Women and Bladder Cancer

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Dr. Hurley obtained his Bachelor of Arts degree from Harvard University and his MD from Boston University School of Medicine in 1986. After spending three years in the U.S. Navy, he completed a General Surgery Residency at St. Elizabeth's Medical Center of Boston and his Urology Residency at the Lahey Clinic in Burlington, MA where he currently is a Clinical Instructor of urology residents.
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Introduction: Bladder Cancer, Why a Woman's Cancer?

- ☑ Bladder cancer is considered a man's cancer
- ☑ More men get bladder cancer than women **BUT**
- ☑ For women, it is more deadly
- ☑ Women are diagnosed at much later stages when the chances of survival decline

It is a serious women's health issue.

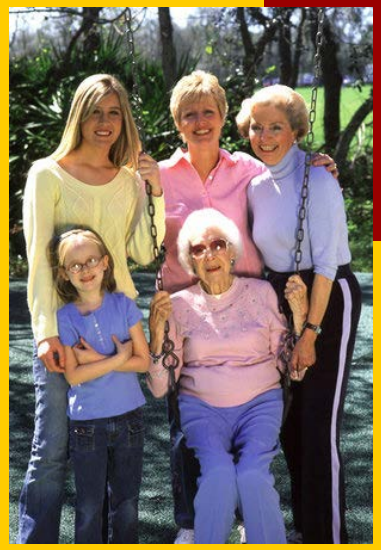
- 62% more women are estimated to be diagnosed in 2009 with bladder cancer [18,170] than cervical cancer [11,270]
- > 500,000 people in the U.S. have/had bladder cancer – highest recurrent rate any cancer, requires constant surveillance
- Bladder cancer incidence in women is comparable to ovarian cancer [≈18,000 and 21,000]
- 2009 estimated new bladder cancer cases in US for all people >70,000; estimated deaths >14,000.

Topics of today's discussion

- Situational analysis: Mortality/ late stage /gender/ race/ smokers/ disparity
- Diagnosing Bladder cancer in women
- Work-up using NMP22 BladderChek Test
- OB/GYN Pathways to early diagnosis
- How NMP22 BladderChek Test fits in
- Benefits of OB-GYN bladder cancer testing

Situation Analysis: Bladder cancer mortality rates for women

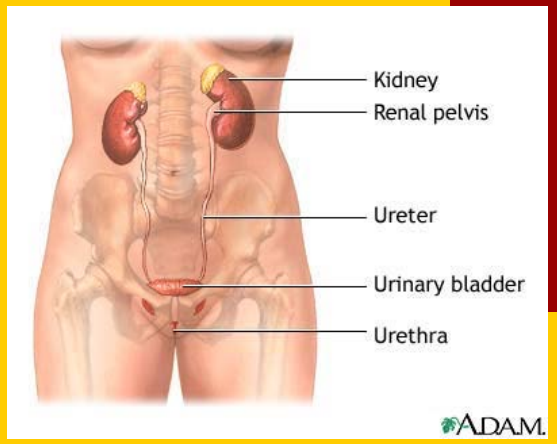
Based on National Cancer Registry SEER records >100,000 pts diagnosed with bladder cancer 1990 to 2003



- Greater mortality from bladder cancer cervical cancer
- Bladder cancer death steady versus fewer deaths from cervical cancer
- Higher mortality rate among African-American women
- Overall, in the first year after BC diagnosis, women are 80-114% more likely to die than men

Emil Scosyrev, MS, Katia Noyes, PhD, MPH, Changyong Feng, PhD, and Edward Messing, MD, Sex and Racial Differences in Bladder Cancer Presentation and Mortality in the US, Cancer. 2009;115:10-12, 68-74.

Women: Diagnosed in Later Stage Disease



A delay in diagnosis can make an easily curable cancer more invasive and difficult to treat

- The risk of mortality increases by 30% when more than 9 months pass between a first positive hematuria and diagnosis (Lee, et al U Michigan, 2006)
- Diagnosis of bladder cancer within the first 3 months of hematuria, adds 2 yrs. to survival
- Typically diagnosed later in woman (often at a more advanced stage) on average, 9 months after symptoms first appear, compared to 3-6 months for men

Bladder cancer: highest rate of recurrence of all cancers

Within 3 Years; recurrence for men/women

- Grade 1- 50%
- Grade 2- 59%
- Grade 3- 80%

- If no recurrence within 3 months of follow-up, >80% chance of never getting another tumor
- If a positive recurrence within 3 months follow-up, >70% chance of additional tumors

Bladder Cancer: Race disparity

- Katz, Steinberg, editorial: Sex and Race in Bladder Cancer; What have we learned...

"Using the SEER data, the authors observed that not only did African American patients (men and women) have **more aggressive tumors** and demonstrate **poorer cancer-specific survival**, BUT women of both races had worse outcomes and **AA women had the worst survival**."

Emil Scosyrev, MS, Katia Noyes, PhD, MPH, Changyong Feng, PhD, and Edward Messing, MD, Sex and Racial Differences in Bladder Cancer Presentation and Mortality in the US, Cancer. 2009;115:10-12, 68-74.

High-risk for bladder cancer Post-menopausal smokers

- Based on the Iowa Women's Health study cohort (37,459 women followed for 13 years), 25% bladder cancer incidence cases attributed to ever-smoking

- Relative risk greatest among Post-Menopausal women

  Cigarette smokers with 20-39 pack year history

Note: Overall, U.S. has a 34% prevalence of female smokers

Triopathi et al. The Iowa Women's Study ICancer 95: 11 2002.

Reproductive risk factors for incidence of bladder cancer

Iowa Women's Health Study 2006 results

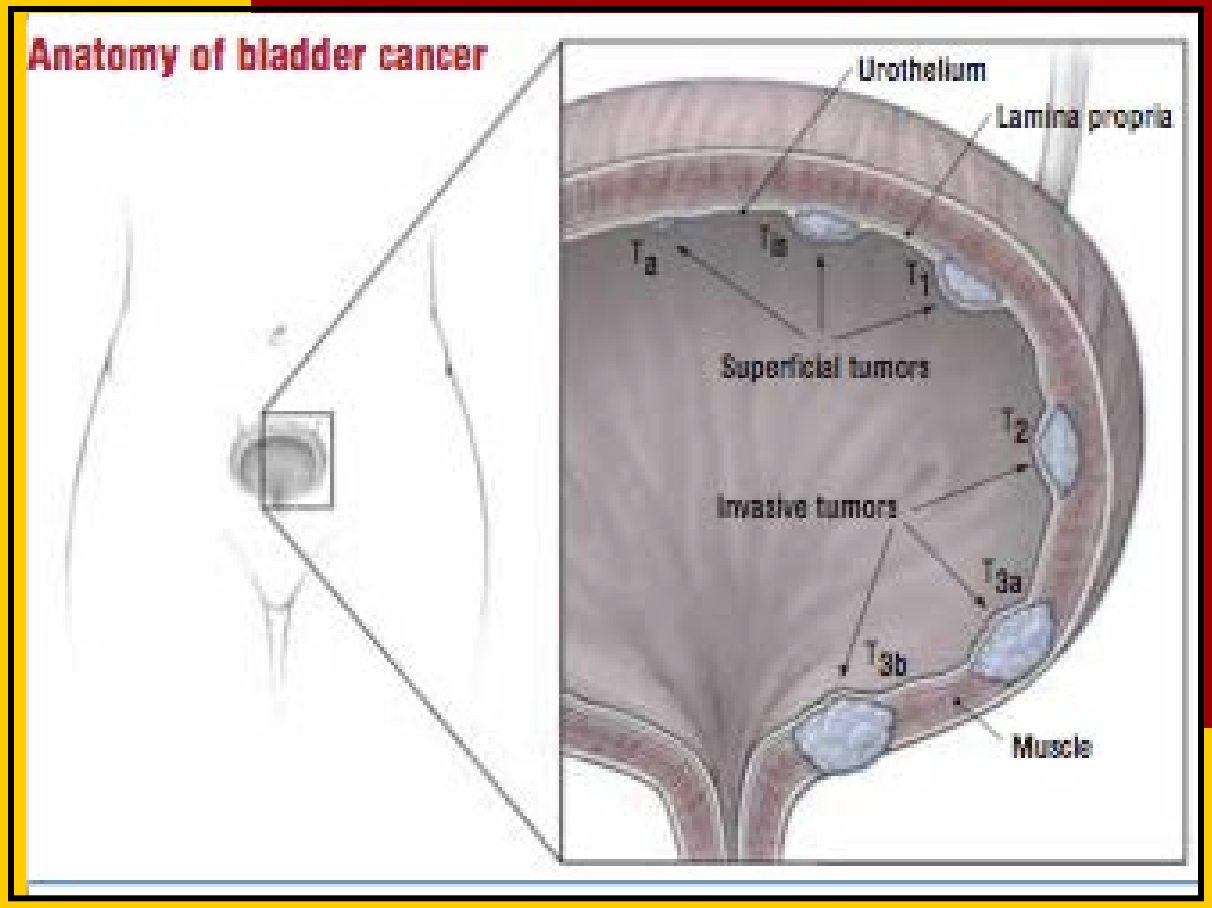
Study cohort of > 37,000 – from 1986-2003

Finding: ***Early menopause increases the risk of bladder cancer*** (confirmed by Harvard U.S. Nurses Health Study)

Women age 42 or younger, experiencing early onset menopause (naturally or surgically), have a 60% greater chance for developing bladder cancer in her lifetime.

"Any time" smoking adds to that risk.

Reproductive risk factors for incident bladder cancer: Iowa Women's Health Study, Anna E. Prizment, Kristin E. Anderson, Bernard L. Harlow and Aaron R. Folsom* Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN. , J. Cancer: 120, 1093–1098 (2006)



Diagnosing Bladder Cancer

Superficial TCC- 80%

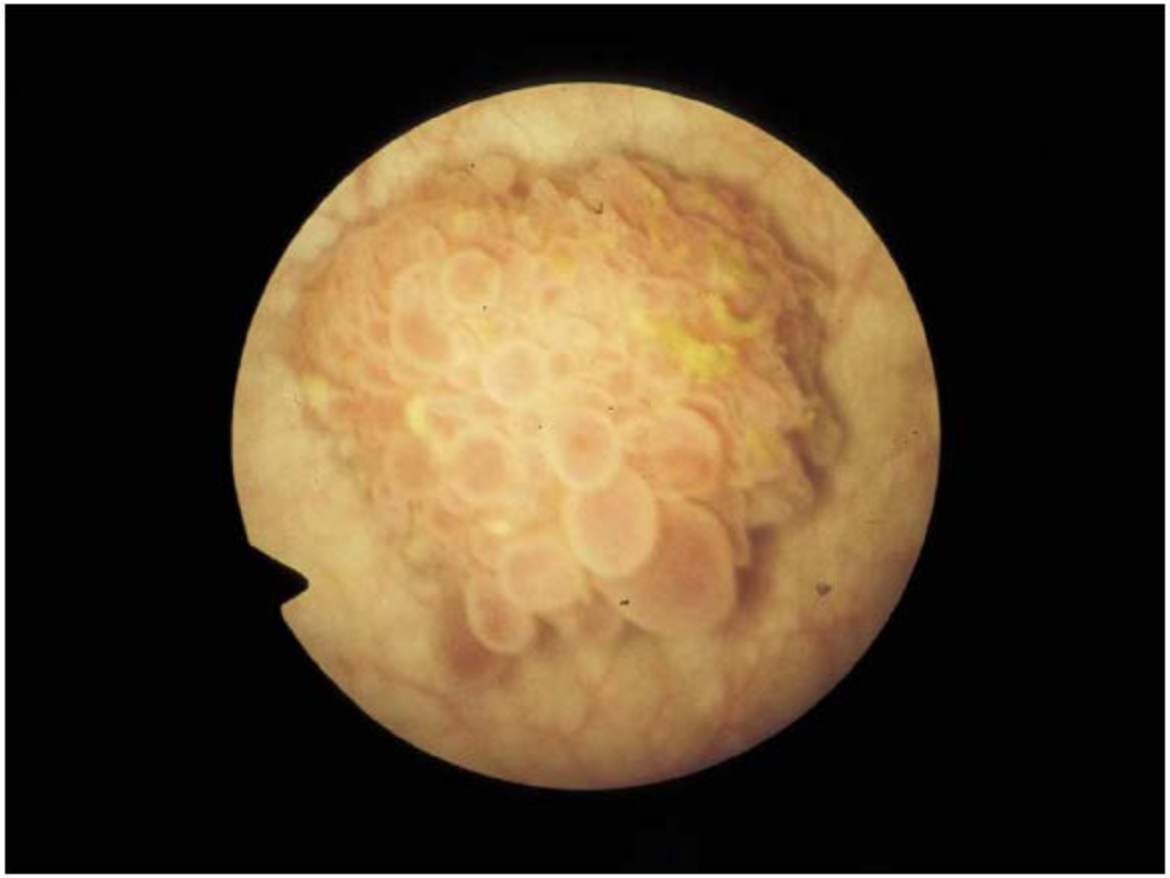


FIGURE 1. *Cystoscopic appearance of low-grade, Ta tumor.*

CIS (Flat Lesion)- 1-2%

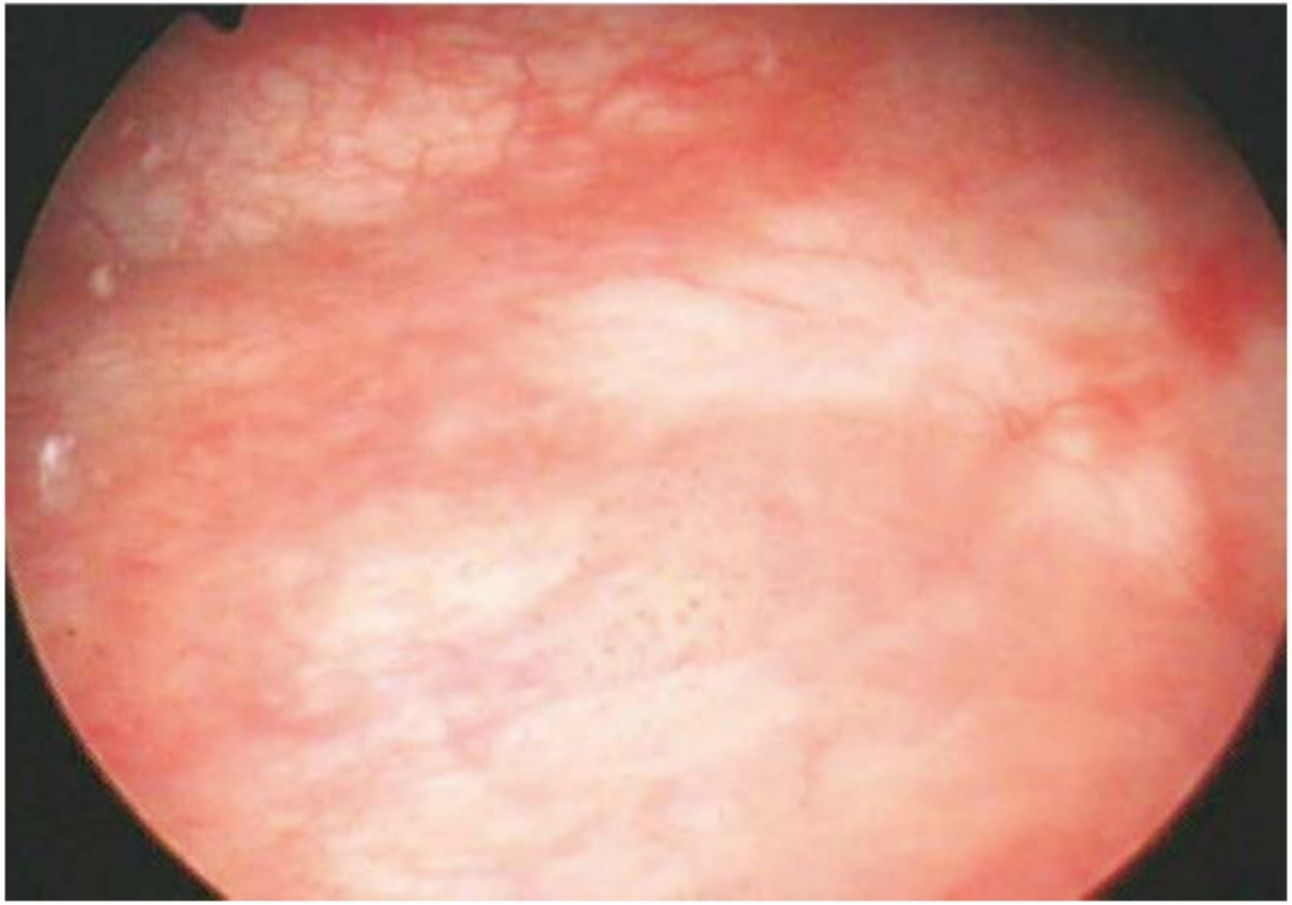


FIGURE 2. *Cystoscopic appearance of carcinoma in situ.*

Invasive Cancer- 20%

Initial Staging

- Bimanual examination –

  ADJUNCTIVE TEST + CYSTOSCOPY

- Urine cytology +/- markers
- Thorough endoscopic evaluation
- Tumor resection (grade and stage)
- Random biopsy procedures including the prostatic fossa
- IVP/RGP
- CT and bone scan. X-ray films as indicated

Adjunctive Test: Cytology

- Sensitivity of urinary cytology is low
  - ranging from 11% - 76%
  - for grade 1-2 tumors sensitivity ranges from 15-30% [1,]
- Requires intact cells
  - Small/low grade less likely to exfoliate cells
- Subjective interpretation
  - Degree of morphologic departure from normal
- Sent to lab, 3-5 days for result

1.Lokeshwar VB et. al. J Urol. 165:1067-1077, 2001

2. 2. Al Suknun et al, Crit. Rev Oncol Haematol 47: 1881-193.2003

NMP22 Test Detects More Than 2X the Cancers as Cytology

SENSITIVITY

Study	N	NMP22 ®	Cytology
Saad, et al BJU International 2002	52	81%	48%
Poulakis et al BJU International 2001	406	85%	62%
Pansy, Zippe et al Journal of Urology 2001	52	89%	31%
Landman et al Urology 1998	47	81%	40%
Miyanaga et al Japan Journal of Cancer 1997	47	86%	50%

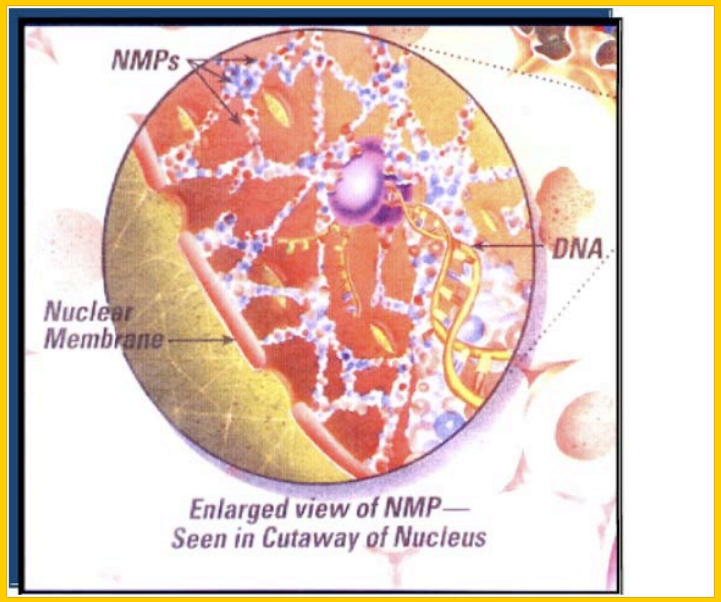
Table 2. Sensitivity of NMP22 Assay and Voided Cytology by Stage and Grade of Cancer (n = 72)

	NMP22 Assay		Voided Cytology	
	No. With Positive Test Result/Total No. With Bladder Cancer	Sensitivity, % (95% CI)	No. With Positive Test Result/Total No. With Bladder Cancer	Sensitivity, % (95% CI)
Stage				
Ta	14/30	46.7 (28.3-65.7)	2/28	7.1 (1.0-23.5)
Tis	4/5	80.0 (28.4-99.5)	3/5	60.0 (14.7-94.7)
T1	13/27	48.2 (28.7-68.1)	5/27	18.5 (6.3-38.1)
T2, T2a	6/6	100 (54.1-100)	2/6	33.3 (4.3-77.7)
T3a, T3b	3/4	75.0 (19.4-99.4)	0/3	0 (0-70.8)
TX	4/7	57.1 (18.4-90.1)	0/7	0 (0-41.0)
Noninvasive: Ta-T1	31/62	50.0 (37.0-63.0)	10/60	16.7 (8.3-28.5)
Muscle invasive: T2-T3	9/10	90.0 (55.5-99.8)	2/9	22.2 (2.8-60.0)
Grade				
Well differentiated	13/27	48.2 (28.7-68.1)	0/25	0 (0-13.7)
Moderately differentiated	9/18	50.0 (26.0-74.0)	3/18	16.7 (3.6-41.4)
Poorly differentiated	18/25	72.0 (50.6-87.9)	9/24	37.5 (18.8-59.4)
GX (grade unknown)	4/9	44.4 (13.7-78.8)	0/9	0 (0-33.6)

Abbreviation: CI, confidence interval.

Grossman, et al, JAMA 2006

NMP22 Antigen
Nuclear matrix proteins (NMPs)



- NMPs are cell type specific and specific for transitional cells in the urinary tract
- Make up the structural framework of the nucleus and are important in gene expression
- Malignant transitional cells contain up to 80X higher concentration of NMP22 protein than normal cells.
- Urine level of NMP22 protein $\geq$ 10 U / ml is associated with a high probability of TCC.

NMP22® BladderChek® Test Point-of-Care Device

Created to identify urine with NMP22 levels above 10 U / ml.

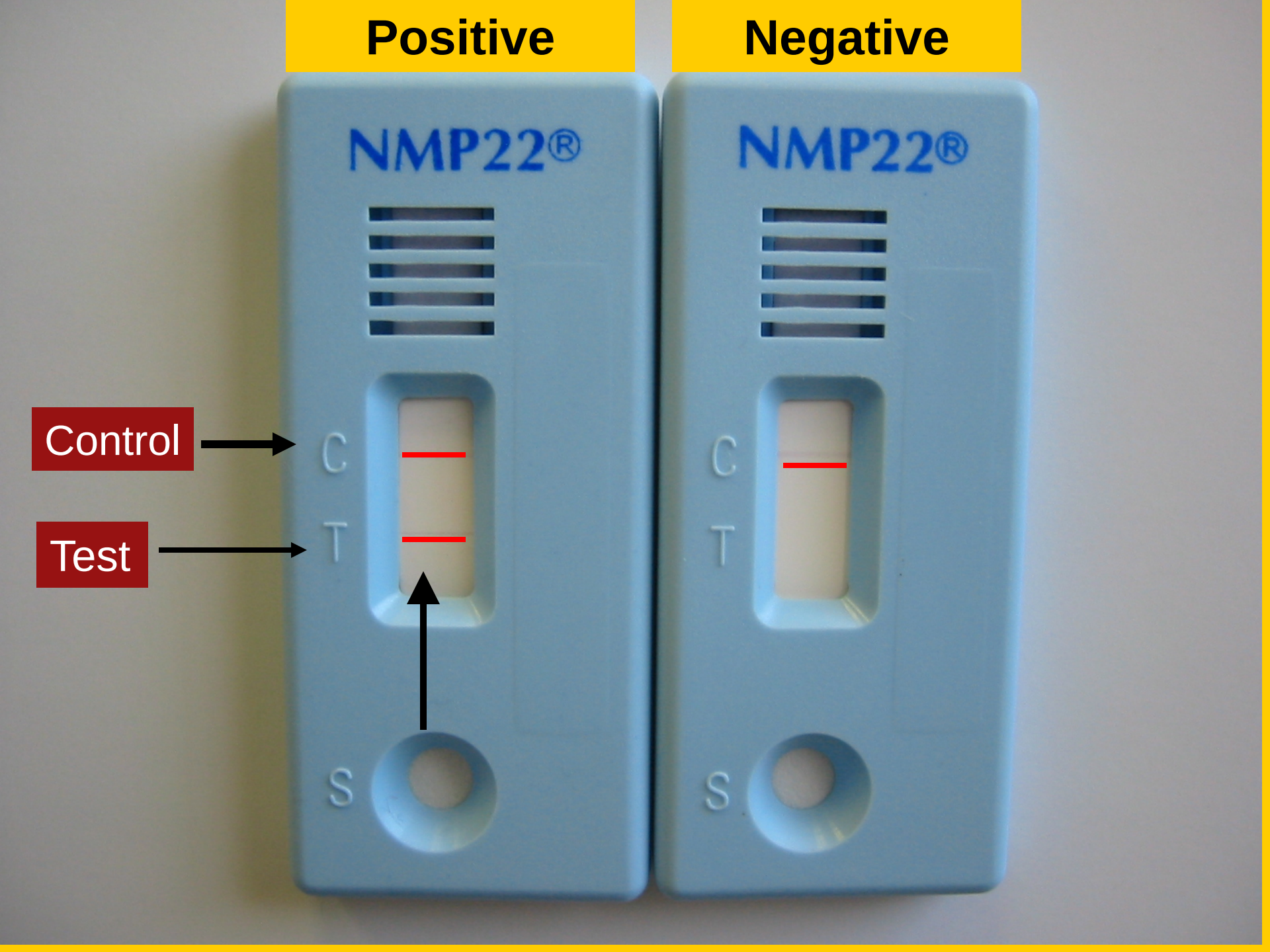
- Can be performed by non-physician staff members (CLIA waived)
- 4 drops of freshly voided urine
- Results available in 30 minutes.
- Built-in quality control
- Low cost
- Easy to read

What do Positive and Negative NMP22 Results tell us?

Positive Result:

- Proceed with diagnostic urologic work-up/referral for suspected bladder malignancy
- Indicates additional testing needed to rule out Bladder Cancer
  - Correlate with dipstick
  - False-positive indicate other etiology of hematuria besides cancer

Negative --- Strong NPV


Positive
Negative
NMP22®
NMP22®
Control
Test
C
T
S
C
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S

Differential Diagnostic Algorithm - UROLOGIST

Pathway #1

NMP22 Test (NEG)
Cystoscopy (NEG)

→

Result: > 99% NPV
Action: Standard Surveillance

Pathway #2

NMP22Test (POS)
Cystoscopy (NEG)

→

Result: Potential undetected cancer
Action: More intensive investigation
- upper tract tests
- follow-up shorter interval

Pathway #3

NMP22Test (POS)
Cystoscopy (POS)

→

Result: Up to 99% cancers detected
Elevated risk muscle invasive and/or high grade cancer
Action: Prioritize for biopsy

Pathway #4

NMP22 Test (NEG)
Cystoscopy (POS)

→

Result: Greater chance non-muscle invasive low grade cancer
Action: Standard biopsy

Pathways to Early Diagnosis

OB-GYNs Can Improve Early Diagnosis; better referrals

Although bladder cancer hasn't been a major focus of gynecological medicine, it is a serious women's health issue.

OB-GYNs see women at a key point for diagnosis, especially in women at-risk.

As primary care for some patients, they also support the surveillance of recurrence.

First step: Differential diagnosis hematuria

- Type of hematuria :

  Gross, microscopic, intermittent

- Repetitive UTIs; kidney stones

- Is it a UTI or not?
  - Culture, positive or negative?
  - How many times treated?

Prompt work-up of hematuria helps diagnose bladder cancer earlier

- 25% of women with bladder cancer are diagnosed with advanced stage tumors
- Mommsen et al. reported 212 pts with bladder cancer; found mean time from initial symptom to treatment was 28 wks
- Front-end hematuria work-up saves time and prioritizes referral for urologic work-up including scheduling cystoscopy

Johnson, Emilie K., Daignault, Stephanie, Zhang,Yingxi, and Lee, Cheryl T. , Patterns of Hematuria Referral to Urologists: Does a Gender Disparity Exist?, UROLOGY 72: 498 –503, 2008.

OB-GYNs accept: Hematuria requires follow-up tests

- The prevalence of asymptomatic microscopic hematuria in postmenopausal women and adult men has been reported to range from 1.0 – 20%
- It is important to determine which patients require urologic studies, consultation, nephrology evaluation, or no intervention

Hematuria Referral to Urology
Does a Gender Disparity Exist? (2 studies)

University Michigan Study: Patterns of urologic referral

Men are 65% more likely to undergo urologic evaluation of hematuria than women

926 health plan insurance records reviewed

Newly diagnosed hematuria (1998-2002)

	559 men		**367 women**
Referred for urologic evaluation of hematuria	**263 (47%)**	**vs.**	**102 (28%)**

Johnson, Emilie K., Daignault, Stephanie, Zhang,Yingxi, and Lee, Cheryl T. , Patterns of Hematuria Referral to Urologists: Does a Gender Disparity Exist?, UROLOGY 72: 498 –503, 2008.

Hematuria: Referral to Urology

Surveyed IM, FP, PC and OB/GYN physicians

- 788 surveys: 270 Miami and 518 Dallas

Referral Rate	Miami	Dallas
Microscopic hematuria	**36%**	**36%**
Gross hematuria	**77%**	**69%**

- OB-GYNs were significantly less likely to obtain imaging studies for their patients with either microscopic or gross hematuria than other medical specialists
- >50% evaluate for infection but only 5%-13% check urinary cytology

Exception to the rule: Absence of Hematuria may not Rule Out Bladder Cancer

- Study of 1,600 women – treated for irritative voiding symptoms, during 1991-2001
- Women with hematuria - cancer rate 1.7%
- Women without hematuria -- 0.45%

Despite presence of hematuria, women are not always evaluated to rule out bladder cancer

- The frequent use of repeat urinalysis may lead to a false sense of security
  - Bladder cancers often will only bleed intermittently
  - Repeat negative UA does not always correlate with the absence of bladder pathology
- 2% to 5% of pts with microscopic hematuria and10% of patients with gross hematuria have UC

Nieder, Alan M., MD, et al, Are patients with hematuria appropriately referred to Urology? A multi-institutional questionnaire based survey, http://dx.doi.org/10.1016/j.urolonc.2008.10.018

Current protocol: Dipstick Urinalysis

- Detects peroxidase activity of hemoglobin
- Convenient, easy to interpret, cost-effective
- Increasingly used over microscopic analysis
- Can be analyzed within minutes of urine collection
- Sensitivity 91-100% and specificity 65-99% for detecting microscopic hematuria
- Primary disadvantage: information may not be very accurate; not quantitative

Dipsticks: Screening for bladder cancer

This study supports bladder cancer screening; suggests screening shifts the diagnosis of high-grade tumors to pre-invasive stages, where treatment and bladder cancer outcomes are more favorable.

Study highlights: **1,575 pts (age > 50 years)**

home screening dipstick for hematuria

mean follow-up 14 yrs

	Unscreened	Screened
Muscle-invasive BC	**60%**	**10%**
Mortality/bladder cancer	**20%**	**0%**
Overall mortality	**74%**	**43%**

Adding NMP22 BladderChek Test to OB-GYN protocol

Dipstick + NMP22	Greater sensitivity Higher Confidence Low cost
Expedite referral	Gross and microscopic hematuria
Clarify high-risk for follow-up	Age, smoking history Occupational risk Environmental exposure
Differential Diagnosis	Repetitive UTI; hematuria
Provides valuable Diagnostic info	False positives can be indicators of other pathology

Detecting Bladder Cancer in Women with the NMP22 BladderChek Test

Multi-center Study (23 sites): 572 women; 93% hematuria; 33% smokers, analyzed by M. Ross, OB/GYN UCLA; G. Katz, urologist

Key findings:

- 3.6% women with hematuria diagnosed with bladder cancer
- Cytology has poor sensitivity for early-stage cancers
- NMP22 BladderChek Test can improve diagnosis and increase appropriate referral
- Other symptoms and risks factors include dysuria, smoking and history of, occupation or environment exposures chemicals

Ross, et al, Evaluation Of A Point-of-Care Assay For Detection of Bladder Cancer in Women At Risk, Society for Gynecologic Investigation (SGI), Scientific Poster 332

Ross et al. continued

NMP22 BladderChek Test

- Detected 53% malignancies
- 100% of the high grade and muscle invasive tumors
- Positive for 7 lesions that required biopsy for diagnosis:

  3 squamous metaplasia,

  1 amyloid nodule

  3 interstitial cystitis, to rule out carcinoma in situ

Ross, et al, Evaluation Of A Point-of-Care Assay For Detection of Bladder Cancer in Women At Risk, Society for Gynecologic Investigation (SGI), Scientific Poster 332

Review: Expanding Pathways Early diagnosis using NMP22

NMP22 BladderChek Test can help guide next steps in the diagnostic process

If a patient presents with UTI;
gross or microscopic hematuria:

- History of repetitive UTIs; antibiotic regiment
- Assessment of risk factors (smoking, etc.)
- Differential diagnosis of hematuria

The NMP22 can be used as an aid for an initial screen and to help improve the timeliness of a more extensive urologic work-up

NMP22 BladderChek Test Adds Value in the OB-GYN Office

NMP22 test is ideal for OB-GYNs

- High confidence level of NPV
- If it is positive, expedite referral for further urologic work-up
- Inexpensive test that provides point-of-care reliable information
- Can improve early diagnosis and save lives

Thank you.

Questions?