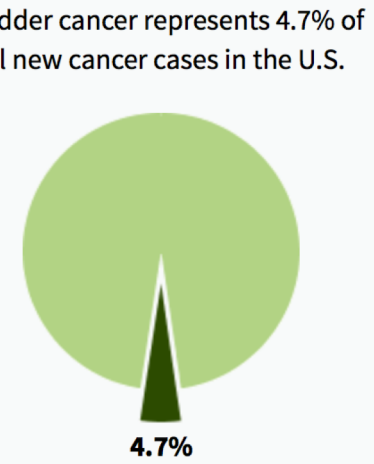
Bladder Cancer Screening

Why Screen?

- Major global health problem
  - 500,000 new cases
  - 200,000 deaths annually
- Major U.S. health problem
  - 81,190 new cases
  - 17,240 deaths annually

	Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1.	Breast Cancer (Female)	266,120	40,920
2.	Lung and Bronchus Cancer	234,030	154,050
3.	Prostate Cancer	164,690	29,430
4.	Colorectal Cancer	140,250	50,630
5.	Melanoma of the Skin	91,270	9,320
6.	**Bladder Cancer**	**81,190**	**17,240**
7.	Non-Hodgkin Lymphoma	74,680	19,910
8.	Kidney and Renal Pelvis Cancer	65,340	14,970
9.	Uterine Cancer	63,230	11,350
10.	Leukemia	60,300	24,370



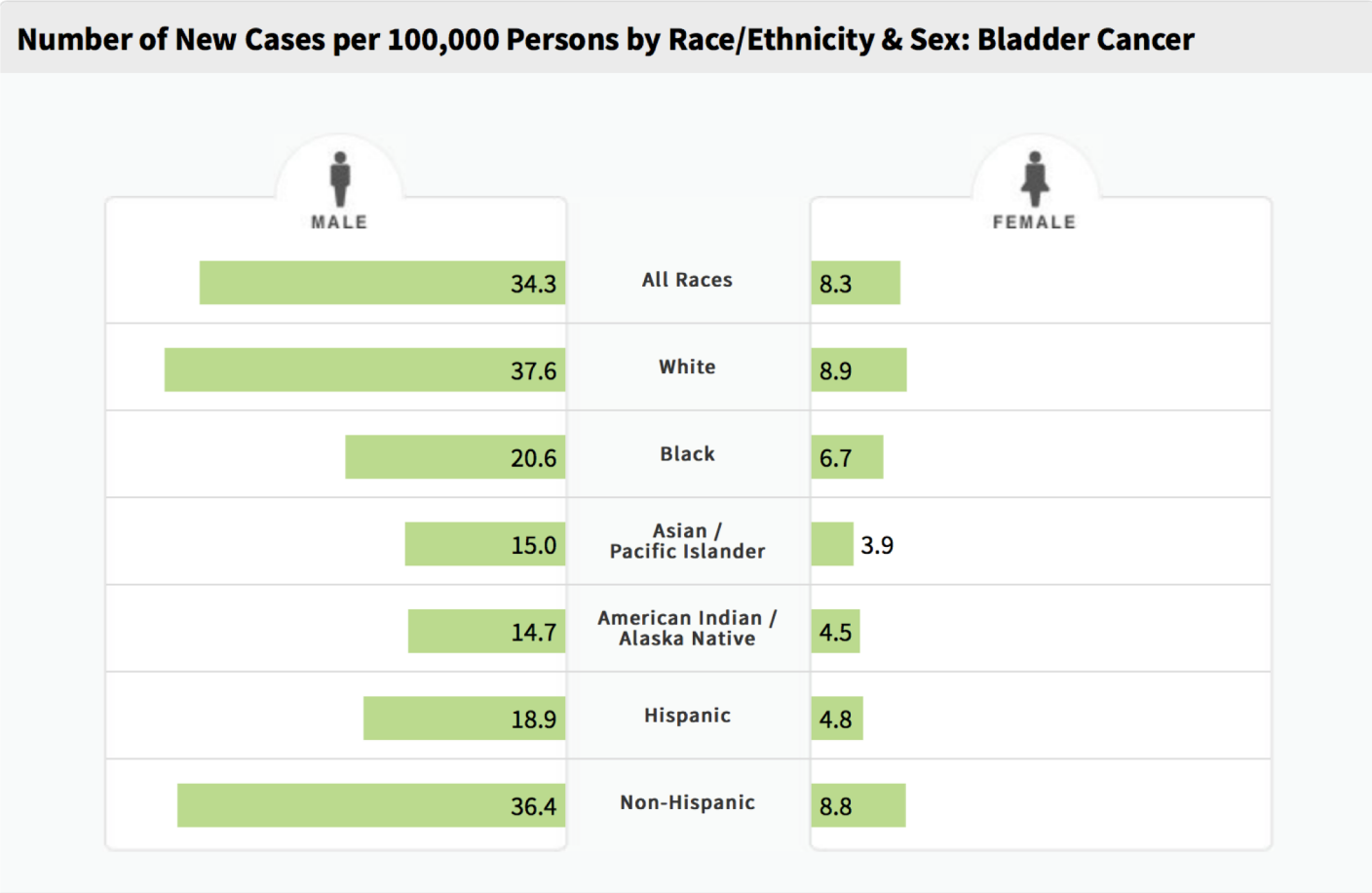
https://seer.cancer.gov/statfacts/html/urinb.html

Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al.. JAMA Oncol 2017; 3:524

Why Screen in the U.S.?

- Top 10 most common cancers
- Incidence: 3:1 male:female
- 4th most common in men
- 9th most common in women
- Lethal: 3% of all cancer deaths

Screening could identify high grade cancers at earlier stages and allow for more effective treatment



https://seer.cancer.gov/statfacts/html/urinb.html

Another reason to screen…$$$….

Table 1 – Cost of bladder cancer care*

	United States†	United Kingdom [72]	Sweden [86]	Germany [46]	Italy [87]
Office cystoscopy	163	520	165		
TURBT	4348	2362	2200	2500	2242
Single dose of MMC 40 mg	219	87	–	–	–
BCG 6 wk	528	630	–	–	975
Cystectomy	23 451	8090	20 570	15 419‡	7222

BCG = bacillus Calmette-Guérin; MMC = mitomycin C; TURBT = transurethral resection of bladder tumor.

* Costs are shown in euros.

† US Medicare rates.

‡ As reported by Stenzl et al. [88].

- Bladder cancer: Most expensive cancer to treat from diagnosis to death
- In 2010, bladder cancer cost the U.S. health care system $4 billion, and is expected to reach $5 billion by 2020

Svatek et al, Eur Urol, 2014, 66, 253-62

What Would Make an Ideal Urine Marker?

- Non-invasive and technically simple
- Highly specific and sensitive
- Affordable
- Reliable and reproducible
- Reduces need for other tests
- Clinically relevant

Possible Uses for Urine Markers

- Hematuria
  - Initial screening test—would want very good negative predictive value
  - Very inexpensive, point of care test
  - Types—would it make a difference?
    - Asymptomatic vs. Symptomatic
    - Microhematuria vs. Gross Hematuria
- Surveillance for Bladder Cancer
  - Recurrence
  - Progression
  - Arbitrate for Atypical Cytology
  - Upper and lower tract detection
  - Anticipatory positive

Who to Screen: Risk factors

- Modifiable Risk Factors
  - Smoking
    - NIH-AARP Diet and Health cohort
    - Current/former smokers
    - Current smokers RR of bladder cancer 4-5x higher than non-smokers
    - Risk never totally abates for formers smokers

Table 2. Incidence Rates and Adjusted HRs for Cigarette Smoking and Bladder Cancer by Sex

	Men				Women			
Category	Person-Years	No.	Age-Standardized Incidence Rates per 100 000 Person-Years (95% CI)	Multivariate-Adjusted HR (95% CI)[a]	Person-Years	No.	Age-Standardized Incidence Rates per 100 000 Person-Years (95% CI)	Multivariate-Adjusted HR (95% CI)[a]
Never smoked cigarettes, pipes, or cigars	677 607	461	69.8 (63.4-76.1)	1.00 [Reference]	821 064	133	16.1 (13.4-18.8)	1.00 [Reference]
Never smoked cigarettes but smoked pipes or cigars	148 810	143	92.5 (77.3-107.7)	1.29 (1.07-1.56)	635	0	NA	NA
Former smoker (overall)[b]	1 540 789	2483	154.6 (148.5-160.7)	2.14 (1.92-2.37)	705 925	288	40.7 (36.0-45.5)	2.52 (2.05-3.10)
Stopped ≥10 y ago	1 237 120	1850	140.2 (133.8-146.7)	1.93 (1.73-2.14)	499 493	171	33.6 (28.6-38.6)	2.08 (1.65-2.61)
Stopped 5-9 y ago	197 325	394	206.9 (186.4-227.4)	2.85 (2.49-3.27)	127 140	69	55.7 (42.5-68.9)	3.49 (2.61-4.67)
Stopped 1-4 y ago	106 344	239	243.3 (212.2-274.4)	3.32 (2.84-3.89)	79 292	48	65.2 (46.7-83.7)	3.97 (2.85-5.53)
1-10 cigarettes/d	314 144	309	96.6 (85.8-107.3)	1.33 (1.15-1.55)	273 297	80	29.4 (22.9-35.8)	1.80 (1.36-2.38)
11-20 cigarettes/d	476 611	709	142.3 (131.8-152.8)	1.90 (1.68-2.15)	214 073	88	41.2 (32.6-49.8)	2.50 (1.91-3.27)
21-30 cigarettes/d	324 709	596	180.4 (165.9-194.9)	2.40 (2.11-2.72)	110 881	66	61.1 (46.3-75.9)	3.75 (2.78-5.04)
31-40 cigarettes/d	222 928	448	197.4 (179.1-215.7)	2.62 (2.29-2.99)	63 451	29	46.8 (29.7-63.9)	2.86 (1.91-4.28)
>40 cigarettes/d	202 397	421	205.7 (186.1-225.4)	2.71 (2.36-3.10)	44 223	25	60.4 (36.6-84.3)	3.65 (2.38-5.60)
Current smoker (overall)[b]	323 114	809	276.4 (256.9-295.8)	3.89 (3.46-4.37)	300 996	206	73.6 (63.4-83.8)	4.65 (3.73-5.79)
1-10 cigarettes/d	66 437	131	204.5 (169.4-239.6)	3.11 (2.54-3.80)	94 120	53	58.3 (42.5-74.0)	3.81 (2.76-5.25)
11-20 cigarettes/d	120 202	319	281.9 (250.7-313.1)	4.14 (3.56-4.81)	127 433	88	72.2 (57.0-87.4)	4.78 (3.64-6.27)
21-30 cigarettes/d	75 950	204	295.4 (253.9-336.8)	4.34 (3.66-5.16)	53 174	44	88.6 (62.0-115.2)	5.93 (4.20-8.37)
31-40 cigarettes/d	43 407	113	283.1 (228.6-337.6)	4.33 (3.50-5.35)	20 666	17	98.3 (49.3-147.3)	6.02 (3.62-9.99)
>40 cigarettes/d	17 118	42	271.5 (185.3-357.7)	4.14 (3.00-5.70)	5605	4	66.4 (0-132.9)	5.19 (1.92-14.05)

Friedman et al, JAMA, 2011, 306(7), 737-45

Who to Screen: Risk Factors

- Modifiable Risk Factors
  - Smoking
  - Occupational exposure to carcinogens
    - 16-23% higher RR
    - Risk persists for 30 years after exposure

Occupational Exposures	
Aromatic hydrocarbons	**Examples**: benzo[a]pyrene, benzene, coal tar, bitumens, diesel exhaust **Uses**: industrial chemistry, asphalt **Occupations**: metal processing, truck drivers, oil and coal production
Aromatic amines	**Examples**: 2-toluidine, 2-naphthylamine, 4-aminobiphenyl, aniline **Uses**: dyes **Occupations**: textiles, painter, hairdresser, chemical plant
N-nitrosamines	**Examples**: N′-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl), 1-butanone **Uses**: rubber, tobacco curing, preservative **Occupations**: smokers, rubber and latex manufacturing
Other	**Examples**: formaldehyde

https://university.auanet.org/core/img/76_table1.png

Who to Screen: Risk Factors

- Modifiable Risk Factors
  - Smoking
  - Occupational exposure to carcinogens
  - Other
- Non-modifiable Risk Factors
  - Lynch Syndrome
  - Family History
    - PLCO Cohort
    - <2% of all bladder cancers

	Training set N=49,873	Validation set N=99,746
Age at randomization	62 (58, 67)	62 (58, 67)
Female	25,348 (51%)	50,666 (51%)
Married	37,717 (76%)	75,193 (75%)
White race	44,139 (89%)	88,104 (88%)
Number of comorbidities		
0	14,752 (30%)	29,645 (30%)
1	16,262 (33%)	32,162 (32%)
2	10,794 (22%)	21,438 (21%)
3+	8,065 (16%)	16,501 (17%)
Smoking history (pack years)		
0 (non-smoker)	23,664 (47%)	47,356 (47%)
1-10	4,766 (10%)	9,491 (10%)
10-20	4,995 (10%)	9,846 (10%)
20-30	3,915 (8%)	7,711 (8%)
30+	12,533 (25%)	25,342 (25%)
Family history of bladder cancer	901 (2%)	1,769 (2%)
Invasive or high grade bladder cancer	264	506.

Vickers et al, Cancer, 2013, 119(1), 143-49

Who to Screen?

- While many patients have risk factors, many patients diagnosed with bladder cancer don’t have identifiable risk factors
- This raises the prospect of screening the general population

Who to Screen: General Population

- Trials of bladder cancer screening general population
  - Messing Study
    - Not randomized
    - Screened n = 1575
      - >50 years
      - Hematuria dipsticks for 14 consecutive days followed cystoscopy if positive
      - Repeated at 9 months if dipsticks negative
    - 16% hematuria, 1.6% Bladder Ca
    - Unscreened n = 509
      - State registry data

TABLE III. *Comparison of grades and stages of bladder cancers diagnosed in Wisconsin men age 50 years and older in 1988 versus those of bladder cancers detected by hematuria home screening*

Bladder Cancer Grade and Stage	Unscreened: New Cases		Screened: New Cases	
	No.	%	No.	%
Low-grade (1,2) superficial (Stage Ta, T1)	290*	56.8	11*	52.4
High-grade (3) superficial (Stage Ta, T1, TIS)	99†	19.4	9†	42.9
Muscle invasive or greater (Stage T2-4 or N+ or M+)	122‡	23.9	1‡	4.8
Totals	511	100.0	21	100.0

*Low-grade superficial unscreened (290 of 511) versus screened (11 of 21) P >0.20.
†High-grade superficial of all high-grade and/or invasive tumors unscreened (99 of 221) versus screened (9 of 10) P = 0.007.
‡Invasive of all high-grade and/or invasive tumors unscreened (122 of 221) versus screened (1 of 10) P = 0.007.

TABLE IV. *Mortality from bladder cancer in all Wisconsin men age 50 and older with bladder cancer diagnosed in 1988 versus those with bladder cancer detected by hematuria home screening*

Bladder Cancer Grade and Stage	Unscreened: Mortality Within 24 Months of Diagnosis		Screened: Mortality Anytime After Diagnosis (30 to 102 Months Follow-up)	
	Number of Deaths All Cases	%	Number of Deaths All Cases	%
Low-grade (1,2) superficial (Stage Ta, T1)	5/290	1.7	0/11	0
High-grade (3) superficial (Stage Ta, T1, TIS)	12/99	12.1*	0/9	0*
Muscle invasive or greater (Stage T2-4 or N+ or M+)	67/122	54.9*	0/1	0*
Overall rates	84/511	16.4†	0/21	0

*Disease-related mortality in men with high-grade or invasive bladder cancers in unscreened (35.7%) versus screened (0) P = 0.014.
†Disease-related mortality in all bladder cancer cases unscreened (16.4%) versus screened (0) P = 0.025.

Messing et al, Urology, 1995, 45, 387-96

Who to Screen: General Population

- USPSTF Recommendations for bladder cancer screening in the non-risk stratified general population
  - Insufficient evidence to recommend

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Chou et al, Ann Intern Med, 2010, 153, 461-8

Who to Screen: Occupational High Risk

- Numerous studies have evaluated detection rates of screened individuals with occupational exposures to aromatic amines or polycyclic aromatic hydrocarbons

- Prevalence in all range from 0-1.6%

- Sample sizes small, not limited to workers with highest risk exposures, complete exposure histories are limited

Larre et al, Eur Urol, 2013, 63, 1049-58

Who to Screen: Defining the Most At-Risk

- Vickers Study
  - Decision analysis of patients in PLCO based on the prevalence of HG or MIBC
    - N = 149,619
    - Age range 55-75

Variable		Assignment
Age >65		2 points
Smoking pack-years	10-19	2 points
	>20	4 points
Male		4 points
+ Family History		1 point

Vickers et al, Cancer, 2013, 119(1), 143-49

Who to Screen: Defining the Most At-Risk

- Vickers Study
  - Decision analysis of patients in PLCO based on the prevalence of HG or MIBC
    - N = 149,619
    - Age range 55-75
  - Results
    - Screening ~25% of population (Risk Score > 6)
      - Prevents 57 HG or MI bladder cancers
      - Screening all prevents only an additional 38

Screening strategy	Percentage of patients screened	Sensitivity	Specificity	Number of patients per 100,000 with event within 5 years (reduction in event rate from screening none)			
				Relative Risk			
				0.50	0.60	0.70	0.80
None	0.0%	0.0%	100.0%	238 (0%)	238 (0%)	238 (0%)	238 (0%)
Risk * Score > 8	8.4%	28.8%	91.7%	204 (14%)	211 (12%)	218 (9%)	224 (6%)
Risk * Score > 6	23.4%	59.8%	76.7%	167 (30%)	181 (24%)	195 (18%)	210 (12%)
All	100.0%	100.0%	0.0%	119 (50%)	143 (40%)	167 (30%)	190 (20%)

Vickers et al, Cancer, 2013, 119(1), 143-49

Who to Screen: Defining the Most At-Risk

- Vickers Study
  - Using this decision analysis, how many people would need to be enrolled in a clinical trial to assess the relative risk of screening?

Power calculations for various trials scenarios. The columns give the sample size requirements for detecting different relative risks of screening.

Relative risk	0.60		0.70			0.80
	N for trial with 80% power	N assessed for eligibility	N for trial with 80% power	N assessed for eligibility	N for trial with 80% power	N assessed for eligibility
Risk Score* > 8	20,268	242,027	37,610	449,114	88,152	1,052,653
Risk Score*> 6	27,338	116,682	50,734	216,539	118,930	507,608
All	69,934	69,934	129,812	129,812	304,368	304,368

80% chance of HG or MIBC who have a score >6, have to assess 507,000 patients and enroll 119,000 in the study

Vickers et al, Cancer, 2013, 119(1), 143-49

How to Screen?

Urinalysis and Biomarkers

How to Screen: the Urine Dipstick Test

- Urine dipstick is designed to detect microscopic hematuria
  - It is the most common screening method in utilization
    - Cheap
    - Easy to perform
    - Automated
  - Sensitivity/Specificity = 91%/99% *for hematuria*, **not bladder cancer**
    - Common finding in the general population
- Home Screening for Hematuria Study (Messing, JUrol, 1992)
  - 16-24% of men >50 have microscopic hematuria, not all have cancer
  - 32% of bladder cancer patients did not have hematuria

Cytology

- Most common; adjunct to cystoscopy
- Available since the 1940s
- Non-invasive, sensitive for high grade tumors (80-90%) and highly specific (90%+) for high grade tumors
- So why move beyond it?
  - Low sensitivity for low grade tumors
  - Dependent on expertise of cytopathologist
  - Range of results

Cytology: Not Useful for Microhematuria

urine cytology is less sensitive than cystoscopy in the detection of bladder cancer (48% vs. 87%),[15] and the AUA guideline no longer recommends it as part of the routine evaluation of microscopic hematuria.[6] Reasons for this include test interpretation subjectivity, a wide variation in what is considered abnormal, and unnecessary and costly workups resulting from diagnoses such as atypical cytology.[42-44] However, in patients with risk factors for carcinoma in situ (e.g., irritative voiding, tobacco use, chemical exposures), cytology may still be useful.[6,45] There are new, rapid urinary

Cytology: Not Very Useful for Bladder Cancer

Non-Muscle Invasive Bladder Cancer

American Urological Association (AUA)/
Society of Urologic Oncology (SUO) Guideline

Urine Markers after Diagnosis of Bladder Cancer

9. In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

10. In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)

11. In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)

New or Emerging in Urine Markers

AssureMDx – Discovery Study

- DNA methylation of three genes:
  - TWIST1, ONECUT2, and OTX1
- Mutation analysis of three genes:
  - FGFR3, TERT, and HRAS

- 154 hematuria patients (74 with bladder cancer)
- AUC 93%
- Sensitivity 97%, Specificity 83%
- PPV 23%, NPV 99.9%

van Kessel et al; J Urol 2016

AssureMDX –Validation

- Prospective study at three centers
- n=200 hematuria (n=97 with bladder cancer)
- AUC 96%
- sensitivity: 93% specificity: 86%
- PPV: 25.7% NPV: 99.6%

(assuming 5% prevalence of BCa in hematuria population)

- 81.7% reduction in diagnostic cystoscopy
- North American multicenter prospective validation in 700 patients ongoing

Cx-Bladder

- quantitative PCR to measure 5 mRNA:
  - MDK, HOXA13, CDC2, IGFBP5, CXCR2

Triage

incorporate patient risk profile
(age, sex, smoking, exposures, characteristics of hematuria)

Detect

qPCR panel alone in high risk patients: gross hematuria + risk factors

Monitor

surveillance of patients with prior NMIBC

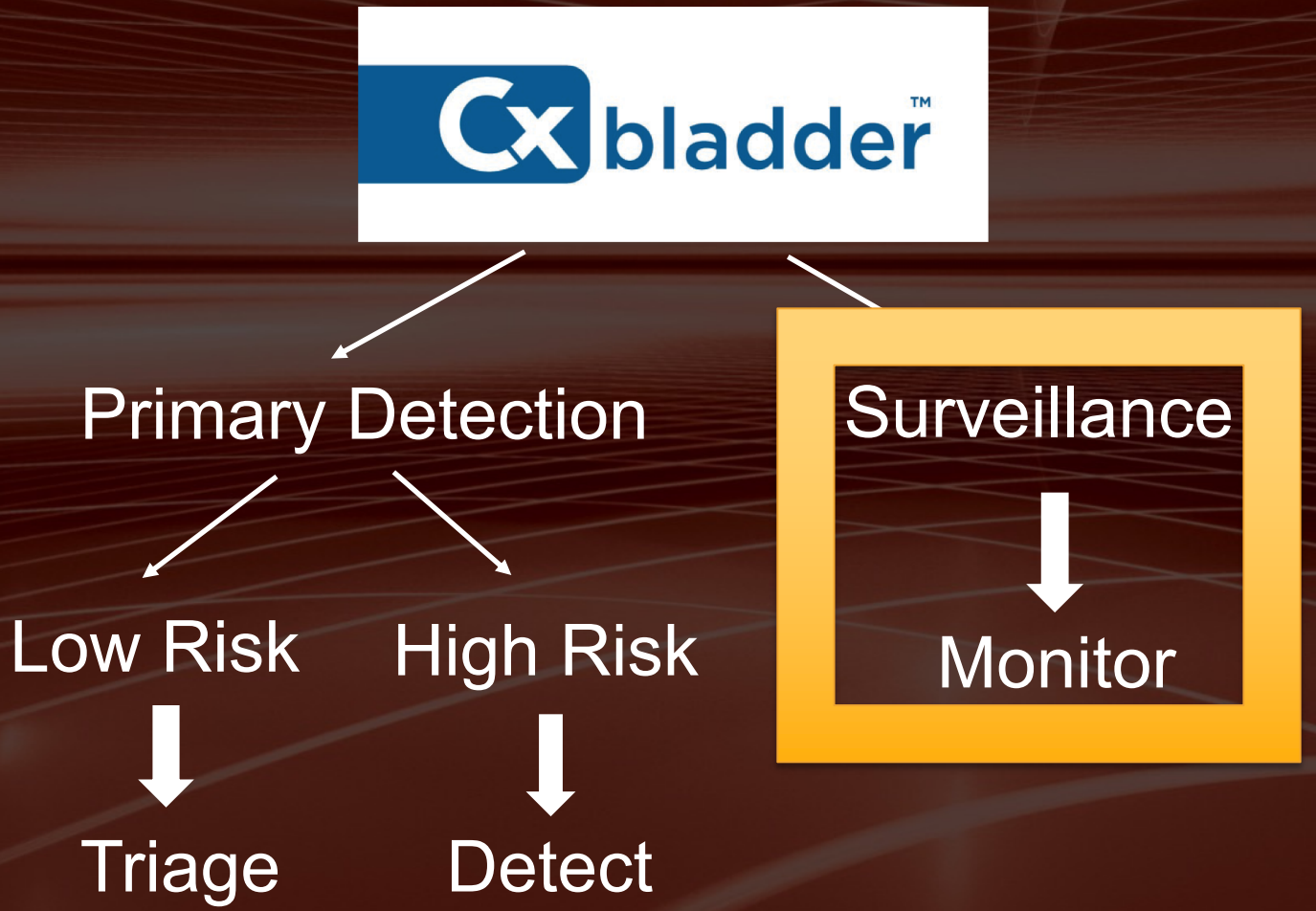
Pacific Edge Diagnostics

Cxbladder

- Measures the gene expression of 5 biomarkers
  - **Multiplex mRNA (uRNA)**
    - CDC2(CDK1)- Mitotic cell division
    - HOXA13- Morphogenesis differentiation of GU tract
    - MDK- Angiogenesis, cell migration and proliferation
    - IGFBP5- Anti-Apoptic
    - CXCR2- cell neutrophil mediator (inflammatory)-reduce false +, and to stratify patients
- Sensitivity of 83%
- Specificity of 85%

O'Sullivan P, et al. J Urol (2012) 188(3), 741

Cxbladder: Clinical Utility



Cxbladder Monitor: Validation

- Prospective study
- 763 patients with prior NMIBC, pre-cystoscopy
  - training (n=339) and validation (n=424) cohorts
- Algorithm includes previous tumor occurrence information
- Sensitivity 93%
- NPV 97%

Kavalieris L, et al. J Urol 2016; 197:1419

Cxbladder Monitor: Validation

- Cxbladder Monitor
  - Sensitivity of 0.93 and NPV 0.97
- Sensitivity was 0.95 for all high risk for progression
  - T1 or higher, all high grade
- Sensitivity was 0.85 for all low grade disease
- Subgroup analysis revealed good performance for patients treated within 6 months with BCG

Kavalieris L, et al. J Urol 2016; 197:1419

Cxbladder Monitor: Comparison

	Sensitivity	NPV
Cxbladder	**0.91**	**0.96**
Cytology	0.22	0.87
NMP 22 ELISA	0.27	0.87
NMP 22 BladderChek®	0.12	0.87
UroVysion® FISH	0.33	0.92

Cxbladder Monitor is an effective rule out test with high sensitivity (91%) and high NPV (96%)

Lotan Y, et al. Urol Oncol: Seminars and Original Investigations (2017)

Comparison Urinary Biomarkers

Biomarker	Overall Sensitivity (%)	Overall Specificity (%)	Sensitivity for high grade cancer (%)	Point of Care
Cytology	20-70	60-100	30-100	NO
UroVysion™ (FISH)	30-86	63-95	66-70	NO
Microsatellite analysis	58-92	73-100	90-92	NO
Immunocyt™	52-100	63-79	62-92	NO
NMP-22™	47-100	55-96	75-92	YES
BTA stat™	29-83	55-86	62-91	YES
CxBladder™	82	85	97	NO
FGFR3/CertNDx™	50-56	>90		NO

Urinary Biomarkers: Guidelines

		AUA	NCCN	EAU
With suspicion of cancer		cytology	cytology	cytology
Followup of cancer Low grade		Not specified	Not recommend	Not specified
Followup of cancer High grade		Not specified	cytology Option: urinary biomarker	cytology

Barriers to Screening

- Many bladder cancer patients don’t have any risk factors to target for screening
  - Smoking: risk factor in 50-65% of men, 20-30% of women with bladder cancer
  - Occupational exposure only in 4% of bladder cancers
- To detect the rest, need a general population screening initiative
- Many of the markers are sensitive/specific in the *symptomatic* or *previously diagnosed* bladder cancers
  - Need enhanced operating characteristics to detect smaller, earlier tumors

Rationale not to Screen

- No RCTs to evaluate the effectiveness of screening in preventing bladder cancer mortality or limiting morbidity from tx of early disease
- Prospective studies confirm low PPV for screening in older men at average risk
- Studies of screening in populations of industrial workers at high risk for bladder cancer confirm that screening can identify noninvasive bladder cancer, but it is not known whether screening has an impact on disease outcome

Recommendations of Expert Groups

- **No** major organization recommend screening for bladder cancer in asymptomatic non-high-risk adults, noting insufficient evidence about screening
- USPSTF (2011) revised recommendation conclude that current evidence is insufficient to assess the benefits or harms of screening
- American Academy of Family Physicians supports the recommendation of USPSTF
- NCI notes inadequate evidence to determine whether screening would impact mortality and fair evidence that screening would result in unnecessary procedures with associated morbidity
- International Consultation on Urologic Diseases (ICUD) - (EAU) 2012 notes that there is insufficient evidence of impact of screening on survival
- American Cancer Society does not include screening for bladder cancer on its list of recommended cancer screening

Future Perspectives

- Need screening tests that detect small, high grade tumors with high risk of progression
- Develop genetic tests with a variety of targets to overcome the heterogeneity of abnormalities
- Holy grail: a screening test to identify *pre-malignant* bladder lesions
- Still need a large study of screening in high-risk individuals, all of whom receive a cystoscopy/biopsy