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Diagnosis of bladder cancer using a point-of-care proteomic assay (NMP22 BladderChek): A multicenter study

A review of the presentation at the 2005 American Urological Association (AUA) podium session: Bladder Cancer Detection and Screening, including a discussion with Giora Katz, MD

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Diagnosis of bladder cancer using a point-of-care proteomic assay (NMP22 BladderChek): A multicenter study[1]

Giora Katz, Gainesville, Fla; Edward M. Messing, Rochester, NY

Introduction and objective: It is standard of care to use a combination of methods for diagnosis of bladder cancer because no single procedure detects all malignancies. Urine tests are frequently part of an evaluation, but have either been nonspecific for cancer or required specialized analysis at a laboratory. This study investigates whether a point-of-care proteomic test (NMP22 BladderChek Test) that measures the nuclear matrix protein NMP22 in voided urine could enhance detection of malignancy in patients with risk factors or symptoms of bladder cancer.

Methods: Twenty-three academic, private practice and veterans' facilities in 10 states prospectively enrolled consecutive patients from September 2001 to May 2002. Participants included 1,331 patients at elevated risk for bladder cancer due to factors such as history of smoking, or symptoms including hematuria and dysuria. All patients at risk for malignancy of the urinary tract provided a voided urine sample for analysis of NMP22 and cytology prior to diagnostic cystoscopy. The reference standard was cystoscopy with biopsy. The performance of the NMP22 test as an aid to cancer diagnosis was compared to voided urine cytology. NMP22 testing was conducted in a blinded manner.

Results: Bladder cancer was diagnosed in 79 patients. Ten of the malignancies were muscle invasive. NMP22 was positive for 9/10 (90%). By comparison, voided cytology was positive in only 2/9 (22%). Overall, the NMP22 assay detected more than three times as many tumors as voided urine cytology, identifying the presence of 32 malignancies that were missed by cytology. The proteomic marker detected 4 cancers that were not visualized during initial cystoscopy; 3 were muscle invasive and one was carcinoma in situ. The specificity of NMP22 BladderChek Test was 90% for patients with no urinary tract disease. The accuracy of NMP22 was 83.7%. The combination of NMP22 with cystoscopy detected malignacies in 74 of 79 patients versus 70 of 79 detected by initial cystoscopy alone. Cytology detected only one cancer that was neither seen during cystoscopy nor detected by NMP22 test.

Conclusions: Combining cystoscopy with the noninvasive point-of-care assay for urinary NMP22 can increase the accuracy of cystoscopy, with results available during the patient visit. The NMP22 BladderChek Test was less than half the expense for voided cytology.

Reprinted with permission from Katz G, Messing EM. Diagnosis of bladder cancer using a point of care proteomic assay: a multicenter study. *J Urol.* 2005;173(4 suppl):230.[1]

Author disclosures

Giora Katz, MD is Staff Urologist, Department of Surgery-Urology Service, Lake City Veterans Administration Hospital, Lake City, Fla; and is in private practice at Lakeshore Urology, Manitowoc, Wisc. He has participated in a scientific study/trial for Matritech, Inc.

Edward M. Messing, MD is Professor of Urology, University of Rochester Medical Center, Rochester, NY. He has participated in a scientific study/trial for Matritech, Inc.; is a consultant/advisor for TAP Pharmaceuticals, Inc., and Fujirebio; and has participated in a scientific study/trial and received grant/research support from Dynacur.

Collaborating investigators

Yitzhak Berger, MD, Associates in Urology, West Orange, NJ; **David Bock, MD**, Kansas City Urology Care, Kansas City, Mo; **Jeffrey Brady, MD**, Winter Park Urology Associates, Orlando, Fla; **M. Patrick Collini, MD**, Urology Associates of North Texas, Fort Worth, Tex; **Martin Dineen, MD**, Atlantic Urological Associates, Daytona Beach, Fla; **H. Barton Grossman, MD**, M.D. Anderson Cancer Center, Houston, Tex; **Vahan Kassabian, MD**, Georgia Urology, Atlanta, Ga; **Shiva Maralani, MD**, Michigan Urology, St. Clair Shores, Mich; **Raoul Salup, MD**, James A. Haley VA, Tampa, Fla; **Mark Soloway, MD**, University of Miami School of Medicine, Miami, Fla; **Barry Stein, MD**, Rhode Island Hospital, Providence, RI; **Kevin Tomera, MD**, Alaska Clinical Research Center, Anchorage, Alaska; and **Alan Treiman, MD**, Urology Treatment Center, Sarasota, Fla.

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Point-of-care NMP22 BladderChek Test shifts the emphasis to "early" diagnosis of bladder cancer

This follow-up to the author's AUA presentation at the Bladder Cancer Detection and Screening podium session further describes the role of tumor markers in relationship to cystoscopy and cytology.

By Giora Katz, MD

Early diagnosis of bladder cancer can save lives. Bladder cancer occurs primarily in men age 60 and older and roughly twice as frequently in white men as in black men. Men are 4 times more likely to be diagnosed with bladder cancer than women; age-adjusted mortality rates from bladder cancer are similarly higher for men than for women. Women, however, tend to be diagnosed at a more advanced stage in the disease. Among US males, the incidence of new bladder cancer cases is almost as high as the incidence of colon cancer.[2]

Bladder cancer is the fifth most common form of cancer in the United States and the ninth most common form of cancer in the world. The American Cancer Society estimates that more than 63,000 new cases of bladder cancer will be diagnosed in the United States this year.[2]

Yearly, more than 13,000 people die of the disease (nearly 9,000 men and 4,000 women). Worldwide bladder cancer accounts for 330,000 new cases and 100,000 deaths each year. It is also one of the most chronic cancers, recurring in almost 70% of patients.[3]

The most common risk factor for bladder cancer is smoking. Smokers are twice as likely to develop bladder cancer as nonsmokers. In the United States, smoking is estimated to be associated with approximately 50% of bladder cancer deaths among men and 30% among women.[2]

Occupational exposure to chemicals (aromatic amines) used in dry-cleaning facilities and the production of dyes, paper, rope, apparel, rubber, and petroleum products have been associated with increased risk for bladder cancer. Soot and carcinogens from exposure to slow burns have put firefighters and arson investigators at increased risk for bladder cancer. Other industrial exposures implicated as risk factors for developing bladder cancer include combustion gases and soot from coal, chlorinated aliphatic hydrocarbons, and chlorination by-products in heated water.

If diagnosed in its early stages, bladder cancer has a 5-year survival rate of 95%. If diagnosed at an advanced stage, however, the 5-year survival rate can be less than 10%. It has been estimated that this year in the United States about 25% of bladder cancer patients will be diagnosed after their disease has become invasive or metastatic, significantly lowering the 5-year survival rate.[2]

HEMATURIA WORK-UP

Hematuria is an early sign of bladder cancer. It is also the most common symptom of bladder cancer. AUA guidelines for workup of hematuria currently include cystoscopy and urine cytology.[4] To expedite early diagnosis, we developed a patient management protocol using the NMP22® BladderChek® Test (Matritech, Inc.) as an adjunct to cystoscopy. This protocol is based on data from the bladder cancer multicenter study (see the list of collaborators on page 2).[1,5]

Earlier this year, *The Journal of the American Medical Association* published NMP22 BladderChek Test results from a multicenter study.[5] Data demonstrated the NMP22 BladderChek Test identified 4 life-threatening cancers missed during cystoscopic examination. The study further showed that when the BladderChek Test is combined with cystoscopic examination, it increases overall bladder cancer detection to 94%.[5]

As a principal investigator for the multicenter study at a Veterans Administration hospital in Florida, I found this test had significant clinical utility as an adjunct to cystoscopy.

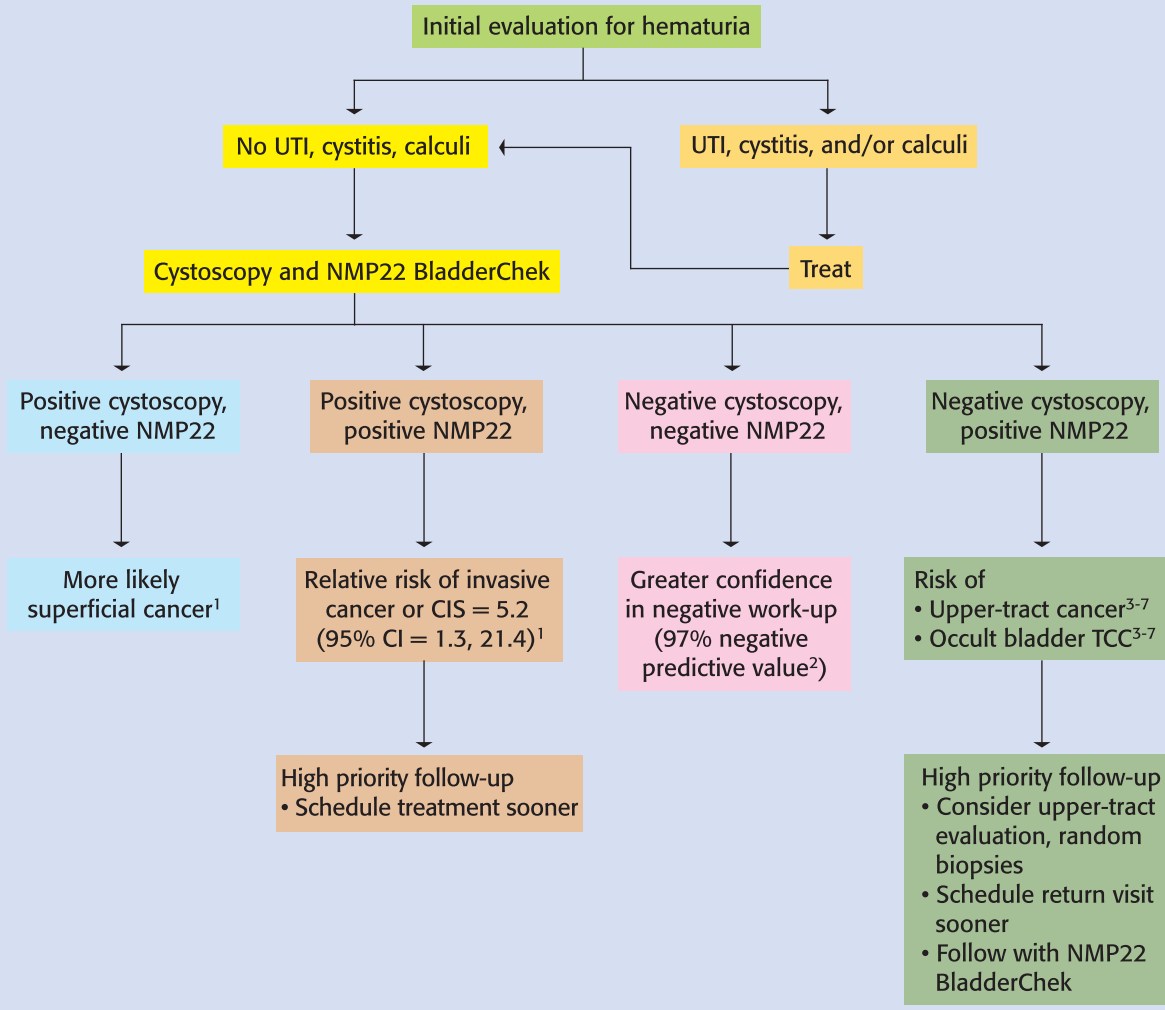
Urologists are challenged to improve detection of bladder cancer at the first sign of hematuria. While men tend to react quickly to signs of hematuria, women or their physicians tend to dismiss initial hematuria indicators. Patient education is essential to communicate the significance of hematuria and the need to follow up on this symptom.

At Lakeshore Urology in Manitowoc, Wisc, and across the United States, the current ratio of adults investigated with hematuria to those diagnosed with bladder cancer is 20:1. This type of work-up typically involves multiple noninvasive tests and invasive procedures. The NMP22 BladderChek Test is being used to help focus our search on those with cancer, expediting early diagnosis and helping urologists to be more confident in determining the cause of hematuria (Figure 1).

Initial evaluation shows that the NMP22 BladderChek Test plays a role in directing attention to benign and malignant causes of hematuria, better directing additional testing and procedures.

Case in point: The Veterans Health Administration (VA) is the largest provider of health care in the country. As part of the multicenter study, we observed a large percentage of VA patients (older males with a history of smoking) at high risk for bladder cancer. At the urology clinic, significant VA resources are used to investigate and find patients with hematuria caused by cancer. The NMP22 BladderChek Test gives the VA a cost-effective, point-of-care test to help direct resources to patients with the highest suspicion of cancer.

FIGURE 1
Diagnostic work-up for hematuria using cystoscopy and NMP22 BladderChek Test



Key: UTI = urinary tract infection; CIS = carcinoma in situ; TCC = transitional cell carcinoma.

REFERENCES: 1. Data on file, Matritech Inc. **2.** PMA 940035 S003. Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA.cfm?ID=7584. Accessed June 10, 2005. **3.** Tomera K, Clark WR, Singsaas ME, et al. Results of screening high-risk patients for urothelial cancers with a new office test-NMP22 BladderChek. *J Urol.* 2003;169(4 suppl):226-227. Abstract 877. **4.** Ozer G, Altinel M, Kocak B, et al. Value of urinary NMP-22 in patients with renal cell carcinoma. *Urology.* 2002;60(4):593-597. **5.** Huang S, Rhee E, Patel H, et al. Urinary NMP22 and renal cell carcinoma. *Urology.* 2000;55(2):227-230. **6.** Poulakis V, Witzsch U, De Vries R, et al. A comparison of urinary nuclear matrix protein-22 and bladder tumour antigen tests with voided urinary cytology in detecting and following bladder cancer: the prognostic value of false-positive results. *BJU Int.* 2001;88(7):692-701. **7.** Soloway MS, Briggman V, Carpinito GA, et al. Use of a new tumor marker, urinary NMP22, in the detection of occult or rapidly recurring transitional cell carcinoma of the urinary tract following surgical treatment. *J Urol.* 1996;156(2 Pt 1):363-367.

The NMP22 BladderChek Test is enhancing the early diagnosis of bladder cancer for these high-risk patients.

NUCLEAR MATRIX PROTEIN AND TRANSITIONAL CELLS OF THE URINARY TRACT

Nuclear matrix proteins (NMP) make up the structural framework of the nucleus and organize its function. NMP22 is specific for transitional cells in the urinary tract. Malignant transitional cells contain up to 80 times higher concentration of NMP22 than normal transitional cells and release it into the urine upon cell death.[6,7] Typically, patients with transitional cell carcinoma of the bladder (TCCB) have higher concentrations of NMP22 in their urine than patients without TCCB. Unlike urine cytology and fluorescence in situ hybridization (FISH) testing, detection of NMP22 in the urine is not dependent on recovery of intact cells. Based on previous studies, an NMP22 level above 10 U/mL in the urine is associated with a high probability of TCCB.[8]

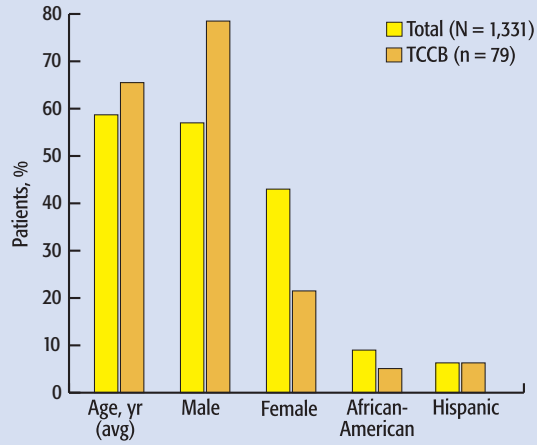
The NMP22 BladderChek Test is a point-of-care device that was designed to identify urine with NMP22 levels above 10 U/mL. This test can be performed by non-physician staff members (CLIA waived). The test cassette requires 4 drops of freshly voided urine, and results are available in 30 minutes. This device has a built-in quality control.

REVIEW OF THE METHODS, STUDY DESIGN, AND EXECUTION OF THE MULTICENTER STUDY

From September 2001 to May 2002, 1,331 patients scheduled for cystoscopy due to suspicion of bladder cancer were included in the study.[1,5] The mix included private, academic, and Veterans Administration urology practices in 23 locales and 10 states. Of this patient population, 92% presented with hematuria. Other risk factors included a history of smoking and irritative voiding symptoms. All patients provided a voided urine sample for analysis of NMP22 and cytology prior to diagnostic cystoscopy. Urologists were blinded to NMP22 results while performing and reporting the results of cystoscopy. Further work-ups were based on clinical findings and results of cystoscopy and cytology. TCCB was diagnosed based on the pathology report of excised tissue.

Of the 1,331 patients enrolled in the study, 79 were diagnosed with TCCB (Figure 2),[9] 10 of whom were found to have muscle-invasive disease.[1,5] While initial cystoscopy visualized 6 of 10 (60%) invasive tumors, the NMP22 BladderChek Test was positive for 9 of 10 (90%).[1,5]

FIGURE 2
Patient demographics and incidence of TCCB



Data from PMA 940035 S003.[9]

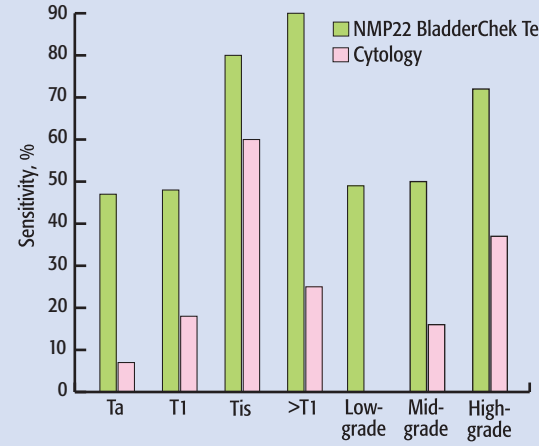
Voided urine cytology, by comparison, was positive in 2 of 9 (22%) patients with muscle-invasive cancer. The NMP22 BladderChek Test identified 4 life-threatening malignancies, including 3 muscle-invasive tumors and a carcinoma in situ (CIS) that were missed on initial cystoscopy.

The NMP22 Test was significantly more sensitive than voided urine cytology (Figure 3).[1,5,9] Study results reported the specificity of cytology to be greater than the NMP22 Test (Table 1).[1,5,9]

MULTICENTER STUDY CONCLUSIONS

Cystoscopy combined with the NMP22 BladderChek Test detects more bladder cancers than cystoscopy alone or combined with cytology (Figure 4).[1] The NMP22 BladderChek Test is significantly more sensitive than cytology in detecting bladder cancer (3× more cancers, $P<0.001$). This test can be performed by clinic staff in any doctor's office with results in 30 minutes, at half the cost of voided cytology. The NMP22 BladderChek Test is consistent with AUA guidelines recommending use of a urine test as an adjunct to cystoscopy.

FIGURE 3
Sensitivity of NMP22 BladderChek Test and cytology in the detection of bladder cancer



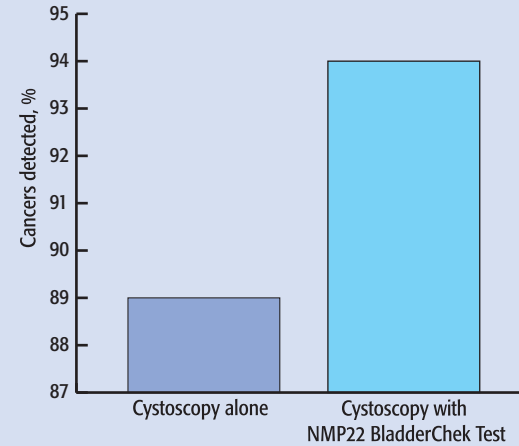
Data from PMA 940035 S003.[9]

TABLE 1
Specificity of NMP22 BladderChek Test and cytology

	Specificity	
Test	**No GU disease found**	**No cancer found**
NMP22 BladderChek	90% (512/567)	86% (1,070/1,249)
Cytology	99% (544/547)	99% (1,198/1,208)

Data from PMA 940035 S003.[9]

FIGURE 4
Sensitivity of cystoscopy with and without NMP22 BladderChek Test



Data from Katz G et al.[1]

BLADDER CANCER DETECTION, DIAGNOSIS, AND MONITORING

The following patient histories are taken from the multicenter NMP22 BladderChek study.[1,5] Voided urine samples were collected prior to cystoscopy and divided. One portion was sent for cytology according to standard practice at each office, and another was used for the NMP22 BladderChek Test. Samples for BladderChek testing were identified by study identification number only, and physicians were blinded to the results. All cystoscopies were conducted by board-certified urologists, and evaluation decisions were based on cystoscopy and cytology results.

CASE 1—February 11, 2002

A 58-year-old male with a history of intermittent hematuria, otherwise asymptomatic

CT scan: No upper tract abnormality, but a mass was identified at the bladder base. A decision was made to evaluate the mass cystoscopically for differential diagnosis of bladder cancer versus enlargement from benign prostatic hypertrophy (BPH).

NMP22 BladderChek Test: Positive.

Cystoscopy: BPH with marked median lobe hypertrophy with ball-valve configuration consistent with mass seen on CT, mild-moderate trabeculations, small clots.

Cytology: Atypical/suspicious.

Management: Ciprofloxacin hydrochloride, tamsulosin hydrochloride, finasteride prescribed. On April 16, 2002, the patient returned because his problems were not resolved by medication.

Second cystoscopy: TCC T2G3 on bladder base.

CASE 2—February 25, 2002

A 68-year-old male presenting with episodes of gross hematuria, history of smoking

NMP22 BladderChek Test: Positive.

Cystoscopy: A cystoscope was passed into the bladder 3 times, with the patient emptying his bladder in between each pass. No bloody efflux from either the left or right ureter was observed, and no papillary lesion or other abnormality was seen.

Cytology: Atypical/suspicious with urothelial fragments.

Management: A second cystoscopy was done on March 20, 2002. Random biopsies demonstrated TCC dome TaG2, left wall CIS, left ureteral orifice T3aG2 with deep muscle invasion.

CASE 3—October 4, 2001

A 68-year-old male presenting with hematuria, history of smoking

NMP22 BladderChek Test: Positive.

IVP: Negative.

Cystoscopy: Performed twice, clear urine noted to efflux from both ureteral orifices and no abnormality seen.

Cytology: Malignant cells.

Repeat IVP: Suspicious.

Management: On November 8, 2001, the patient underwent radical ureteral nephrectomy; T2G2 of the right ureter.

Q&A WITH GIORA KATZ, MD

Based on questions and answers following the presentation by Dr. Katz at the May 23, 2005, AUA podium session: Bladder Cancer Detection and Screening, Abstract 846.[1]

Q: *How many cancers were detected by cytology versus the NMP22 Test?*

Katz: The NMP22 BladderChek Test detected 32 cancers missed by cytology and 4 cancers not visualized during initial cystoscopy. There was only 1 case where the cytology was positive and the NMP22 and cystoscopy were negative.

Q: *Can you explain why the cytology numbers for invasive cancers in this study are much lower than those typically reported around the country?*

Katz: This study included 23 facilities in 10 states. Cytology specimens were sent to their usual laboratories according to standard practice at each office. These results reflect the subjectivity and variability of cytology results.

Q: *What accounts for invasive tumors missed by cystoscopy?*

Katz: Cystoscopy is an excellent tool, but as other studies have shown, conventional cystoscopy can miss up to 50% of cancers.[10] Blood in the urine can hamper visibility, and some cancers are mistaken for benign conditions. When NMP22 is positive, a flag of warning is raised. Even when you do not see something on the initial cystoscopy, you sometimes have a sense that you should look again. Adding a test that gives you new information helps determine the next course of action.

Q: *Who was involved in the study?*

Katz: The study involved 23 clinical sites in 10 states, and included qualified urologists, pathologists, and laboratories. Each site followed its own internal protocols and procedures. Laboratories analyzing cytology are directed by qualified pathologists. I believe this data to be representative.

Q: *You seem to suggest that cytology can be replaced by the NMP22 BladderChek Test. Is that the case?*

Katz: The AUA guidelines, written in 2001, support the use of ancillary tests. At the time the AUA guidelines were written, the NMP22 BladderChek Test had not yet been developed. This study was conducted to identify the clinical utility of the NMP22 Test as an ancillary test to be used with cystoscopy in the clinic.[1] Our multicenter study data demonstrate that the NMP22 Test performed in the clinic delivered much more meaningful results than cytology.[1,5]

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