Supplement to

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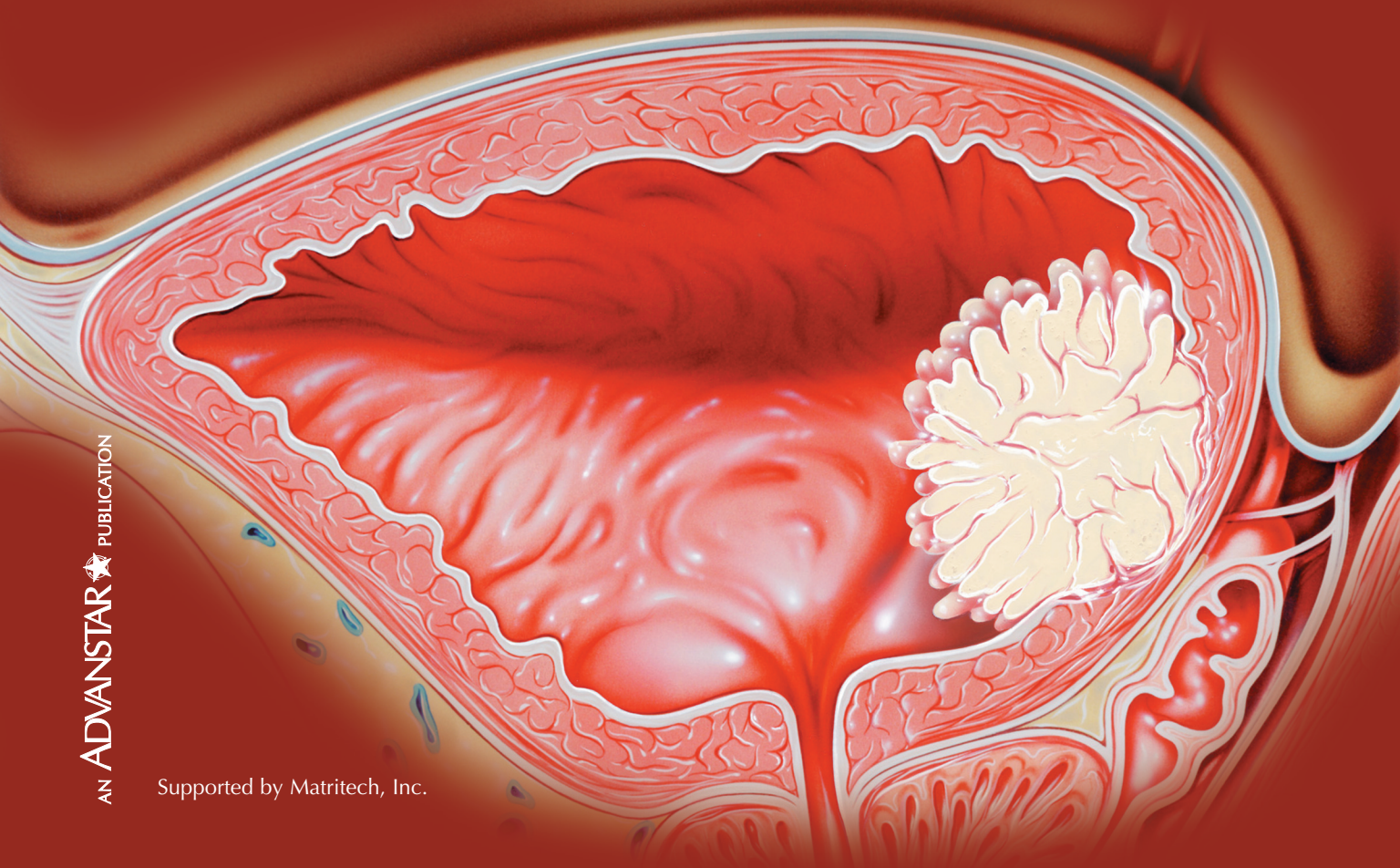
CONTEMPORARY UROLOGY®

IMPROVING BLADDER CANCER DETECTION: THE VALUE OF COMBINING A MOLECULAR TEST WITH CYSTOSCOPY

A review of the 2006 American Urological Association (AUA) Bladder Cancer Detection and Screening podium and poster sessions, including scientific findings reported at EAU and SGSU.



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INTRODUCTION

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EARLY DIAGNOSIS OF BLADDER CANCER

Bladder cancer, in contrast with prostate cancer, is a malignancy in which there has been no change in the last 20 years in terms of the opportunities to diagnose this cancer earlier. We're all well aware that once a patient presents to us with muscle-invasive bladder cancer, despite dramatic improvements in surgery, radiation therapy, and chemotherapy, we will lose 50% of the people (men and women) to this cancer. Our only hope is to diagnose more people with this cancer earlier—giving us the opportunity to cure them with less morbid treatments.

Look at prostate cancer. We have made dramatic changes. Why? Prostate-specific antigen (PSA), public awareness, and celebrities stricken with prostate cancer who have come forward to say, "I had prostate cancer. I was provided an opportunity to be diagnosed early with biopsy, and here I am free of cancer." We've not seen any of this to date with bladder cancer.

This supplement provides pathways to a new understanding about the role of urine markers. I believe we now have an opportunity to make a change with earlier diagnosis in men and women with bladder cancer. The point-of-care multicenter study on bladder cancer provides new insights into at-risk groups and how these markers perform in association with cystoscopy. In practical application, when a marker is positive, there's a heightened awareness for the clinician to say, "There might be a tumor here; I have to review this urinary bladder very carefully. If it is a male, I have to look at the interior bladder wall, I have to make sure I look at the prostatic urethra." On the other hand, it could be a false-positive and that's okay, but there's the heightened awareness that this gentleman, as opposed to the next with a negative test, might have a chance of having a urothelial cancer.

I see these studies being complementary, the urine-based marker and cystoscopy. I hope you will read this supplement thoroughly and open a dialogue with your colleagues about how to improve your clinical protocols for diagnosing bladder cancer earlier.

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DIAGNOSIS AND SURVEILLANCE OF BLADDER CANCER USING A POINT-OF-CARE ASSAY

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Surveillance data were presented during the AUA podium session on May 21, 2006, AUA, Atlanta, Georgia, and diagnosis data were presented during the EAU podium session on April 6, 2006, EAU, Paris, France.

Cystoscopy is integral to diagnosing bladder cancer, but adjunctive tests are useful to avoid missing cancers that are difficult to visualize. We investigated whether a point-of-care test (NMP22® BladderChek® Test) could enhance detection of bladder cancer.

Twenty-three private practice, academic, and veterans' hospitals prospectively enrolled a total of 1999 patients. Of these, 1331 had symptoms or risk factors for bladder cancer, such as hematuria or history of smoking, and were undergoing an initial evaluation for bladder cancer; 668 were under surveillance for a history of bladder cancer. Patients provided a voided urine sample for analysis of the NMP22 marker and cytology prior to cystoscopy. Testing for the NMP22 tumor marker was conducted in a blinded manner, and cytology was performed within the institution or at a reference laboratory, according to the standard practice at the facility.

Among the 1331 initial diagnosis patients, 79 had pathologically confirmed transitional cell carcinoma. Cystoscopy alone detected 68/79 of the cancers, while the combination of cystoscopy with the NMP22 assay identified 74/79, a significant difference (P=.014). The 6 malignancies not seen during cystoscopy but detected by the NMP22 BladderChek Test included a CIS, T2, and T3 of the bladder; a T2 of the ureter; and T1 and T3 tumors of the renal pelvis. The NMP22 BladderChek Test was positive in 10/11 of muscle-invasive cancers, compared with 6/11 by cystoscopy.

Compared with cytology, the NMP22 BladderChek Test detected 91% (10/11) of the muscle-invasive and 78% (21/27) of the high-grade cancers versus 20% (2/10) and 39% (10/26), respectively. Overall, the point-of-care test was more than 3 times as sensitive as the laboratory test, 57% for the NMP22 BladderChek Test, compared with 16% for voided cytology (P<.001) (Figure 1). Cytology detected only 2 of the cancers not visualized during cystoscopy, which did not result in a significant improvement in sensitivity compared with cystoscopy alone (P=.26).

Among the 668 patients undergoing surveillance cystoscopy, 103 had recurrent tumors. Cystoscopy alone identified 91% (94/103) of the cancers, while the combination of cystoscopy with the NMP22 assay detected 99% (102/103) (P=.005). The NMP22 assay was positive for 8 out of 9 cancers that were not visualized during initial cystoscopy. Two of the 8 tumors were metastatic and 7 were high-grade.

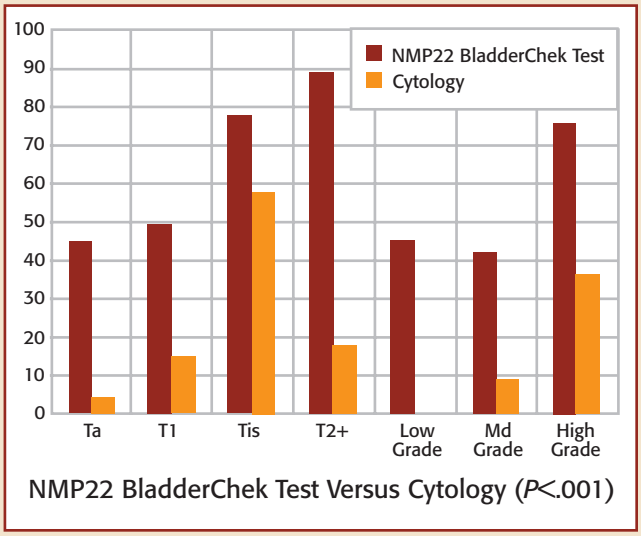

FIGURE 1. Sensitivity for transitional cell carcinoma: diagnosis study.

Voided cytology detected only 3 of the occult cancers, all carcinoma in situ, and did not significantly increase the sensitivity of cystoscopy (P=.083). The NMP22 BladderChek Test detected 91% (10/11) of muscle-invasive and 75% (24/32) of high-grade malignancies, compared with 0% (0/10) and 19% (6/31) by cytology, respectively. Overall, the point-of-care test was significantly more sensitive than voided cytology (50% vs 12%, P<.001) (Figure 2).

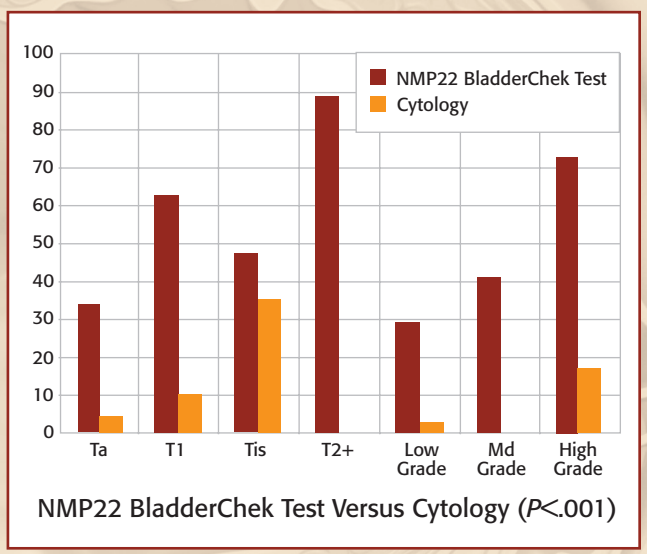

FIGURE 2. Sensitivity for transitional cell carcinoma: surveillance study.

The positive predictive value of the NMP22 BladderChek Test and voided cytology were similar at 41.5% and 41.4%, respectively. However, the point-of-care assay had better negative predictive value (91%) than cytology (86%) because of fewer false-negative results (*P*=.012).

In both investigations, the sensitivity of voided cytology was lower than has been seen in some publications. Most of the earlier studies are from single sites, typically academic hospitals. The performance in the 2 current studies reflects the "real world" variability across 23 clinical sites.

The rate of false-negative cystoscopies ranges from 10% to 40% in other publications. In these 2 studies, 14% of the malignancies were not visualized among the diagnosis patients and 9% among those undergoing surveillance. In some cases this was because the tumors were outside the range of the cystoscope in the ureter or renal pelvis. Carcinoma in situ is notoriously difficult to discern from normal urothelium, but some of the occult cancers were papillary tumors in the bladder. The false-negative cystoscopies occurred at 10 geographically diverse clinical sites. Such cases underscore the value of the NMP22 BladderChek Test.

Earlier detection can improve prognosis for patients with both non–muscle-invasive and later-stage cancers. Recurrence and progression vary among patients with microscopic differences in invasion of T1 tumors and studies have demonstrated that a delay in surgery in patients with muscle-invasive malignancy is associated with a more advanced pathological state and poorer prognosis.

Combined with cystoscopy, the point-of-care assay for elevated urinary NMP22 protein marker can significantly improve detection of bladder cancer (Table) at half the cost of voided cytology, with test results available during the patient visit.

Improved Detection With NMP22 BladderChek Test and Cystoscopy

	DIAGNOSIS	SURVEILLANCE
Cystoscopy and NMP22 BladderChek Test	**94%** (74/79)	**99%** (102/103)
Cystoscopy alone	**86%** (68/79) *P*=.014	**91%** (94/103) *P*=.005

Cancers not seen by cystoscopy but detected by NMP22 BladderChek Test

Diagnosis: Bladder CIS, T2, T3; Ureter T2; Renal Pelvis T1, T3
Surveillance: Bladder Ta, T1, 2 CIS, 2 T2, 2 T4

DETECTING BLADDER CANCERS IN SYMPTOMATIC VA PATIENTS MISSED BY TRADITIONAL LABORATORY TESTS

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Subgroup data: Diagnosis of bladder cancer among military veterans as presented in January 2006 at the 53rd Annual James C. Kimbrough Urological Seminar (sponsored by the Uniformed Services University of the Health Sciences and the Society for Government Service Urologists).

Military veterans with blood in their urine are reported to have twice the incidence of bladder cancer as other individuals. Subgroup data from the multicenter bladder cancer study were analyzed from the 2 participating veterans' hospitals. Patients from these facilities represented 9% of the sites in the multicenter bladder cancer study, but accounted for 16% of the cancers. That was because, although the patients at all sites presented with the same symptoms, such as hematuria, or painful or frequent urination, the percentage of those diagnosed with bladder cancer at the veterans' hospitals was 11.1%, compared with 5.7% at the community and academic practices. In addition, most of the malignancies at veterans' hospitals were already in an early invasive stage, compared with the other non-veterans sites, where the most common stage was noninvasive.

The NMP22® BladderChek® Test detected 3 times more cases of bladder cancer in these symptomatic patients than the traditional laboratory test, cytology. Results were documented in a recent analysis from the large clinical trial published in *JAMA* in February 2005. *JAMA* (January 2006) also reported that the point-of-care NMP22 BladderChek Test significantly increased the detection of recurrent bladder cancer, finding 99% of the malignancies when used with cystoscopy.

We evaluated the effectiveness of the NMP22 BladderChek Test for diagnosis of bladder cancer in patients with hematuria (blood in the urine). The data presented showed the NMP22 BladderChek Test detected 4 life-threatening cancers missed by cystoscopy: 3 muscle-invasive tumors and 1 noninvasive, but high-grade aggressive malignancy. When the NMP22 BladderChek Test was combined with the diagnostic standard, cystoscopy, it significantly increased overall bladder cancer detection. New data confirmed similar findings of the test's effectiveness in detecting recurrent bladder cancer published in the January 18, 2006, issue of *JAMA*.

The US Department of Veterans Affairs (VA) is the largest provider of health care in the country, and it provides excellent

medical care to those who have served this country. It is not a surprise that the bladder cancer rate is high here. The American Cancer Society statistics show that bladder cancer occurs most commonly in men over the age of 60 years, and they make up a large proportion of the VA patient population. Moreover, smoking and occupational or environmental exposure to chemicals substantially increase the risk of urological malignancy, and many of these patients have these risk factors.

We need to educate our patients and to use the best tools we have to diagnose their bladder cancer early. The NMP22 BladderChek Test is noninvasive, provides a result while the patient is in the office, is proven to improve detection of cancer, and is half the cost of other laboratory tests. Considering the limited resources for health care in the VA and everywhere else, using the NMP22 BladderChek Test will help identify those who need more urgent evaluation within a shorter period of time than others.

EVALUATION OF RISK FOR MUSCLE-INVASIVE AND HIGH-GRADE BLADDER CANCER USING A POINT-OF-CARE ASSAY

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Presented during the AUA Bladder Cancer Detection and Screening Poster Discussions on May 23, 2006, AUA, Atlanta, Georgia.

The NMP22® BladderChek® Test, combined with cystoscopy (a visual examination of the bladder with a lighted scope), provides information about the stage and grade of a bladder cancer prior to a biopsy. The NMP22 BladderChek Test is able to indicate whether a bladder malignancy is likely to be potentially life-threatening, ie, muscle-invasive and/or aggressive, or confined to the bladder and slower growing. This information is essential for determining the best course of treatment.

Data analyzed from multicenter studies demonstrated that when a tumor was seen during cystoscopy and the NMP22 BladderChek Test result was positive, the cancer was almost 3 times as likely to have progressed into muscle and/or be high-grade (aggressive). Conversely, when a tumor was visible during cystoscopy but the result of the NMP22 BladderChek Test was negative, the cancer had a greater likelihood of being confined to the bladder lining and of being less aggressive. This was true for both newly diagnosed and recurrent cancers. Using the NMP22 BladderChek Test with cystoscopy added useful information to enhance the physician's ability to detect and treat the cancer.

The 2 studies published in *JAMA* in February 2005 and January 2006 showed that the NMP22 BladderChek Test identified cancers not seen during cystoscopy, either because they were outside the viewing field of the cystoscope or because they were difficult to differentiate from normal tissue.

If cystoscopy is negative but the NMP22 BladderChek Test is positive, consider the possibility of an upper tract or occult cancer. The NMP22 BladderChek Test also provides clinically useful information when cystoscopy is positive. Knowing the relative risk that a cancer is advanced and/or aggressive, or earlier stage, can help in patient management. Ideally, every tumor is biopsied, but some decisions must be made without pathology results available—for example, whether a patient is a good candidate for nonsurgical management (fulguration), whether surgery can be safely delayed to resolve another medical condition, or whether the patient is at elevated risk of a dangerous cancer and biopsy should be expedited.

Twenty-five percent of primary bladder cancers are invasive at first diagnosis and one third are high-grade. Among patients with a history of bladder cancer, 50% or more have recurrences, and progression of stage or grade occurs in 10% to 50%. In patients with muscle-invasive disease, a delay in surgery is associated with a more advanced pathological state and poorer prognosis.

If detected early, bladder cancer is highly curable, with 94% of patients surviving 5 years or more. Approximately 1 in 4 patients is not diagnosed until the cancer has spread, decreasing 5-year survival by half. Until now, there has not been a simple in-office test to reliably diagnose this disease. It is important because too often we see men and women who have blood in the urine or symptoms that could be bladder cancer, but who are treated for suspected (urinary tract) infections for several months before they're diagnosed. Unfortunately, those months can make a significant difference in the ability to cure their cancers.

The NMP22 BladderChek Test is a critical tool for evaluating patients at high risk for bladder cancer, including long-time smokers; people who work around particulates in manufacturing, or who work with chemicals like those in hair dyes; as well as firefighters.

PRACTICAL APPLICATIONS

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Dr. Bensen practices in the Pacific Northwest where the rates of bladder cancer are high because of high-risk occupations, such as pulp mill workers who are exposed to bleaching agents, and retirees with histories of smoking.

CASE IN POINT:

Male, 77 years old, quit smoking in 1982, now retired.

History includes transitional cell carcinoma T2 treated by resection in 1986. Monitoring: cystoscopy–no recurrent tumors detected. April 2004: cystoscopy–negative, CAT scan–negative, gross hematuria evident, repeated cystoscopy–negative, ultrasound–negative, hematuria persistent, positive NMP22® BladderChek® Test; biospy: high-grade carcinoma in situ.

When Dr. Bensen tells patients with a history of smoking that they have bladder cancer, they are always surprised by the connection. A common response is, "Had I known, I would have quit." Dr. Bensen also recognizes that her older patients with cardiovascular disease typically have a prior history of smoking. They are often on Coumadin® and microscopic hematuria is typical, but should be monitored. Dr. Bensen uses the NMP22 BladderChek Test as part of a monitoring protocol.

"A negative NMP22 BladderChek Test result provides a higher degree of confidence that I have not missed a tumor."

(Based on Q&A session with Dr. Giora Katz at the May 2006 Wisconsin Urological Society meeting, Milwaukee, Wisconsin)

QUESTION 1

How will tumor markers change the way I treat my patients?

Dr. Katz:
This is a common question and a very valid one. Simply put, tumor markers help us manage the unseen. So what do I mean by this? Well, the best way to understand this is to look at a textbook population of patients who present with hematuria, let's say 200. As we all know, only about 3% to 5% of these patients will have a bladder cancer detected. Let's assume this works out to about 10 patients. We also know that cystoscopy will detect between 85% and 90%, or about 9, of these malignancies right away. The problem comes with the remaining 190 patients who are positive for blood, but no tumor is visible in the bladder. An undetected cancer is lurking in this group. What the NMP22® BladderChek® Test does is give us a molecular analysis of the bladder that is complementary to the view by the cystoscope. When a negative NMP22 BladderChek Test is combined with a negative cystoscopy, we can be 99% certain that the patient does not have bladder cancer. These "negative-negative" patients are a group in which you can have the greatest degree of comfort that there is not an occult cancer lurking. In contrast, the smaller group of patients—those with a negative cystoscopy and a positive NMP22 result—has a much higher risk that an occult cancer is present. This group should have a much closer, more frequent follow-up.

QUESTION 2

Why do bladder cancer markers have more false-positives than cytology?

Dr. Katz:
All tumor marker tests have a balance and tradeoffs between sensitivity and specificity. Typically, if the reference value is selected for a test to have a high sensitivity, the specificity will be lower. Tests with high specificities will tend to have lower sensitivities. For example, cytology has high specificity, but poor sensitivity. A high specificity is of little value if so few cancers are detected. What we really should be looking at is the balance between the 2 aspects of testing: sensitivity and specificity. A study in a recent *JAMA* article indicated that the NMP22 BladderChek Test was 4 times more sensitive than cytology, while maintaining a high level of specificity at 87.7%. It is this type of balance that we should be looking for. One should ask the question, "Is it more important that I do not miss a cancer?"

QUESTION 3

What do I do with a positive NMP22 test and a negative cystoscopy?

Dr. Katz:
A tumor marker can provide clinically actionable information even when it disagrees with cystoscopy. A patient with a positive NMP22 result and a negative cystoscopy could have a nonmalignant cause (urinary tract infection, calculi), an occult urothelial cancer, or both conditions simultaneously. It makes sense to follow this patient more frequently with shorter intervals until a cause is found or until both tests are negative. Then resume standard follow-up.

BLADDER CANCER DETECTION ALGORITHM

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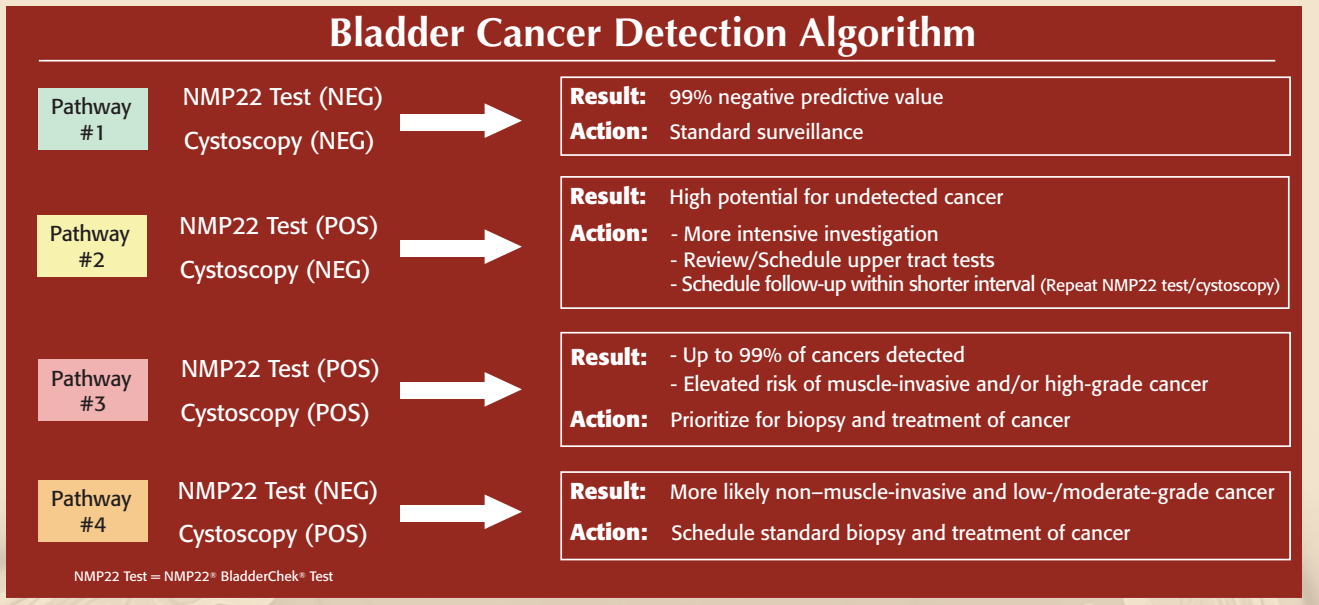
Tumor markers give the urologist a "molecular" view of the bladder that is complementary to the "macro" view with the cystoscope. Recently published multisite clinical trials have concluded that combining tumor markers with cystoscopy can identify more tumors than cystoscopy alone, giving the urologist the best opportunity to detect a cancer earlier.

Valuable clinical information can be gleaned both when a tumor marker agrees with cystoscopy as well as when it disagrees. Combining cystoscopy with the NMP22 tumor marker affords the urologist an opportunity to "individualize" a patient's care. Below is a simple algorithm that distributes patient status and treatment into 4 pathways (Figure).



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