancer. Performance of urine test in patients monitored for recurrence of bladder cancer: a multicenter study in the United States.

Messing EM, Teot L, Korman H, Underhill E, Barker E, Stork B, Qian J, Bostwick DG, From the Departments of Urology (EMM) and Pathology (LT), University of Rochester Medical Center, Rochester, New York, Departments of Urology (HK) and Pathology (JE), William Beaumont Hospital, Detroit, Michigan, Medical Lab Associates (EB, BS), Seattle, Washington, and Bostwick Laboratories, (JQ, DGB), Glen Allen, Virginia. J Urol. 2005 Oct;174(4 Pt 1):1238-41.

FDP-Fibrin/Fibrinogen Degradation Products

FDP has shown high sensitivity even for low-grade and non-invasive tumors, and its diagnostic ability could be superior to NMP22 according to a recent study (Nippon Hinyokika Gakkai Zasshi 2001 Jan;92(1):1-5] Oeda T, Manabe D Department of Urology, Onomichi Municipal Hospital.PMID: 11235137)

The FDP test detects the presence of fibrin and fibrinogen degradation products in urine. It is a simple test that can be performed in the office, and results are available in about 10 minutes. Fibrin and fibrinogen degradation products are protein fragments generated by the action of the fibrinolytic system on fibrin and fibrinogen. Plasma proteins leak from blood vessels in tumors into the surrounding tissue. Clotting factors rapidly convert the fibrinogen in the plasma into an extravascular fibrin clot, which is degraded by plasmin and activated by urokinase. The FDP test can detect these degradation products and is positive in two thirds of patients with bladder cancer. The FDP assay is more accurate than urine cytology and has high specificity (negative in 96% of healthy subjects). The FDP test was found to be superior to the BTA test in at least one study*.

Telomerase is another substance currently being assessed for its potential usefulness in diagnosing transitional cell cancer (TCC) and in monitoring for recurrence. It will soon be made available to doctors and patients. Telomerase is a ribonucleoprotein enzyme responsible for production of telomeres, which are DNA sequences that occupy the ends of chromosomes and protect their integrity during DNA replication and may be involved in the immortalization of a cancer cell 3

Comparison of screening methods in the detection of bladder cancer

In a study done in ’99, researchers prospectively evaluated and compared the sensitivity and specificity of urine

cytology, BTA stat, NMP22, fibrin/fibrinogen degradation products (FDP), telomerase, chemiluminescent hemoglobin and hemoglobin dipstick to detect bladder cancer ; within each tumor grade and stage telomerase had the strongest association with bladder cancer among all tests (69% overall concordance). Telomerase was positive in 91% of the patients (10 of 11) with carcinoma in situ. The combination of sensitivity and specificity (70 and 99%, respectively) was the highest for bladder cancer screening in these patients. Telomerase outperformed cytology, BTA stat, NMP22, FDP, chemiluminescent hemoglobin and hemoglobin dipstick in the prediction of bladder cancer. 4

Telomerase - October, 2005 According to a study published in JAMA (2005; 294:2052-6) Italian researchers reported the assay showed 90% sensitivity and 88% specificity. Specificity increased to 94% for those aged 75 years or younger. The same predictive capacity of activity levels was observed for patients with low-grade tumors or with negative cytology results. In particular, sensitivity was 93%, 87%, and 89% for tumor grades 1, 2, and 3, respectively.

Although the test is proven to identify low-grade tumors, it is not recommended for use in routine screening programs because of the low incidence of bladder cancer and should be aimed at high-risk subgroups, noted the authors, from Morgagni-Pierantoni Hospital, Forli. PubMed abstract

Relevance of Urine Telomerase in the Diagnosis of Bladder CancerMaria Aurora Sanchini, MSc; Roberta Gunelli, MD; Oriana Nanni, MSc; Sara Bravaccini, BSc; Carla Fabbri, MSc; Alice Sermasi, BSc; Eduard Bercovich, MD; Alberto Ravaioli, MD; Dino Amadori, MD; Daniele Calistri, PhD JAMA. 2005;294:2052-2056.

An online article in the Urology Times (www.urologytimes.com) reported over the JAMA article;

Theoretically, urine telomerase appears more promising than do noninvasive tests for bladder cancer to date, according to Michael A. O'Donnell, MD, professor of urology and director of urologic oncology, University of Iowa, Carver College of Medicine, Iowa City.

"It looks like we are looking at something with about 90% sensitivity and 90% specificity. That is about 10 points higher than any other test that is out there," said Dr. O'Donnell, who was not involved with this study.

The main advantages of the test, according to Dr. Calistri, are that it is noninvasive, can be performed under local anesthetic, and is significantly less expensive, at $20, than the approximately $100 for cystoscopy or $50 for urinary cytology.

"... [I]t could be a good marker for high-risk screening groups," Dr. Calistri told Urology Times. "Furthermore, it shows a high sensitivity for the diagnosis of low-grade tumors that can escape detection during cytological examination. Results are usually available in 2 to 3 days." article link

Hyaluronidase and hyaluronic acid

Hyaluronan seems to be directly involved in tumor growth and progression, and recent reports have shown this marker has high accuracy in detecting bladder cancer and evaluating its grade, according to three articles published by pioneer in the field Dr. VB Lokeswahr in the Journal of Urology (2000-2001). 9

Hyaluronidase and hyaluronic acid are associated with induction of angiogenesis. Dr. Lokeswahr and colleagues at the U.of Miami S.O.M. have shown that Hyaluronic acid (HA), the urinary HAase levels of intermediate (G2) to high- grade (G3) bladder cancer patients are five- to seven-fold elevated as compared to those of normal individuals and patients with other genitourinary conditions or low-grade (G1) bladder cancer. The increase in urinary HAase levels is due to the secretion of a tumor-derived HAase which is elevated eight-fold in G2/G3 tumor tissues. The HAase in bladder tumor tissues is secreted by tumor epithelial cells and is associated with the invasive/metastatic potential of the tumor cells.5

You can read Dr. Lokeswahr's page at the U of Miami website:
http://urology.med.miami.edu/urologic_research_research_projects.asp

2006: update on HA

An article published in a 2006 issue of European Urology, researchers from Brazil investigated the usefulness of HA for the detection of residual tumors that may remain after incomplete TUR. 10 The authors concluded, "HA- in addition to being one of the best markers for the initial evaluation of bladder carcinoma- can be used to determine the presence of a residual tumor. This is associated with poor prognosis....Furthermore, hematuria does not seem to influence the content of urinary HA....Other tumor markers such as oncotic cytology, FISH (Fluorescence in Situ Hybridization) and NMP22 might be affected by instrumentation and therefore could not be evaluated this early."

Low values of urinary HA after TUR indicate a favorable prognosis and could probably avoid the second procedure.

The reserachers suggest that after more experience and follow-up using this assay in the clinical setting, it might be possible to predict not only the cases with residual tumor, but also those who require early radical surgery or those in whom this can be delayed.

In addition to being a good marker in the initial evaluation of bladder carcinoma thanks to its excellent sensitivity (83.1%) and specificity (90.1%) [according to the Lokeswahr studies referenced below], HA potential uses include follow-up, prognostic evaluation, preventing unnecessary interventions and/or to indicate cases where early radical intervention is necessary."10

BLCA-4

Robert H. Getzenberg, PhD, Director of Research at the Prostate and Urologic Cancer Center of the University of Pittsburgh Cancer Institute, and colleagues have identified several components of the nuclear matrix, one of which is called BLCA-4, that differentiate human bladder tumor cells from normal bladder cells. Normal samples from unaffected individuals did not react with the antibody, and importantly, BLCA-4 appears to be present throughout the bladder (i.e., in both normal and tumor areas) in bladder cancer patients. This "field effect" permitted development of a urine immunoassay for BLCA-4 that detects the presence of tumor anywhere in the bladder, regardless of stage or grade. The BLCA-4-urine immunoassay has a specificity of 100% and a sensitivity of 95%. According to Dr. Getzenberg, the assay is currently being tested by the Pittsburgh researchers in a clinical trial of individuals at high risk for bladder cancer. [1999]6

Dec. 2005 - Using a prospectively determined cutoff, 67 of the 75 samples from patients with bladder cancer were positive for BLCA-4, resulting in an assay sensitivity of 89%. Also, 62 of the 65 samples from individuals without bladder cancer were negative for BLCA-4, resulting in an assay specificity of 95%.

ConclusionsThe high sensitivity and specificity of the sandwich BLCA-4 immunoassay may allow for earlier detection and treatment of disease, thus greatly improving patient care. 7

Feb. 2004 BLCA-4, appears to be associated with a "field effect" of the disease, and in clinical trials is able to separate individuals with bladder cancer from those without the disease with high sensitivity and specificity. BLCA-4 is a bladder cancer marker that is highly specific and occurs early in the development of the disease. It appears to be a transcription factor that may play a role in the regulation of the gene expression in bladder cancer. BLCA-4 is a marker with significant clinical utility that may have an active role in the disease.

Functional characterization of the bladder cancer marker, BLCA-4.Van Le TS, Myers J, Konety BR, Barder T, Getzenberg RH.Department of Urology, University of Pittsburgh and University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania 15232, USA. JClin Cancer Res. 2004 Feb 15;10(4):1384-91. Free, online article PubMed:14977841

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Bladder Cancer: Twenty Years of Progress and the Challenges That Remain. Donald L. Lamm, M.D. CAJournal for Clinicians, Guest Editorial