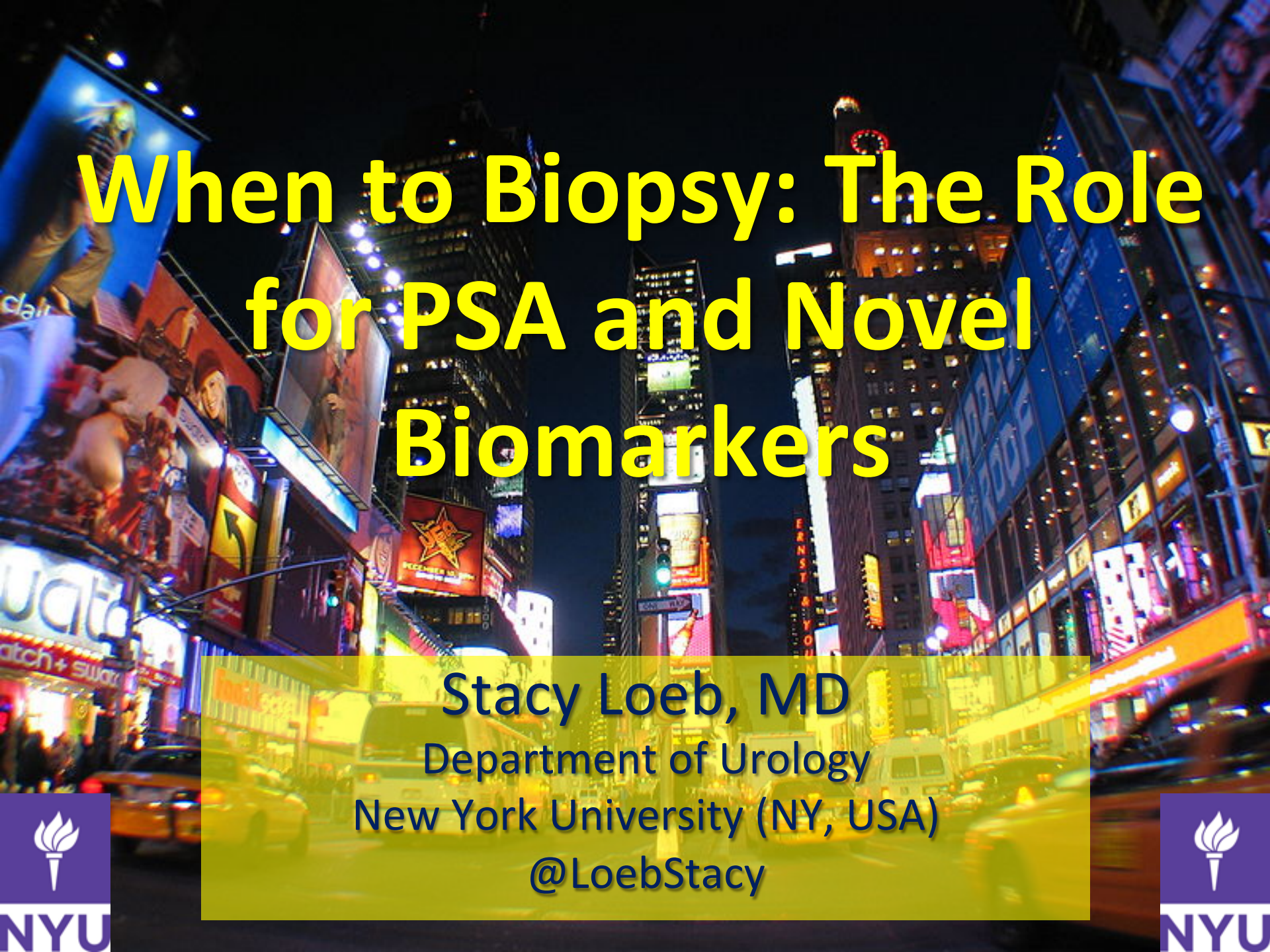

When to Biopsy: The Role for PSA and Novel Biomarkers

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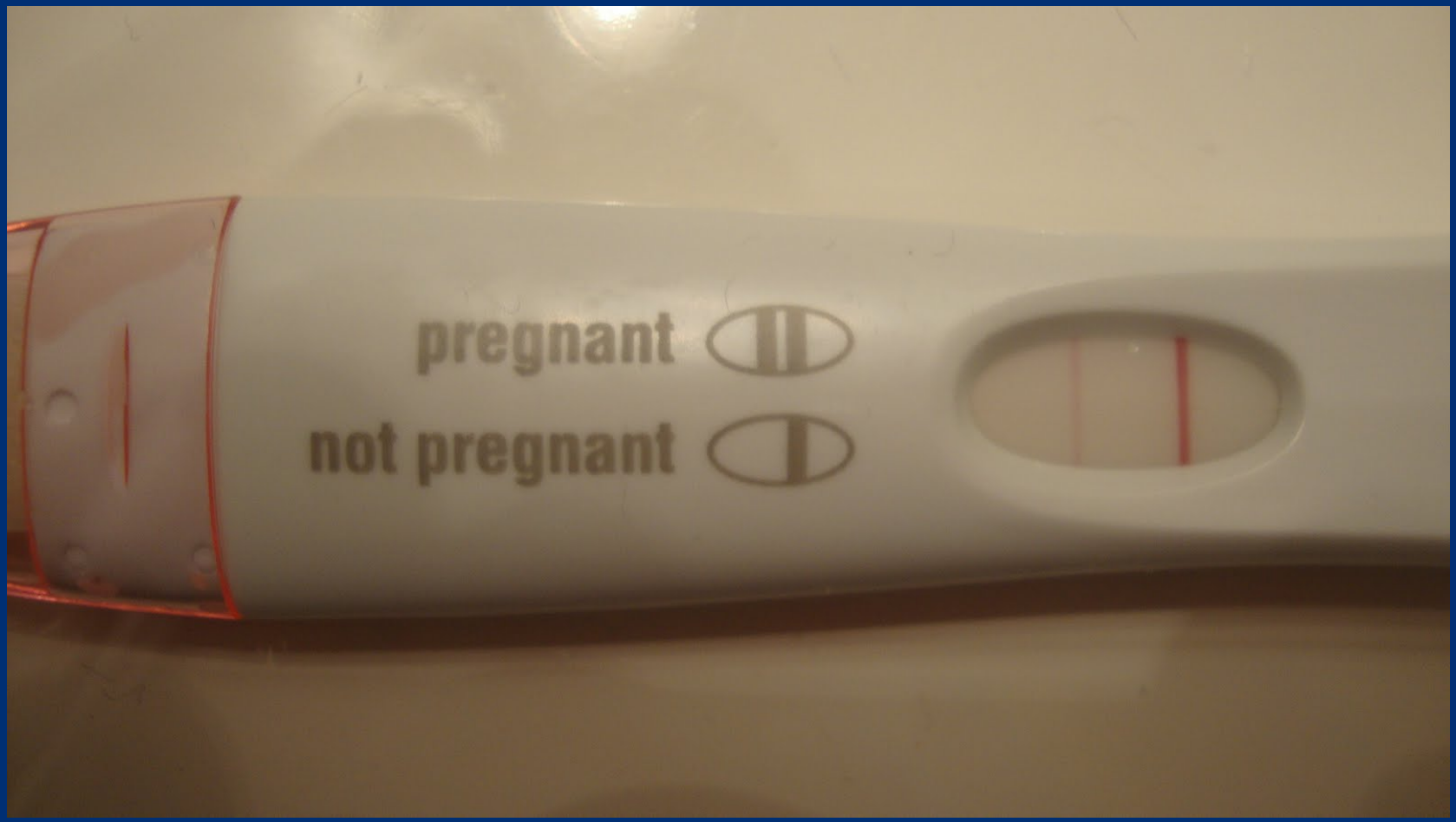
Total PSA Threshold for Biopsy (1990's)

- FDA approved as an aid to early prostate cancer detection in 1994 using a threshold of 4 ng/ml

- Total PSA thresholds also used to recommend prostate biopsy in the major randomized screening trials
  - US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO): PSA >4 ng/ml
  - European Randomized Study of Screening for Prostate Cancer (ERSPC): PSA >3 ng/ml

PSA Reflects Risk Continuously



PSA Provides a Spectrum of Risk

- Prostate Cancer Prevention Trial- empiric biopsies at PSA<4

PSA	% Prostate Cancer Detection
≤0.5	6.6%
0.6-1.0	10.1%
1.1-2.0	17%
2.1-3.0	23.9%
3.1-4.0	26.9%

- High-grade: 12.5% at PSA ≤0.5, 25% at PSA 2.1-4 ng/ml
- Conclusion: No PSA below which cancer can be definitively excluded

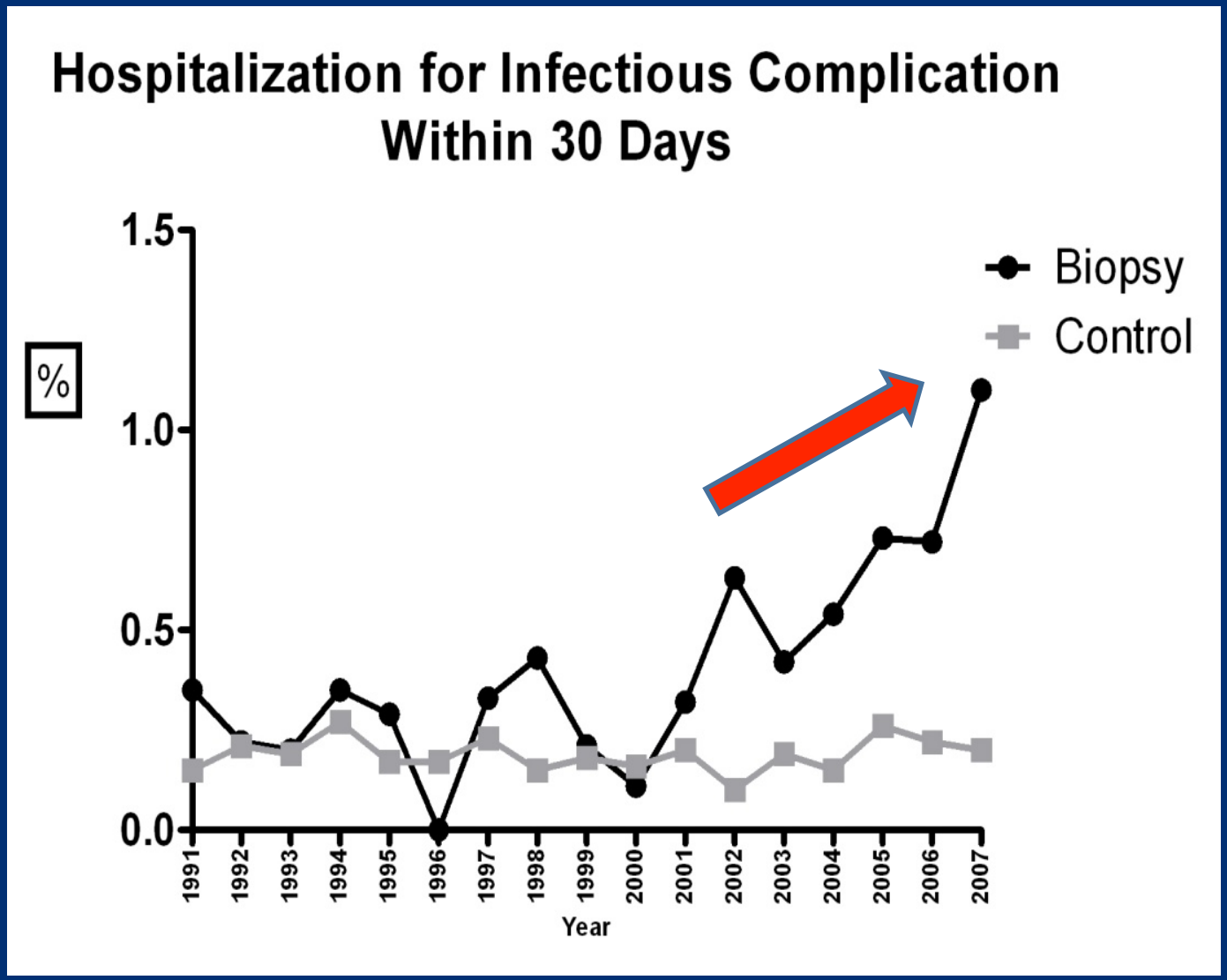
Thompson et al. NEJM 2004; 350: 2239

Many Factors Affect PSA Levels

- Age (increase)
- Race (African American > Caucasian)
- Prostate volume (~4% increase per mL)
- Androgens (lower in hypogonadal men)
- Obesity (lower due to hemodilution)
- Assay (use same assay for serial measurements)
- Medications (anti-inflammatories, statins, 5ARI)
- Genetic factors (several SNPs associated with PSA)
- Benign prostatic conditions (BPH, infection)
- Urinary tract manipulation (ex: catheter, cysto)

Limited specificity → downstream harms including unnecessary biopsies with potential associated risks

Why Limited Specificity of PSA Matters



Increasing infectious complications after prostate biopsy due to antimicrobial resistance

Loeb et al. J Urol 2011; 186: 1830

Biopsy Triggers with Greater Specificity

- Variations on PSA
  - Age-specific cutoffs, PSA density, PSA velocity, free PSA
- Newer PSA-based markers
  - Prostate Health Index (phi)
  - 4K Score
- Other Markers
  - PCA3 urine test (+TMPRSS2:ERG)
  - ConfirmMDx (tissue)
- MRI
- Multivariable approach

Age-Specific PSA Cutoffs

Age	Threshold for Biopsy
40's	2.5 ng/ml
50's	3.5 ng/ml
60's	4.5 ng/ml
70's	6.5 ng/ml

- AUA guidelines discuss using a PSA threshold of 10 ng/ml for biopsy in men >70 (to reduce harms by targeting a group most likely to benefit)

Oesterling et al. JAMA 1993; 270: 860
www.auanet.org

PSA Density

- Reduce confounding from BPH by dividing PSA by prostate volume
  - PSAD >0.15 → greater risk of cancer, aggressive disease
- Volume typically estimated by TRUS (r=0.65 compared to RP specimen)
  - Used primarily in men who have already undergone ≥1 biopsy (ex: PRIAS and Hopkins active surveillance)
  - Although DRE is not very precise (r=0.27), can be used to make gross estimate (ex: ERSPC risk calculator)
  - Expanding use of MRI may allow greater use

Benson et al. J Urol 1992; 147: 815
Loeb et al. J Urol 2005; 173: 63

PSA Velocity (PSAV)

Value	Implications
0.15 ng/ml/year	Average in men with moderate to severe BPH symptoms
>0.4 - 0.75 ng/ml/year	Thresholds proposed to distinguish cancer from BPH
>2 ng/ml/year	In the year before diagnosis, predicts greater death after treatment
>3 ng/ml/year	Increasing risk of prostatitis

- Conflicting data on the utility of PSAV: not informative with insufficient number or frequency of tests (<3 tests, interval >2y)

D'Amico et al. NEJM 2004; 351: 125
D'Amico et al. JAMA 2005; 294: 440

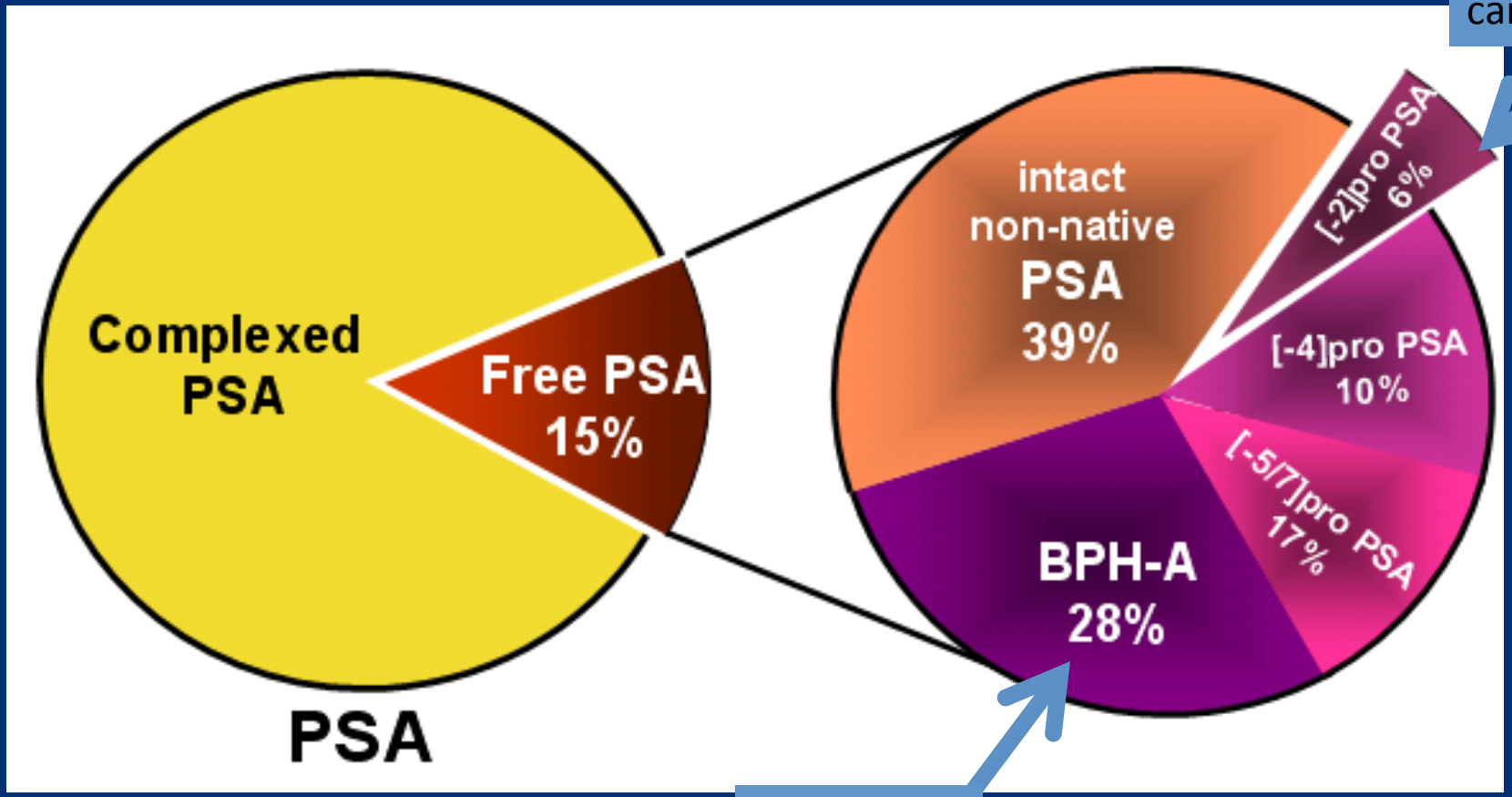
Free PSA

- PSA circulates in 2 ways: complexed to proteins and free
- Higher percent of PSA in free form (%fPSA) → "free from cancer"
  - Lower risk of high-grade disease

%Free PSA	NCCN Guidance
≤10%	Biopsy
10-25%	Indeterminate
>25%	Consider deferring biopsy

www.nccn.org

PSA Isoforms



Mikolajczyk, Urology 2002

Prostate Health Index (“*phi*”)

- Mathematical formula that combines [-2] proPSA, free and total PSA: ***phi = ([-2]proPSA/free PSA) x √ PSA***
- Multi-institutional prospective study in US
  - n=892 with PSA 2-10
  - *Phi* improved detection of total and Gleason ≥4+3=7 CaP compared to free PSA and total PSA
  - Validated in large studies in Europe and Asia
- Improvement in cost-effectiveness compared with PSA
- Predicts prostatectomy outcomes and progression during active surveillance
- Approved by US FDA in 2012, regulatory approval in >50 countries worldwide

Catalona et al. J Urol 2011; 185: 1650.
Nichol et al. BJUI 2012; 110: 353

Phi Report

PSA =4.4

p2PSA =41.9

%fPSA =21

phi =97

Patient				
Name: Case Study	Phone #: 804-123-1234	Patient ID#: 10-063-0025		
Fasting Status: Unknown	Gender: Male	Birthdate: 6/15/1957	Age: 55	
Height: 5 ft. 6 in.	Weight: 173	BMI:		

Specimen	
Collection Time: 9:54 am	Specimen ID: 10030400027
Collection Date: 1/4/2014	Report Type: Complete
Received Date: 1/5/2014	Report Date: 1/10/2014

Provider	
Requesting Provider: Bob Johnson, MD 123 Broad St. Ste 456 Richmond, VA 12345	
Client ID: 11-22222-33-4444444	

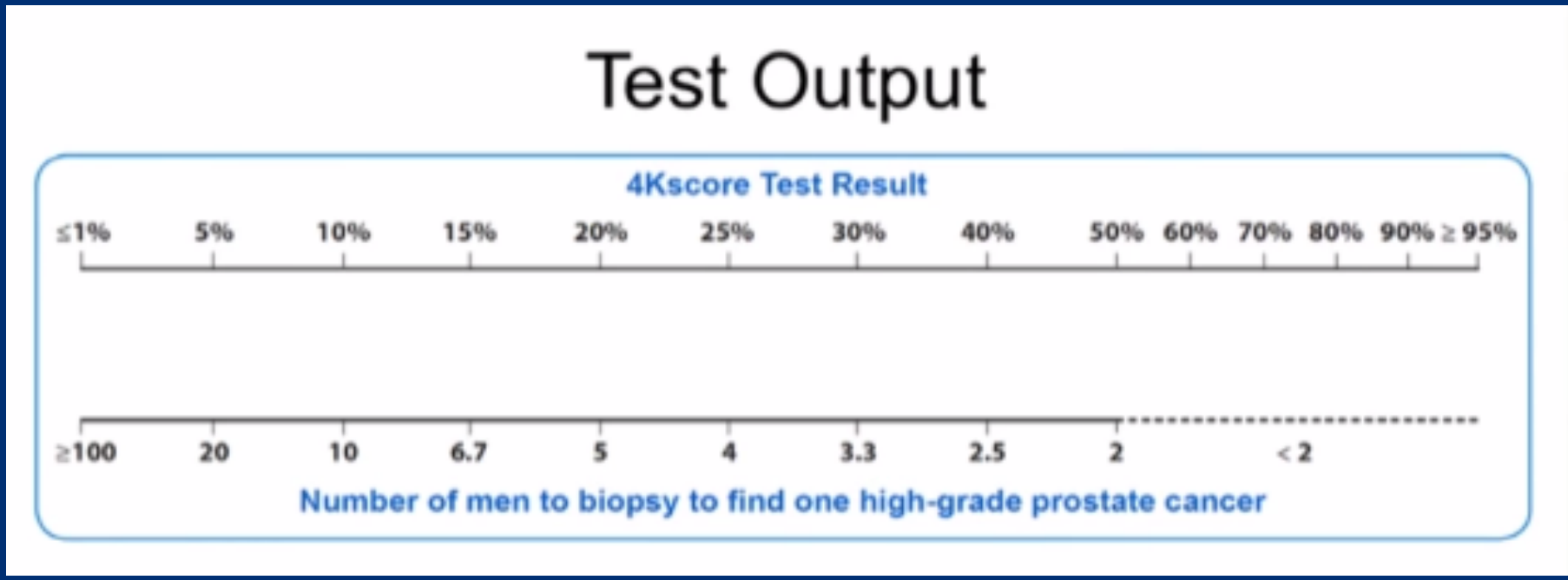
Tumor Markers	Result	Reference Interval	Probability of Cancer
Total PSA (ng/mL)	**4.4**	Normal <2.0 and at risk ≥2.0	
free PSA (ng/mL)	0.9	See %free PSA	
p2PSA (pg/mL)	41.9	See *phi*	
%free PSA	21%	**Prostate Cancer Probability by Age** **%free PSA** / **<60yr** / **60-70yr** / **>70yr** <7 / 85% / 95% / 96% 7-15 / 25% / 50% / 60% 16-25 / 11% / 27% / 35% 2% / 6% / 10%	
Prostate Health Index *phi*	97	***phi* (calculated)** / **Cancer Probability** 0-24.9 / 11.0% 25.0-34.9 / 18.1% 35.0-54.9 / 32.7% >55.0 / 52.1%	52.1%

Audience Question 1

- Which is NOT a component of the prostate health index?
- A) PSA
- B) free PSA
- C) intact PSA
- D) proPSA

4 Kallikrein Panel ("4K score")

- Panel of kallikrein markers: total PSA, free PSA, intact PSA, and hK2
  - Conceptually similar to the Prostate Health Index (phi) by combining various isoforms, but uses proprietary algorithm also containing age, DRE and prior biopsy status



4K Score

- Improved specificity for overall and clinically significant prostate cancer on biopsy in several European populations
- Subsequent publication of US validation study of men undergoing prostate biopsy
  - AUC of 0.82 for high-grade prostate cancer (better than AUC of 0.74 for PCPT risk calculator)
- Also predicts prostatectomy pathology and future risk of metastatic disease
- Not FDA approved (CLIA), similar performance to phi
  - Both included in 2015 NCCN guidelines

Vickers et al. JCO 2010; 28: 2493
Carlsson et al. Eur Urol 2013; 64: 693
Parekh et al. Eur Urol 2014 epub Oct.

PCA3

- Noncoding mRNA overexpressed in prostate cancer tissue compared to normal tissue
  - Can be measured in urine → calculate as: PCA3 mRNA / PSA mRNA x 1000
- Numerous studies showed better prediction of prostate cancer on repeat biopsy using PCA3 vs PSA
- 2/12: FDA Approved for men ≥ 50 years with previous negative biopsy and other indications for repeat biopsy
  - "Negative" (<25) → lower probability of prostate cancer

Bussemakers et al. Cancer Res 1999; 59: 5975. Hessels et al. Eur Urol 2003; 44:8. Marks et al. Urology 2007; 69: 532. Aubin et al., J Urol 2010; 184:1947.

Drawbacks to PCA3

- Significant intra-individual variability
- Only 50% cancer detection at PCA3 >100
- Performs better in repeat biopsy than initial
- Conflicting data on relationship with aggressiveness
  - Multiple studies show that phi is a better predictor of clinically significant prostate cancer than PCA3
- Performance may be improved through combination with other urinary markers (ex: Mi-Prostate combines PCA3 + TMPRSS2:ERG)

Ahn et al. AUA 2013 abstract 2052
Marks et al, Urology 2007:69:532

Audience Question 2

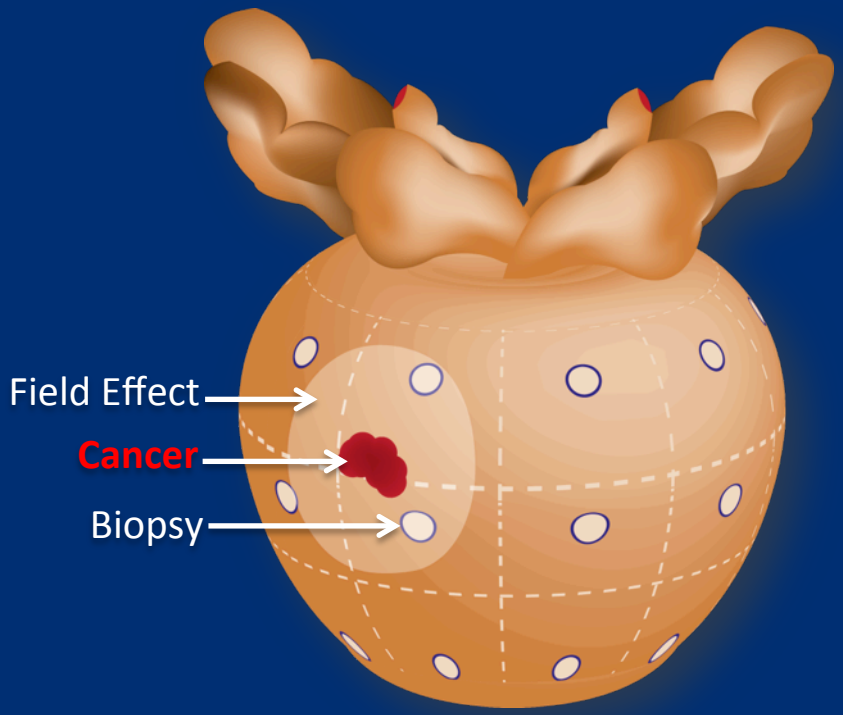
- All of the following are considered options for both initial and repeat biopsy decisions in the 2015 NCCN Guidelines EXCEPT
- A) 4KScore
- B) Prostate health index
- C) PCA3
- D) free PSA

ConfirmMDx

ConfirmMDx measures for epigenetic changes associated with the presence of prostate cancer at the DNA level

–Hypermethylation of 3 markers (GSPT1, APC, RASSF1)

- Field effect around a cancer lesion can be present despite normal appearance under the microscope
- Absence of methylation changes helps rule out malignancy (NPV 88%)
- Presence of methylation changes indicates increased risk for malignancy



Epigenetic Field Effect

Henrique et al. Mol Cancer Res 2006;4:1-8
Partin et al. J Urol 2014; 192: 1081.

ConfirmMDx Report

Patient Result: **DNA Methylation Positive**

The DNA methylation positive test result for this patient indicates a 88% likelihood of detecting prostate cancer, with a 38% probability for low-grade disease (GS ≤6) versus a 50% probability of high-grade disease (GS ≥7), on repeat biopsy.

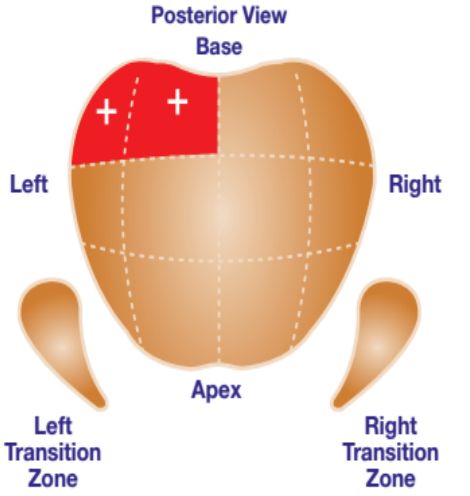
Likelihood of prostate cancer on repeat biopsy

The ConfirmMDx test result indicating the likelihood of low and high-grade prostate cancer being detected on repeat biopsy is calculated by using a logistic regression model, incorporating DNA methylation intensity with clinical risk factors, including PSA, DRE, age, and histopathology of the previous biopsy, yielding an area under the curve (AUC) of 0.762 (95% CI: 0.679-0.844). Performance is based on the presence of all relevant data elements and AUC may vary if all data are not available. Cancer association with DNA methylation of these gene markers has been reported on ~4,500 patients.[1-53]

DNA Methylation Status Table

Biopsy Site	GSTP1 Methylation	APC Methylation	RASSF1 Methylation
Left Lateral Base:	Positive	Positive	Positive
Left Lateral Mid:	Negative	Negative	Negative
Left Lateral Apex:	Negative	Negative	Negative
Left Base:	Positive	Positive	Positive
Left Mid:	Negative	Negative	Negative
Left Apex:	Negative	Negative	Negative
Left Transition Zone:	Negative	Negative	Negative
Right Base:	Negative	Negative	Negative
Right Mid:	Negative	Negative	Negative
Right Apex:	Negative	Negative	Negative
Right Lateral Base:	Negative	Negative	Negative
Right Lateral Mid:	Negative	Negative	Negative
Right Lateral Apex:	Negative	Negative	Negative
Right Transition Zone:	Negative	Negative	Negative

Distribution of DNA Methylation Diagram



ConfirmMDx positive

- **Manage patient as if ASAP pathology result**
- **Consider repeat biopsy with additional cores in the region of methylated hot spots**

Multiparametric MRI (mpMRI)

- PI-RADS scoring system (score 1-5) is used to assess the degree of suspicion for each sequence and overall
  - 1-2: Significant cancer unlikely, 3: Indeterminate, 4-5: Probably/ highly suspicious for malignancy
- PI-RADS 3, 4, and 5 → ~2x, 5x and 8x greater risk of CaP detection
- MRI-targeted biopsy improves detection of clinically significant prostate cancer with greater sampling efficiency
- NYU protocol: 3T multiparametric MRI (no endorectal coil) → 12-core biopsy plus targeted biopsies of suspicious lesions (Artemis or cognitive fusion)

Radtke et al. J Urol 2015; 193: 87.
Siddiqui et al. JAMA 2015; 313: 390.

Cost-Effectiveness of MRI Before Biopsy

- Netherlands *(de Rooij et al. Eur Urol 2014)*:
  - Markov model comparing in-gantry MR-targeted biopsy (no biopsy if MRI negative) vs. standard TRUS biopsy for all men with PSA >4 ng/ml
  - Incremental cost effectiveness ratio of €323 per QALY with MRI strategy (well below the typical threshold for willingness to pay)

- USA (*Davuluri et al. AUA 2015):*
  - Cost-effective to do MRI prior to repeat biopsy but not before initial biopsy

Multivariable Risk Stratification

- Many factors modify prostate cancer risk and should also be considered in biopsy decisions in addition to PSA
  - Ex: comorbidities, prostate volume, family history, race, prior biopsy history
- Numerous guidelines incorporate multivariable risk stratification (European Association of Urology, Melbourne Consensus Statement)
- Risk calculators available online and as apps to facilitate use in clinical practice

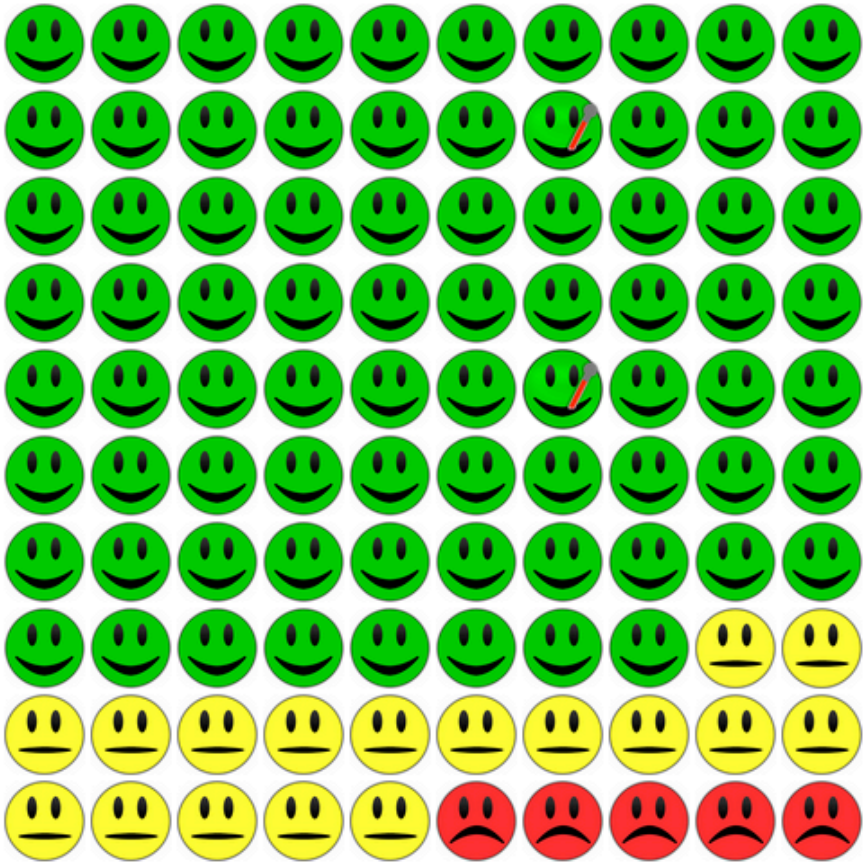
PCPT Risk Calculator

Original Variables	Additional Variables
Age	Obesity
PSA	PCA3
Race	Finasteride
Family History	% Free PSA
DRE	[-2] proPSA
Prior Biopsies	% Free PSA and [-2] proPSA
	Prostate Volume
	# Biopsy Cores
	Urinary Symptoms

http://prostatecancerinfolink.net/risk-prevention/pcpt-prostate-cancer-risk-calculator/

PCPT Risk Calculator

Results



Please consult your physician concerning these results.
Click here to watch a video overview of these results.

Based on the provided risk factors a prostate biopsy performed would have a:

5% chance of high-grade prostate cancer,

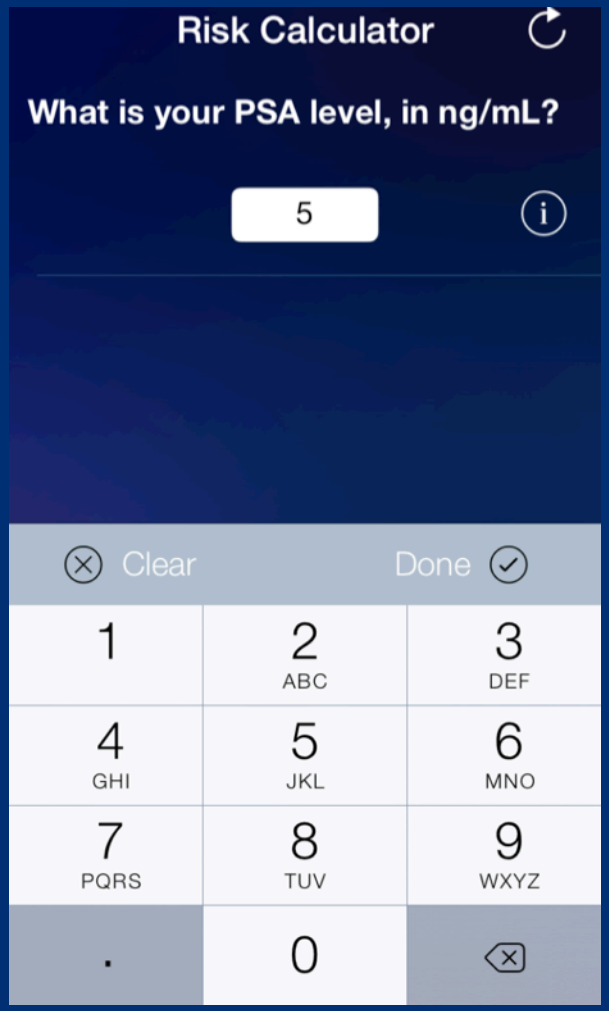
17% chance of low-grade cancer,

78% chance that the biopsy is negative for cancer.

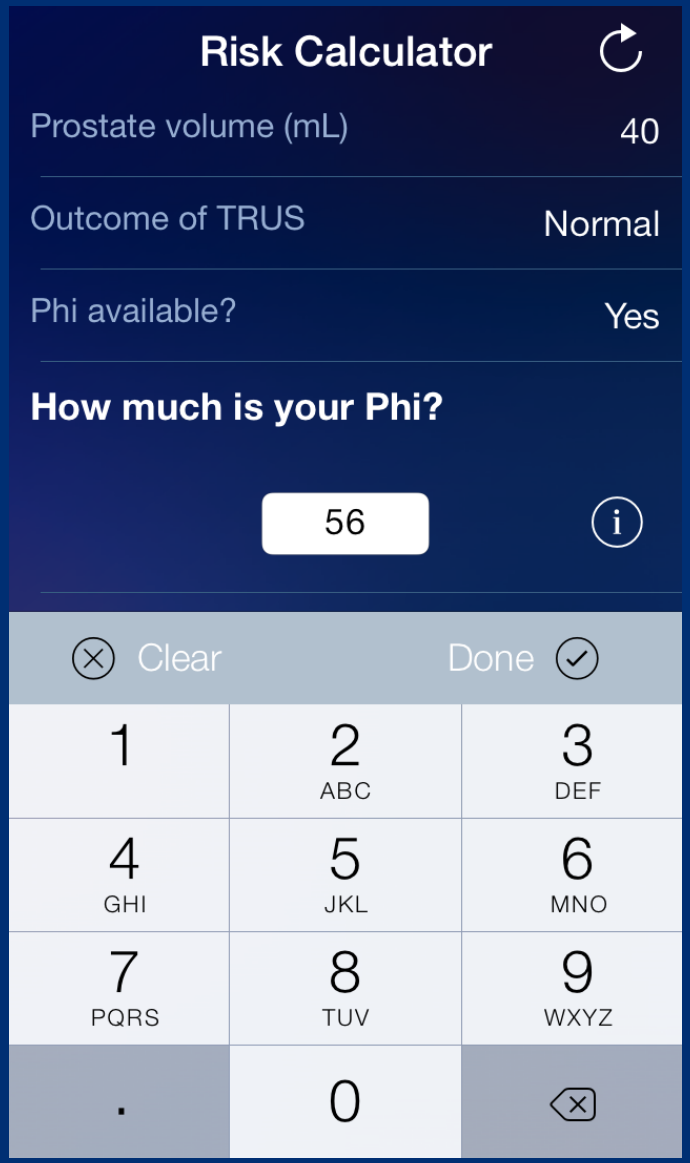
About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

ERSPC Rotterdam Risk Calculator App

- Available for smartphone and tablet
- Inputs: PSA, DRE, prior biopsy, prostate volume if available, Prostate Health Index (phi)
- Output: risk of detectable and significant prostate cancer on biopsy



ERSPC Risk Calculator App



Conclusions

- Multiple variations on PSA with greater specificity
  - Higher risk of aggressive disease: PSAD >0.15, PSA velocity >0.35 ng/ml/yr, %fPSA ≤10
- New PSA-based markers phi and 4K have greater specificity for clinically significant prostate cancer
  - Both are included in 2015 NCCN guidelines as options prior to initial or repeat biopsy
- PCA3 is FDA approved and included in 2015 NCCN guidelines for repeat biopsy
  - Conflicting data on relationship to aggressiveness

Conclusions

- ConfirmMDx looks for field changes (hypermethylation) suggesting undiagnosed prostate cancer in a negative biopsy
- Increasing evidence supports the use of multiparametric MRI prior to repeat > initial biopsy
- <u>One-size-fits all with total PSA is out → Multivariable approach is in!</u>
  - Decision for biopsy should take into consideration multiple risk factors and general health status