Improving diagnostic accuracy in prostate cancer

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Medical Update

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Acknowledgement/Disclaimer

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- Slides with the University of Florida Urology logo at the bottom are courtesy of Dr. Liming Su and Dr. Thomas Stringer.

Outline

- Prostate cancer screening, biopsy, diagnosis, treatment/cure
  - Difference between screening and diagnosis
  - Screening: Prostate Specific Antigen (PSA) blood test
  - Screening: Digital Rectal Exam (DRE) exam
  - Sampling: Prostate Biopsy, PBx (Systematic, Targeted, Fused)
  - Diagnosis: Pathology exam of biopsied samples
  - Treatment: Watchful waiting, Active surveillance, Radiation therapy, Surgery, Other
- Learning from US downgrading PSA screening
- Prostate biopsy specificity/False negatives
  - Implications of false negatives

Outline

- Our research to reduce prostate biopsy false negatives

- My personal journey with prostate cancer

Terminology: Screening vs Diagnosis

	Screening tests	Diagnostic tests
Purpose	To detect potential disease indicators	To establish presence/absence of disease
Target population	Large numbers of asymptomatic, but potentially at risk individuals	Symptomatic individuals to establish diagnosis, or asymptomatic individuals with a positive screening test
Test method	Simple, acceptable to patients and staff	maybe invasive, expensive but justifiable as necessary to establish diagnosis
Positive result threshold	Generally chosen towards high sensitivity not to miss potential disease	Chosen towards high specificity (true negatives). More weight given to accuracy and precision than to patient acceptability
Positive result	Essentially indicates suspicion of disease (often used in combination with other risk factors) that warrants confirmation	Result provides a definite diagnosis
Cost	Cheap, benefits should justify the costs since large numbers of people will need to be screened to identify a small number of potential cases	Higher costs associated with diagnostic test maybe justified to establish diagnosis.

https://www.healthknowledge.org.uk/public-health-textbook/disease-causation-diagnostic/2c-diagnosis-screening/screening-diagnostic-case-finding

Goal of Prostate Cancer Screening

- Identify high-risk, localized prostate cancer that can be successfully treated
- Prevent the mortality and morbidity associated with incurable advanced or metastatic disease including urinary obstruction and painful metastases

Principles of Population Screening: Benefit, Risk and Cost

- Significant burden of disease in a defined target population
- Preclinical stage is detectable and prevalent
- Early detection improves outcome (mortality) with acceptable morbidity and with effective treatment for detected disease
- Screening tests are acceptable to population, inexpensive and relatively accurate
- Cost of screening (including diagnosis and treatment) should be economically balanced in relation to possible expenditure on medical care as a whole

Wilson JMG, Jungner G., 1968, *Principles and practice of screening for disease*. Public Health Paper, Number 34. Geneva: WHO

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Prostate Specific Antigen (PSA) blood test

The PSA test is a **blood test** used primarily to screen for prostate cancer (PCa)

The test measures the amount of prostate-specific antigen (PSA) in your blood. PSA is a protein produced by both cancerous and noncancerous tissue in the prostate, a small gland that sits below the bladder in men.

https://www.mayoclinic.org/tests-procedures/psa-test/about/pac-20384731

PSA Era

- Increased incidence of prostate cancer
  - Peaked in 1992
  - Incidence remains higher than baseline pre-PSA

- 60% drop in metastatic disease at diagnosis
  - Powerful stage migration

- 49% mortality decline 1991-2009
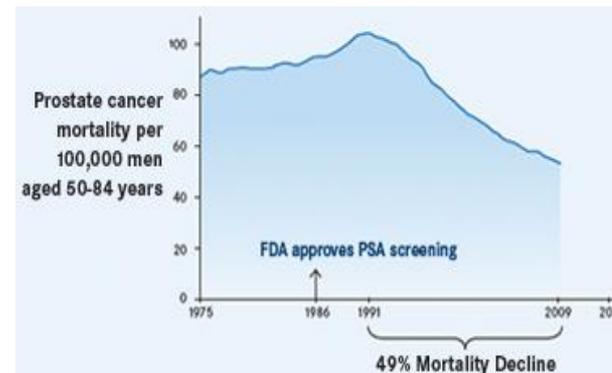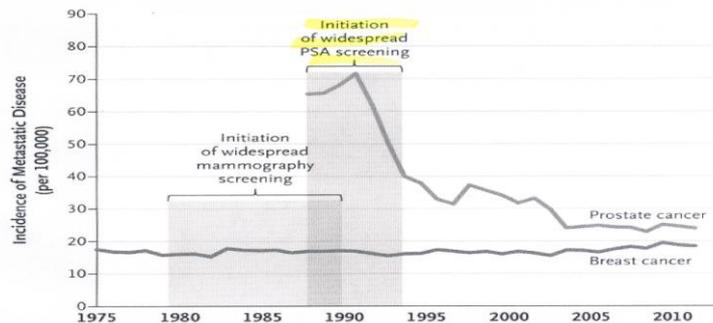
Florida Prostate Cancer Advisory Council (PCAC)
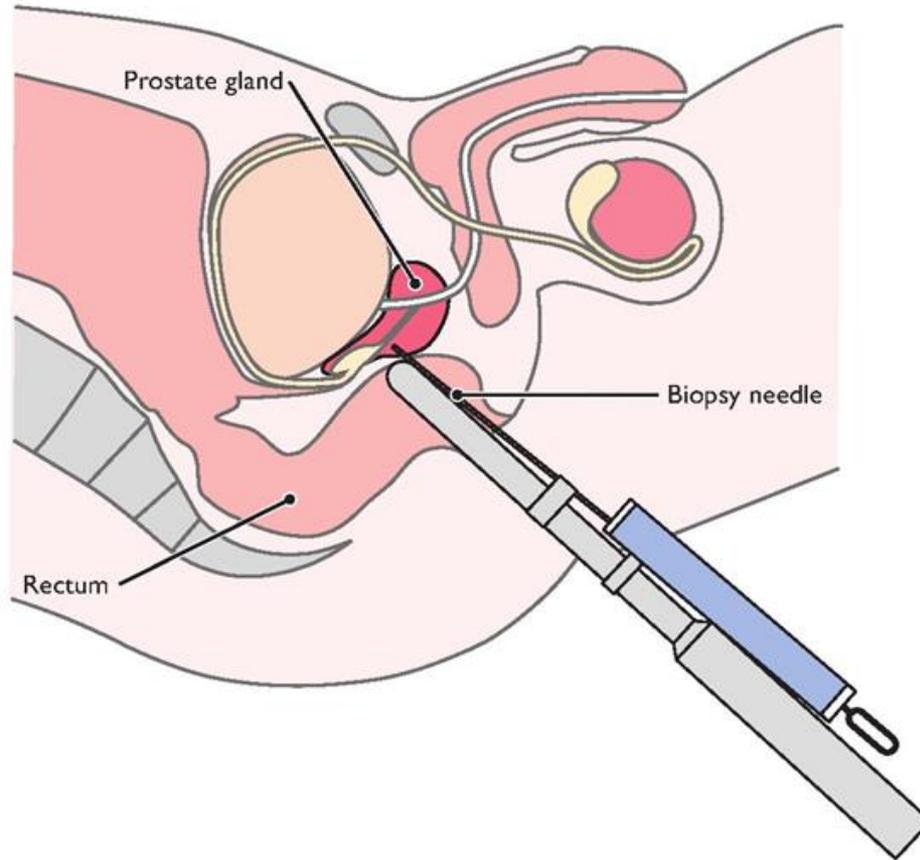**Prostate Cancer Early Detection Guidelines (2016)**

- All Florida men beginning at age 50 and at average-risk for prostate cancer should be encouraged to undergo early detection testing. Men with limited life expectancy (less than 5-10 years) should be discouraged from routine prostate cancer screening

- All Florida **African-American men and men with first and second degree relatives with prostate cancer** are at higher risk for prostate cancer and should be encouraged to undergo early detection screening beginning **at age 40**

- Early detection testing should include a PSA test or newer markers (4K, PHI, ExoDx) and digital rectal exam by a health care professional. Up-to-date recommendations on early detection are additionally available on the NCCN website, www.nccn.org
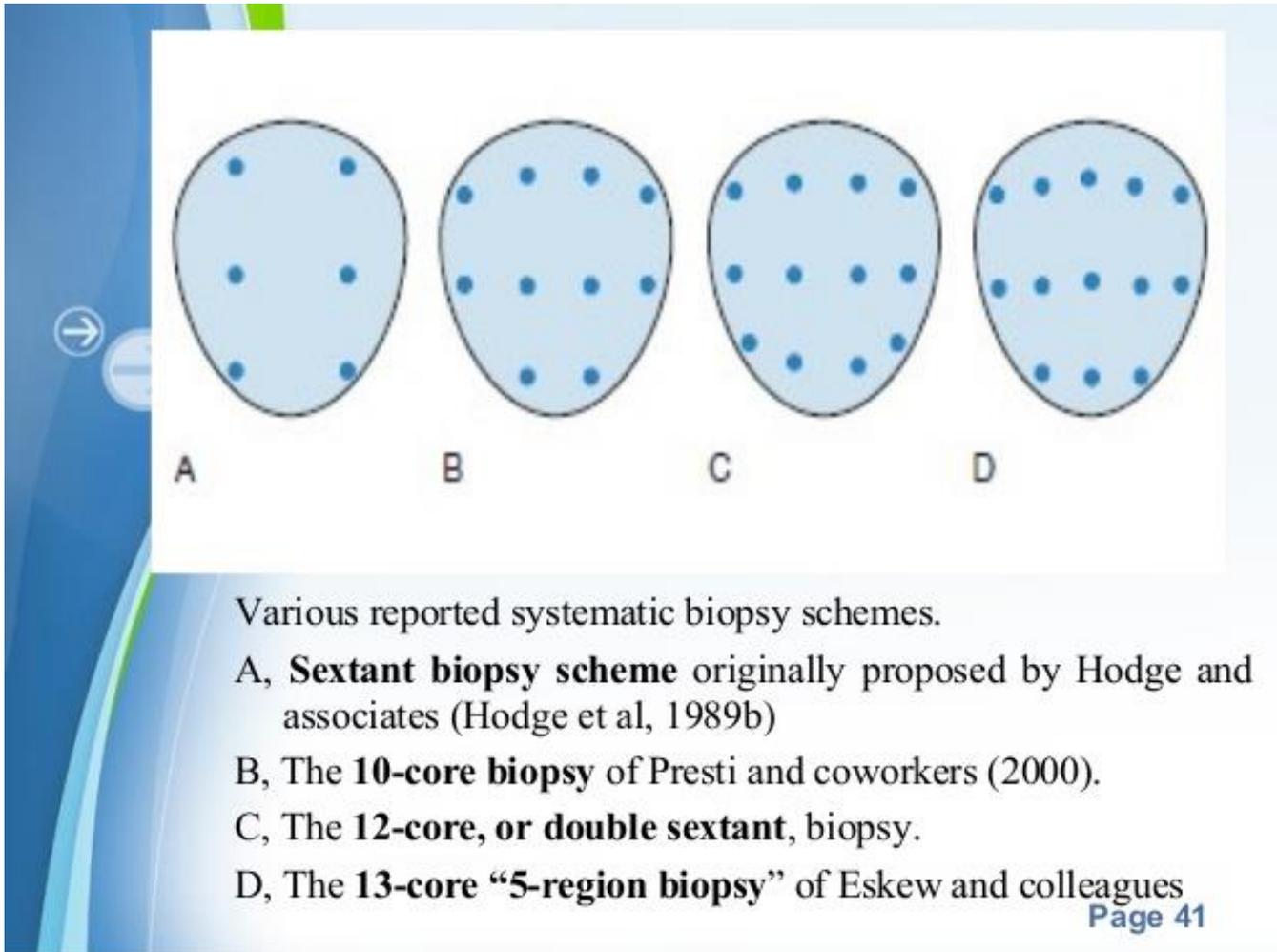
Digital Rectal Exam
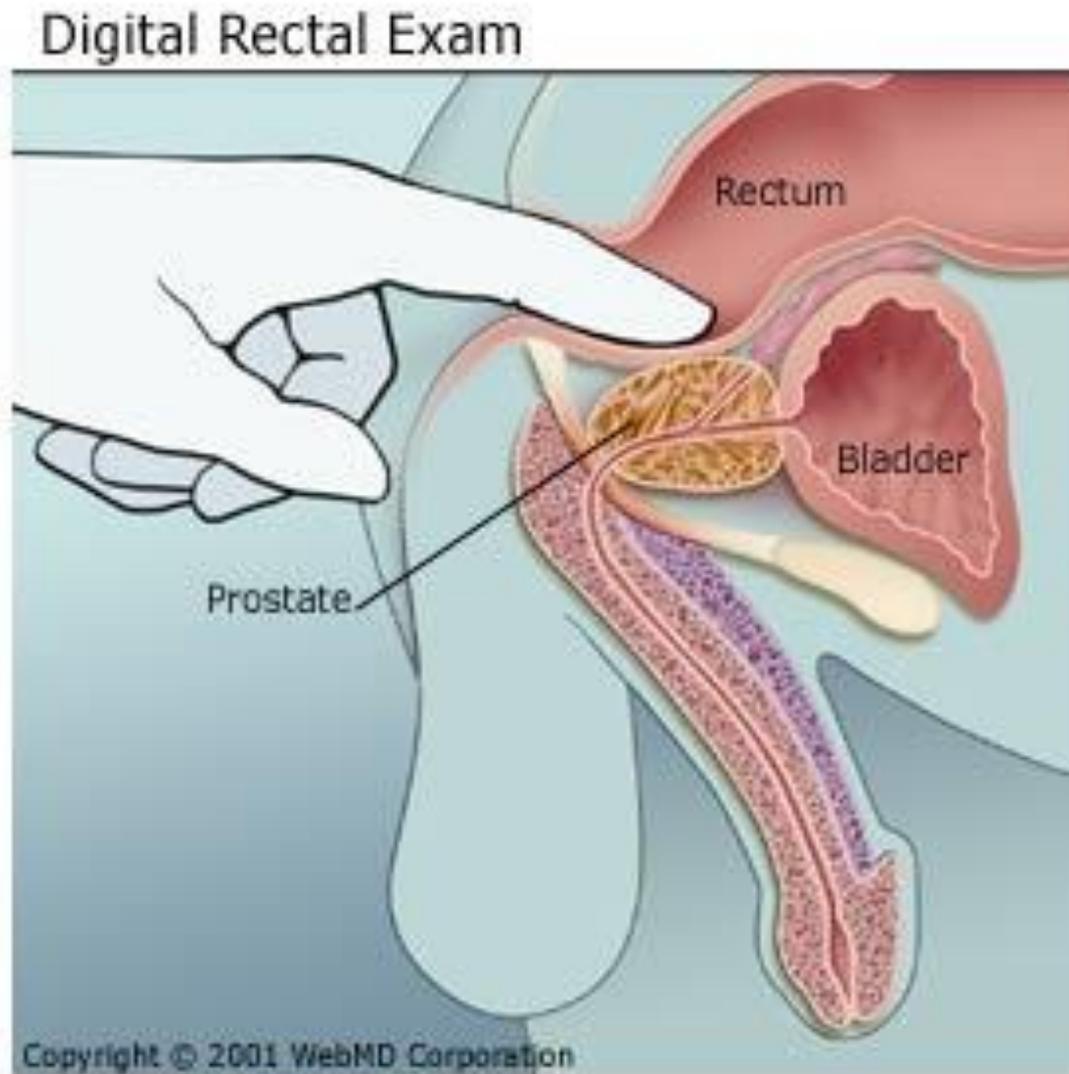
https://kattermonran.files.wordpress.com/2013/07/prostate_problems_digitalrectalexam.jpg

Prostate Biopsy (PBx)

Systematic Prostate Biopsy Templates

Various reported systematic biopsy schemes.

A, **Sextant biopsy scheme** originally proposed by Hodge and associates (Hodge et al, 1989b)

B, The **10-core biopsy** of Presti and coworkers (2000).

C, The **12-core, or double sextant**, biopsy.

D, The **13-core "5-region biopsy"** of Eskew and colleagues

Page 41

http://image.slidesharecdn.com/trusbiopsyprostate-150621060724-lva1-app6892/95/
trus-biopsy-prostate-41-638.jpg?cb=1434866959
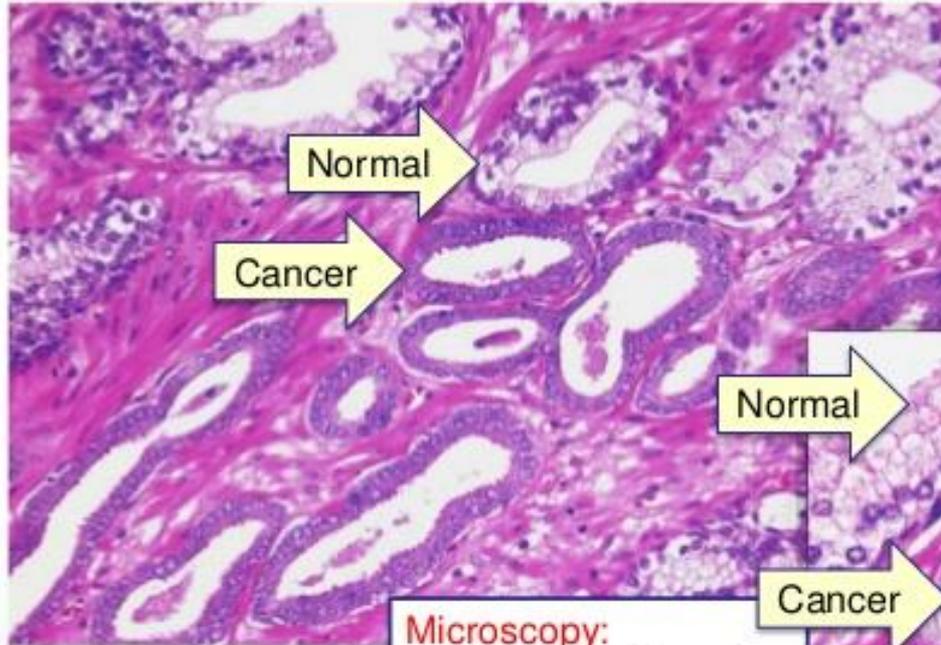
Prostate Biopsy Template

- Sextant biopsy - 1989
    - 6 sites para-sagittal, apex, mid and base each lobe
        * 9% more cancers compared to target biopsy alone
- Sextant modifications - 2001
    - Extended core biopsy 12 versus 6 cores
        * Lateral plus para-sagittal biopsies
        * Increase cancer detection by 10%
- Saturation biopsy - 2001
    - 20 or more systemic core biopsies
        * Detection rate improved over 12 biopsy in patients with prior negative biopsy
        * Detection plateaus beyond 20 cores
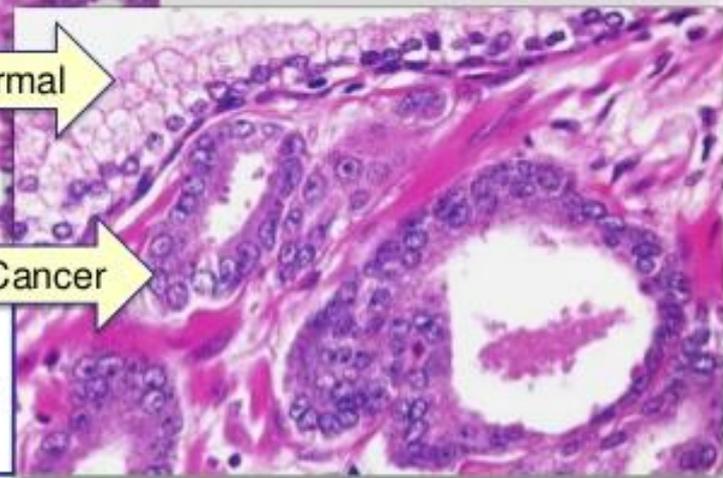
Pathology Exam

Prostatic Cancer: Microscopy

Normal

Cancer

Gross: Hard, gritty / stoney

Normal

Cancer

Microscopy:
1. Pleomorphic cells
2. Single layer glands
3. No secretions.

https://image.slidesharecdn.com/bph4prostateca-150925003508-lva1-app6892/95/
pathology-of-prostate-cancer-7-638.jpg?cb=1443141348

Pathology Exam

- Provides a Gleason score that can guide treatment options

Cancer Risk Categorization

	Very Low	Low	Intermediate	High
PSA	≤ 10	≤ 10	10-20	>20
Gleason Score	≤ 6, <3 cores, <50% core involvement	≤ 6	7	8-10
Clinical Stage	T1c	T1-2a	T2b-T2c	T3a
Treatment Options	• Active Surveillance	• Active Surveillance • Radiation • Surgery	• Radiation • Surgery	**Multimodality Therapy** • Surgery +/- Radiation • Radiation + Hormonal Therapy

Treatment for Clinically Localized Disease

- **Active Surveillance**
- **Radiation**
  - **External beam (IMRT)**
  - **Proton beam**
  - **Radioactive seed implant (Brachytherapy)**
- **Surgery (radical prostatectomy)**
  - **Open surgery**
  - **Robotic (da Vinci®) surgery**
- **Investigational**
  - **Cryosurgery (freezing the prostate)**
  - **HIFU (heating of the prostate)**
  - **Cyberknife**
  - **Focal therapy**

Choosing a Treatment

- **Not a 'cookie cutter' decision**
  - **To treat or not?**
  - **If treatment, what type?**

- **Depends on multiple factors:**
  - **Patient's health and life expectancy**
  - **Medical and surgical history**
  - **Grade and stage of cancer**
  - **Risk categorization**
  - **Patient's desires and expectations**
  - **Understanding of side effects**

PCa Sequence

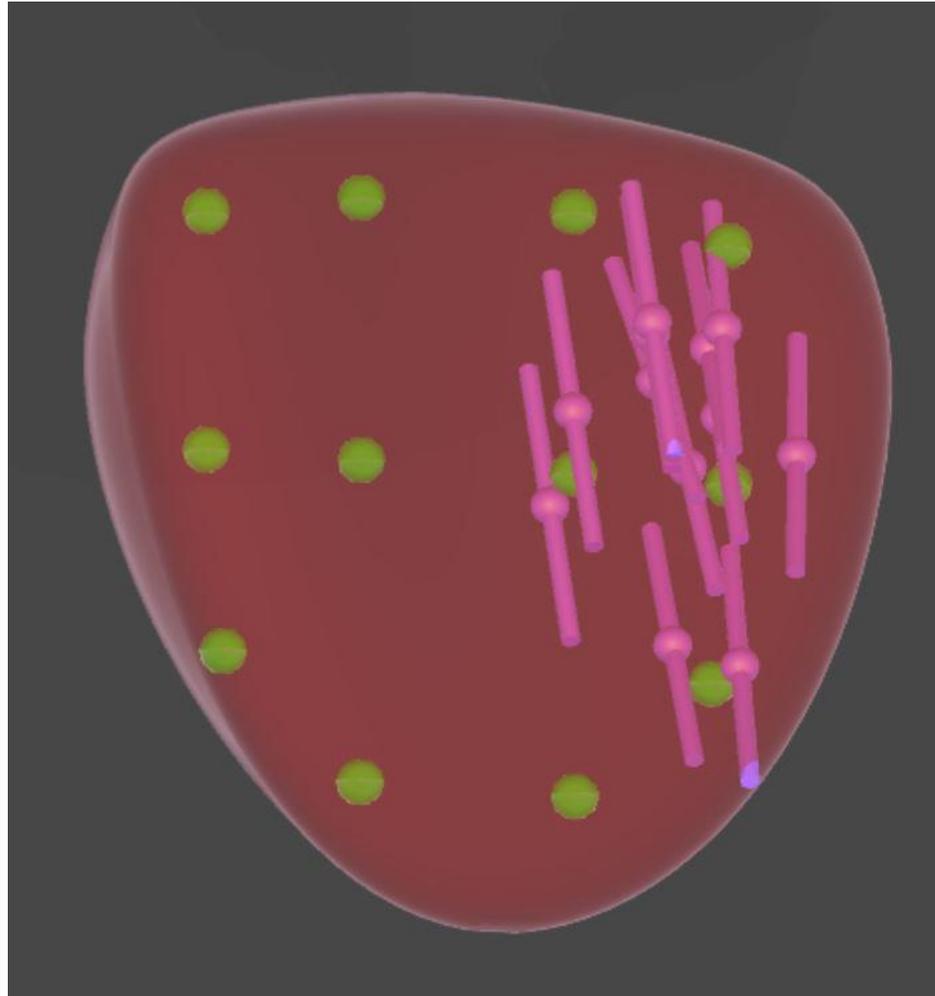Screening: PSA/DRE → Sampling: Biopsy → Pathology: Diagnosis → Cure/Treatment: Options
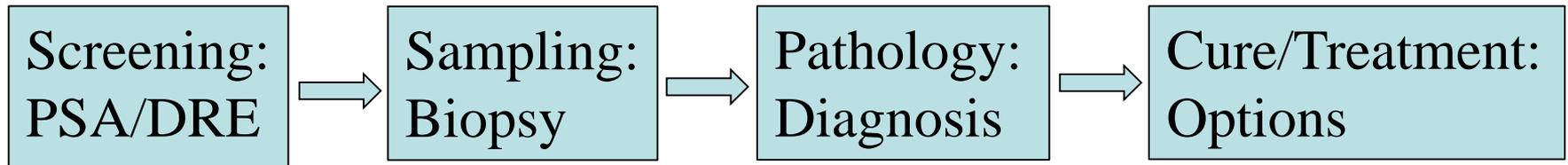
False negative prostate biopsy
Biopsies deviate from template

US Experience with Downgrading PSA Test to D

Burden of Disease

- Lifetime Risk of Diagnosis:
  - 11% (1/9), 20% (1/5) for AA
  - 2015 - 10,874 new cases in Florida
  - Non-clinically evident
    * 30% of men age 55 and 60% of men age 80 on autopsy
- Lifetime Risk of Dying from Prostate Cancer: 2.5%
  - Down 47% from peak rates secondary to early detection and improved treatment
    * 4.2% AA
    * 2.9% Hispanic
    * 2.3% White
    * 2.3% Asian and Pacific Islander
- Median Age at Diagnosis: 66
- Median Age of Death: 80

*National Cancer Institute SEER data https://seer.cancer.gov/statfacts/html/prost.html

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Benefits of Screening

- Reducing the burden of disease on the community and individuals
- Reducing mortality from the disease
- Reducing morbidity from the disease
- Improving disease outcomes

Harms of Screening

- False positives: when a screening test and assessment delivers a positive result but the individual does not have the disease
- False negatives: when a screening test and assessment delivers a negative result but the individual does have the disease
- Over-diagnosis: is terminology used to explain that some cancers and conditions that are found and treated may not have become life-threatening in an individual's lifetime. It does not refer to error or misdiagnosis
- Over-treatment: other physical and psychological harms that might be experienced as a result of screening or treatment

Potential Harms of Testing, Early Detection and Treatment

- Biopsy related complications: 1% hospitalization rates, 4% infection (up to 7.5% AA)
- Over diagnosis (identification of latent prostate cancer)
  - 21% (PLCO) to 50% (ERSPC)
- Overtreatment
  - Surgery
    - ED: 2/3 men following prostatectomy
    - Stress Incontinence: 1 in 5 men require long term use of pads
  - Radiation
    - ED: Greater than half
   - Bowel Complications: Up to 1 in 6 men

PSA Test Rated D in 2012 in US

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.

Results now coming in..

Decline in PSA Screening Across All Age Groups

Figure 2: Smoothed curve demonstrating use of PSA screening by age in men presenting to their primary care physician for preventative care.
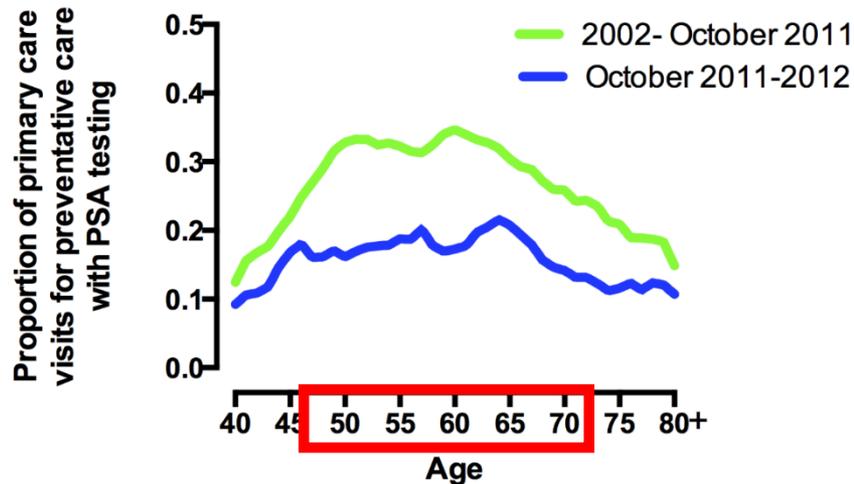
Shoag J, et al. J Urol 2016

Effect on PSA Testing and DRE

A — PSA Testing
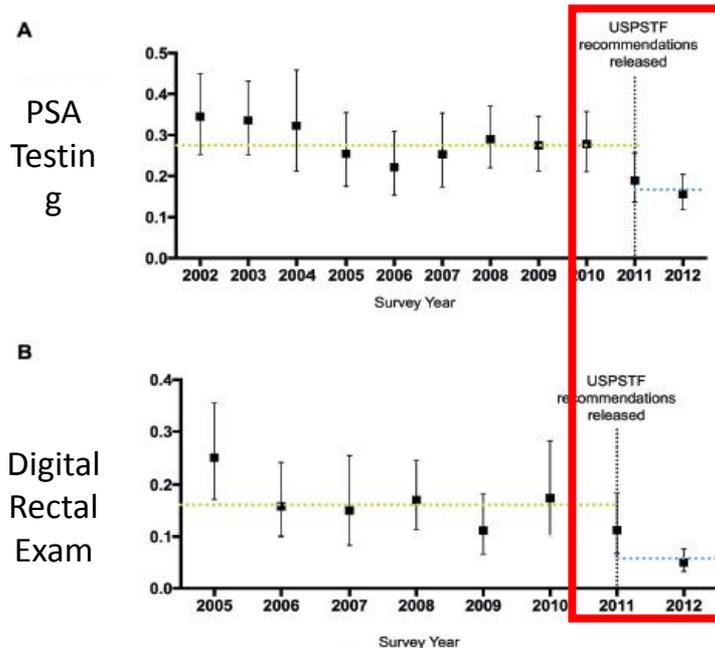
B — Digital Rectal Exam

Figure 1. Mean and 95% CI of proportion of primary care visits for preventive care in men older than 40 years in whom PCP prostate cancer screening was performed before and after USPSTF recommendation release. Blue dotted line indicates mean before release. Green dotted line indicates mean after release. A, DRE. B, PSA test.

- **National Ambulatory Medical Care Survey**

- **Primary care physicians**

- **~150M patient visits**

Results:

- **39% decrease in PSA testing**

- **64% decrease in DRE**

Shoag J, et al. J Urol 2016

Other Unintended Consequences

- **High grade cancers** (Gleason 8-10) increased from 8.4 to 13.5%

- **Lymph node involvement** increased over 3-fold from 2009 to in a large multicenter surgical series

- **Biochemical recurrence** increased from 6.2 to 17.5% at one year following surgery

American Cancer Society, Surveillance Research, 2018.
Ahlering, Thomas; World J Urol (2019) 37:489-496

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Specificity

- Specificity; the probability that a person NOT having a disease will be correctly identified by a clinical test

- Specificity = 100 – false negative %

- False negative prostate biopsy: 21 - 47%

https://medical-dictionary.thefreedictionary.com/specificity

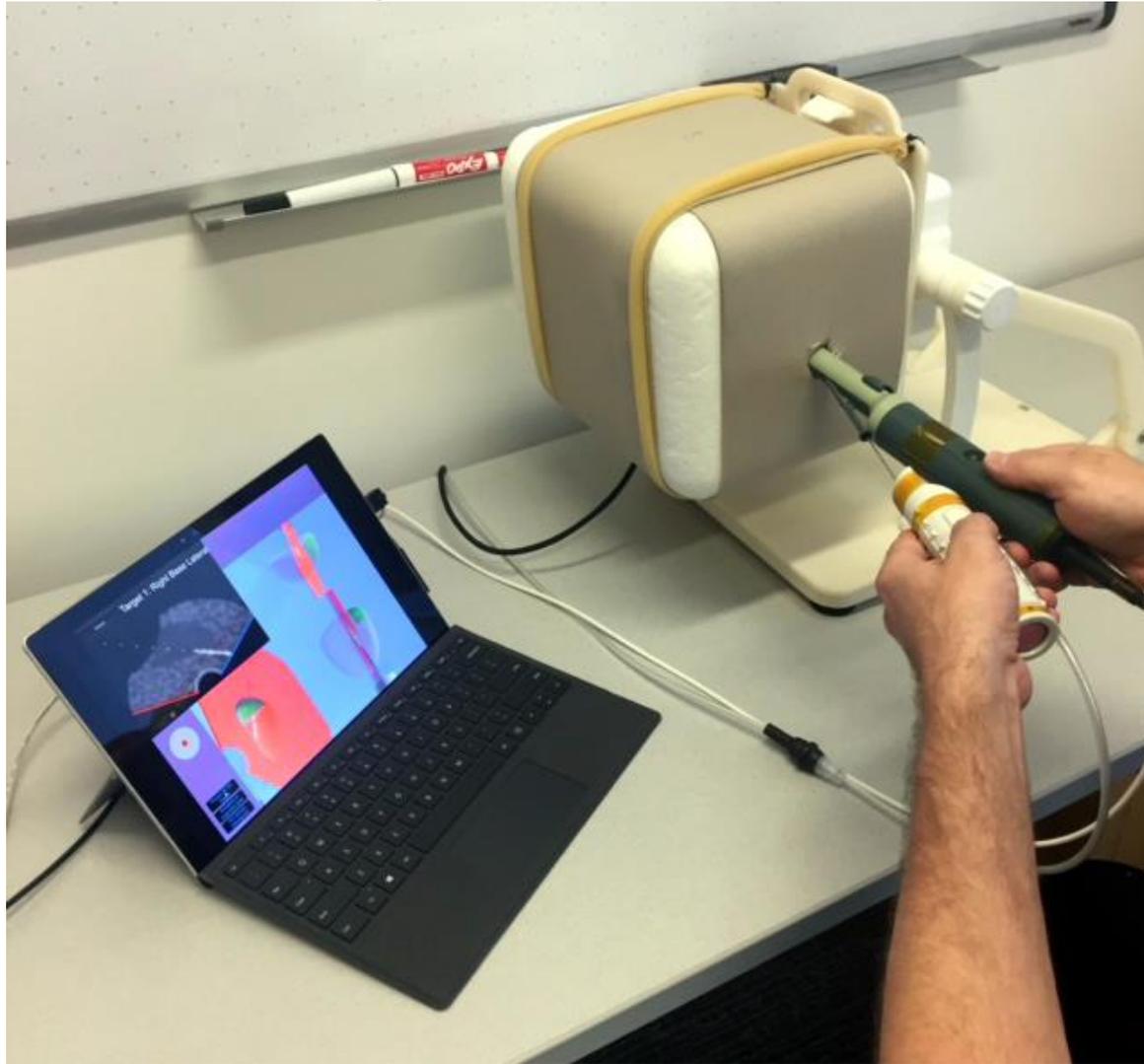# False Negative (FN) **Gatekeeper** in **High-Stakes** Office Procedure
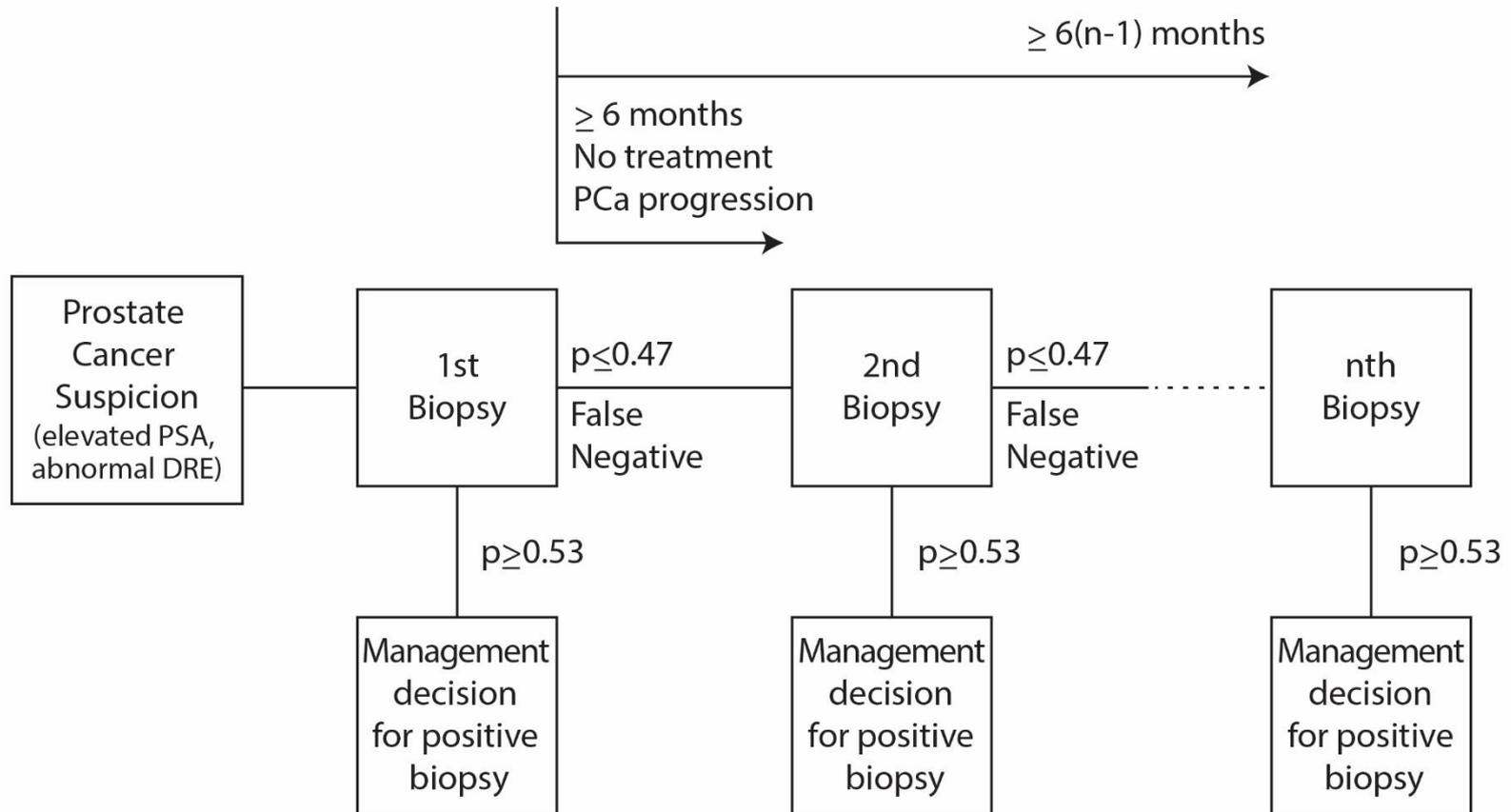
Le et al (2014) reported TRUS PBx false negative proportions as high as 47%

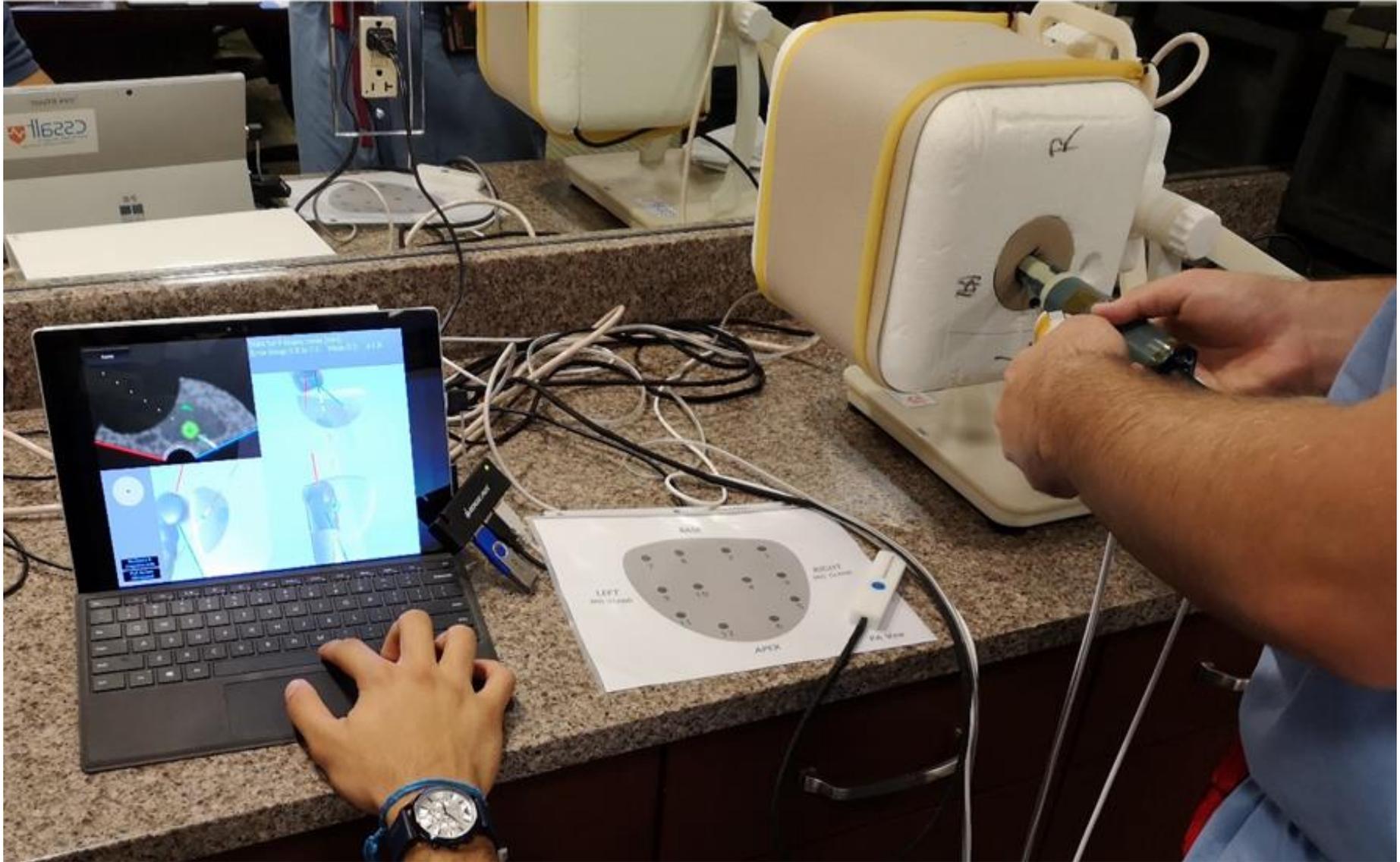# Our research to reduce prostate biopsy false negatives

Our research

- Designed, built and evaluated a prostate biopsy simulator for training urologists and oncologists

- Quantitative documentation of skill/training gaps

- Created with simulator a new systematic PBx technique that improves accuracy

- Established a quantitative competency threshold and proved it was attainable with simulation-based training

- Established that in simulated prostate biopsy, false negative proportion is related to average mean error during systematic prostate biopsy

Mixed reality TRUS PBx simulator

Simulator-based study

Video – TRUS PBx Simulator

- Video of TRUS PBx simulator
- URL: https://youtu.be/MY4pXcp_OFY

Baseline Point Accuracy
(Templated TRUS PBx)
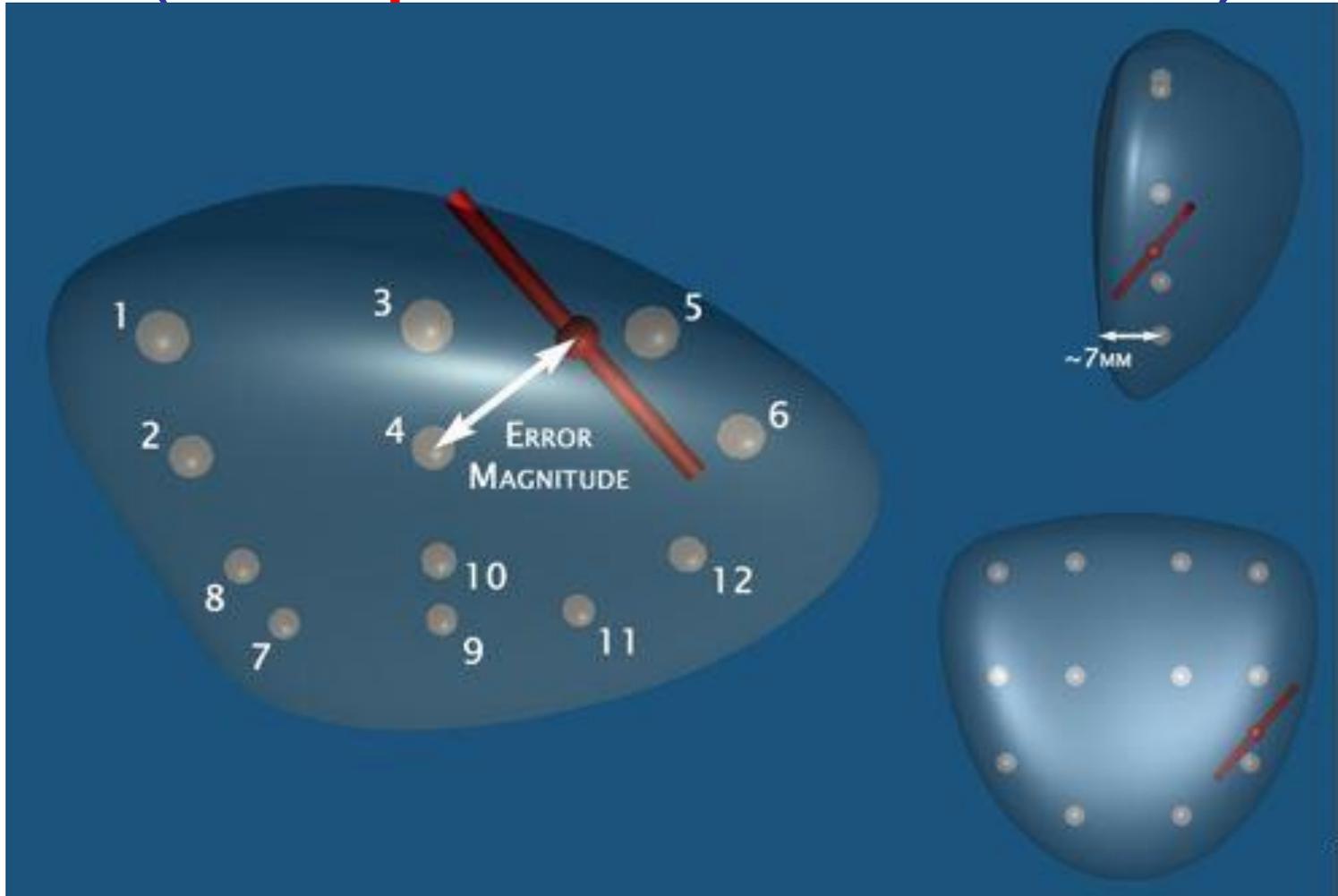
Baseline Point Accuracy (Templated TRUS PBx)

Subject	Error; Mean±SD (mm)	Range; Min-Max (mm)	Median (mm)
1	9 ± 4.7	3.5-16.7	7.7
2	9.4 ± 3	5.1-15	8.9
3	11.7 ± 6.7	3.9-25.3	9.65
4	9.6 ± 3.6	5.7-18.2	8.15
5	8 ± 3.6	3.4-15.1	7.35
6	24.5 ± 8.1	11-40.9	24.1
7	7.1 ± 4.5	1.3-17.9	5.8
8	6.5 ± 2.9	2.2-10.9	6.25
9	13.5 ± 9.3	3.7-35.5	8.8
10	19.1 ± 10.1	2-41.2	17.8
11	10.7 ± 3.8	5.8-18.2	11.25
12	9.1 ± 4	3.9-18.7	8.2
13	20.1 ± 6.3	12.1-30.7	21
14	7.1 ± 3.1	3.2-14.2	6.45
15	7.7 ± 4.8	2-18.2	6.45

For all 15 Center A participants,
mean error averaged over 12 cores did not meet minimum 5 mm accuracy threshold

100% prevalence of ≥ 5 mm mean error (n=15) at baseline

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Virtual spherical lesions
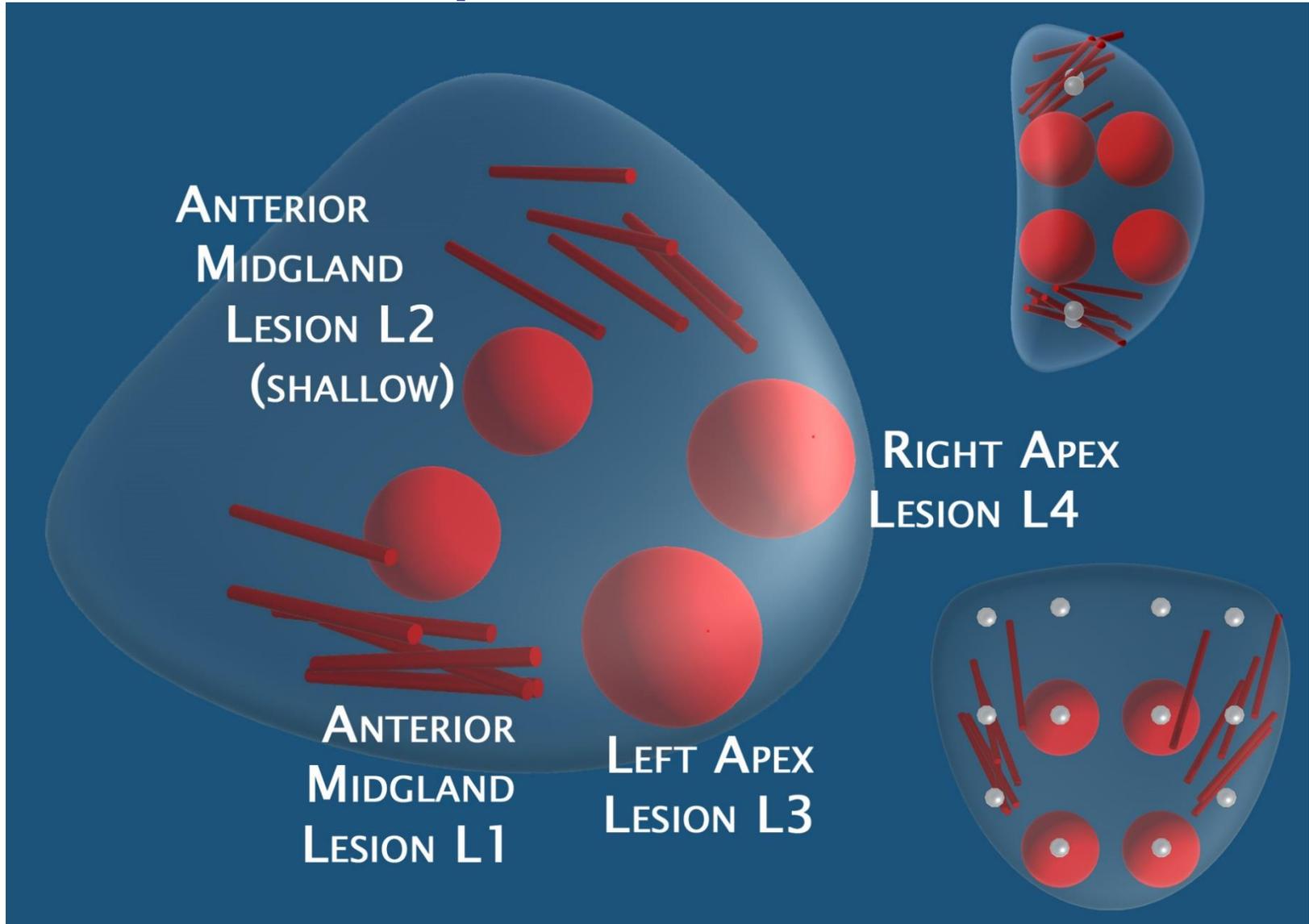
Baseline simulated FN proportion (Spherical lesions; 4.924 mm radius)

Subject	False Negative L1 (L Ant)	False Negative L2 (R Ant, shallow)	False Negative L3 (L Apex)	False Negative L4 (R Apex)	False Negative L3&4 (Both Apex Lesions)	False Negative L1&L2&L3&L4 (All Lesions)
1	Yes	YES	YES	YES	YES	YES
2	YES	YES	YES	YES	YES	YES
3	YES	YES	YES	YES	YES	YES
4	YES	YES	NO	NO	NO	NO
5	YES	YES	NO	YES	NO	NO
6	YES	YES	YES	YES	YES	NO
7	YES	YES	YES	NO	NO	NO
8	YES	YES	NO	YES	NO	NO
9	YES	YES	YES	NO	NO	NO
10	YES	YES	YES	YES	YES	YES
11	YES	YES	NO	YES	NO	NO
12	YES	YES	YES	NO	NO	NO
13	YES	NO	YES	YES	YES	NO
14	YES	YES	NO	NO	NO	NO
15	YES	YES	YES	NO	NO	NO

YES means a FN occurred

Disc-shaped lesions

**FN proportion Left Apex lesion: 10/15 = 66.7%**

Competency-based simulation training
Achieving ≤ 5 mm accuracy threshold using the methodical TRUS PBx technique at Center B

Trainee	Year	Baseline Accuracy (12-core)		12-core Practice Sets Taken	Best/Competency Accuracy (12-core)	
		Mean	Range		Mean	Range
B2	PGY1	8.7	5.7-11.3	7	4.6	1.1-11.8
B7	PGY2	9.2	0.9-17.7	6	3.3	0.8-6.9
B12	PGY2	9.2	2-16	7	4.9	1.5-8.9
B1	PGY4	6.0	2.7-13	6	4.6	1.7-8
B8	PGY4	9.6	1.3-22.2	4	4.2	0.9-8.9
B9	PGY4	11.9	2.9-19.8	10	4.7	1.6-10.7
B10	PGY4	9.0	4.5-16.4	5	4.9	1.4-10
B3	PGY5	4.9	1.1-10.1	1	4.9	1.1-10.1
B4	PGY5	14.8	6.9-22.5	7	4.9	2.2-8.7
B5	PGY5	7.2	2.6-13.2	7	2.9	1.5-4.8
B6	PGY5	11.7	3.8-26.7	6	4.2	1.9-7.1
B11	PGY5	5.5	2.7-9.7	4	4.5	1.8-6.5
Prg B	**-**	**9.0**	**0.9-26.7**	**5.8±2.2**	**4.4**	**0.8-11.8**
A9	PGY1	10.7	5.8-18.2	3	7.3	0.9-15.5
A3	PGY2	8.0	3.4-15.1	6	5.9	1.6-12.7
A5	PGY2	7.1	1.3-17.9	6	5.1	2.1-11.4
A7	PGY2	13.5	3.7-35.5	6	4.6	1.7-8.5
A8	PGY3	19.1	2-41.2	6	4.6	1.9-11.2
A10	PGY3	9.1	3.9-18.7	6	5.2	1.9-9.6
A12	PGY3	7.1	3.2-14.2	6	7.1	2.5-12.5
A6	PGY4	6.5	2.2-10.9	6	6.2	0.8-11.4
A11	PGY4	20.1	12.1-30.7	3	20.1	12.1-30.7
A13	PGY4	7.7	2-18.2	6	6.0	1.3-10.1
A1	PGY5	9.0	3.5-16.7	3	8.5	1.9-15
A2	PGY5	11.7	3.9-25.3	3	7.7	2.2-27.8
A4	PGY5	24.5	11-40.9	6	8.4	3.2-15.3
Prg A	**-**	**11.9**	**1.3-41.2**	**5.1±1.4**	**7.4**	**0.8-30.7**
C3	-	6.6	3.2-11.4	4	4.9	1.6-11.6
C6	Fellow	7.3	4.1-15.5	3	4.6	2-8
C10	Fellow	14.9	4-26.9	8	4.3	2.5-6.2
C4	Fellow	16.8	6.4-32.9	5	10.4	2.8-27.4
C7	PGY1	10.0	5.2-14.2	4	6.1	2-12
C8	PGY1	12.9	1.6-31.8	5	6.0	2.4-8.8
C11	PGY1	8.4	1.9-14.2	8	4.0	1.9-7.7
C14	PGY1	10.1	3.3-22.9	5	4.1	2-6.6
C16	PGY1	13.3	5.2-21	3	4.9	1.6-10.5
C1	PGY3	13.6	4.5-25.2	2	13.6	4.5-25.2
C5	PGY3	18.1	7.2-31.2	14	4.5	1.9-8.1
C12	PGY3	8.1	1.8-14.5	6	4.5	1.4-7.9
C13	PGY4	11.5	4.1-17.4	7	4.6	1.4-12.5
C15	PGY4	10.6	3.6-24.7	5	4.9	2.9-9.8
C2	PGY5	9.1	3.7-14.3	8	4.8	3.1-9.4
C9	PGY5	11.2	2.7-19.8	7	3.6	0.4-7.2
Prg C	**-**	**11.4**	**1.6-32.9**	**5.6±3.0**	**5.6**	**0.4-27.4**

Improvement in mean spatial error during systematic TRUS side-fire prostate biopsy after simulator-based training in three academic health centers (all units in mm)

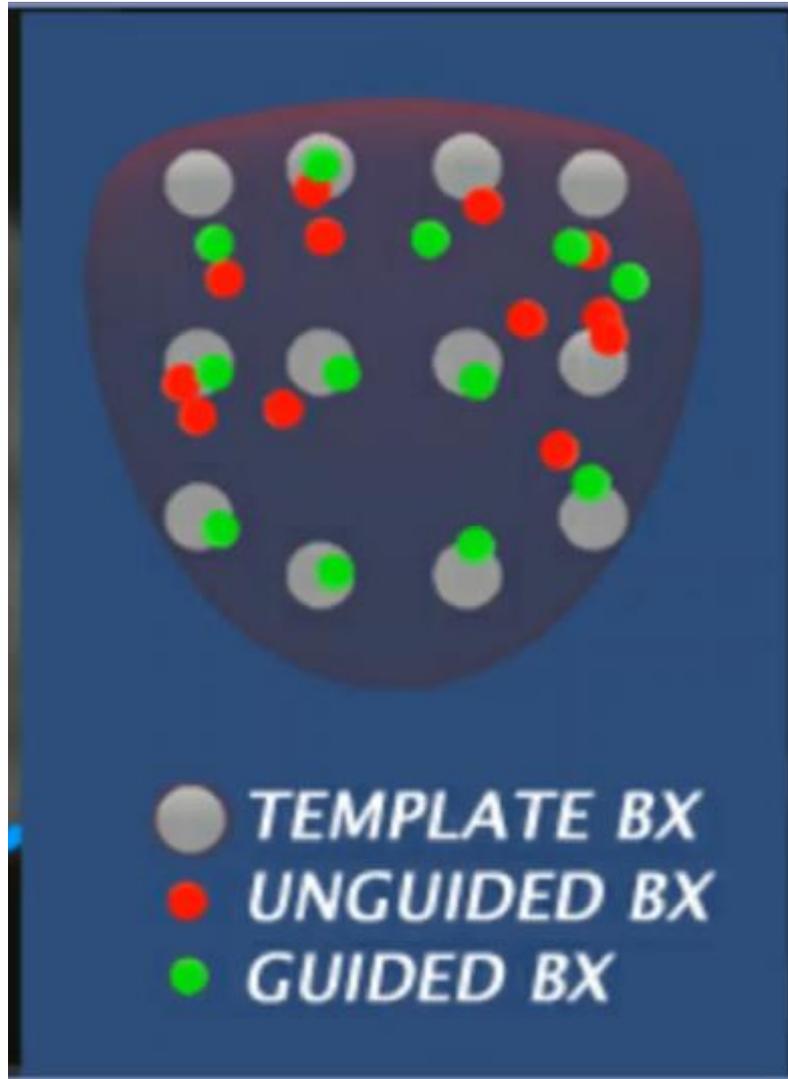# FN decreases with average mean error (p=0.0007) – Left Apex
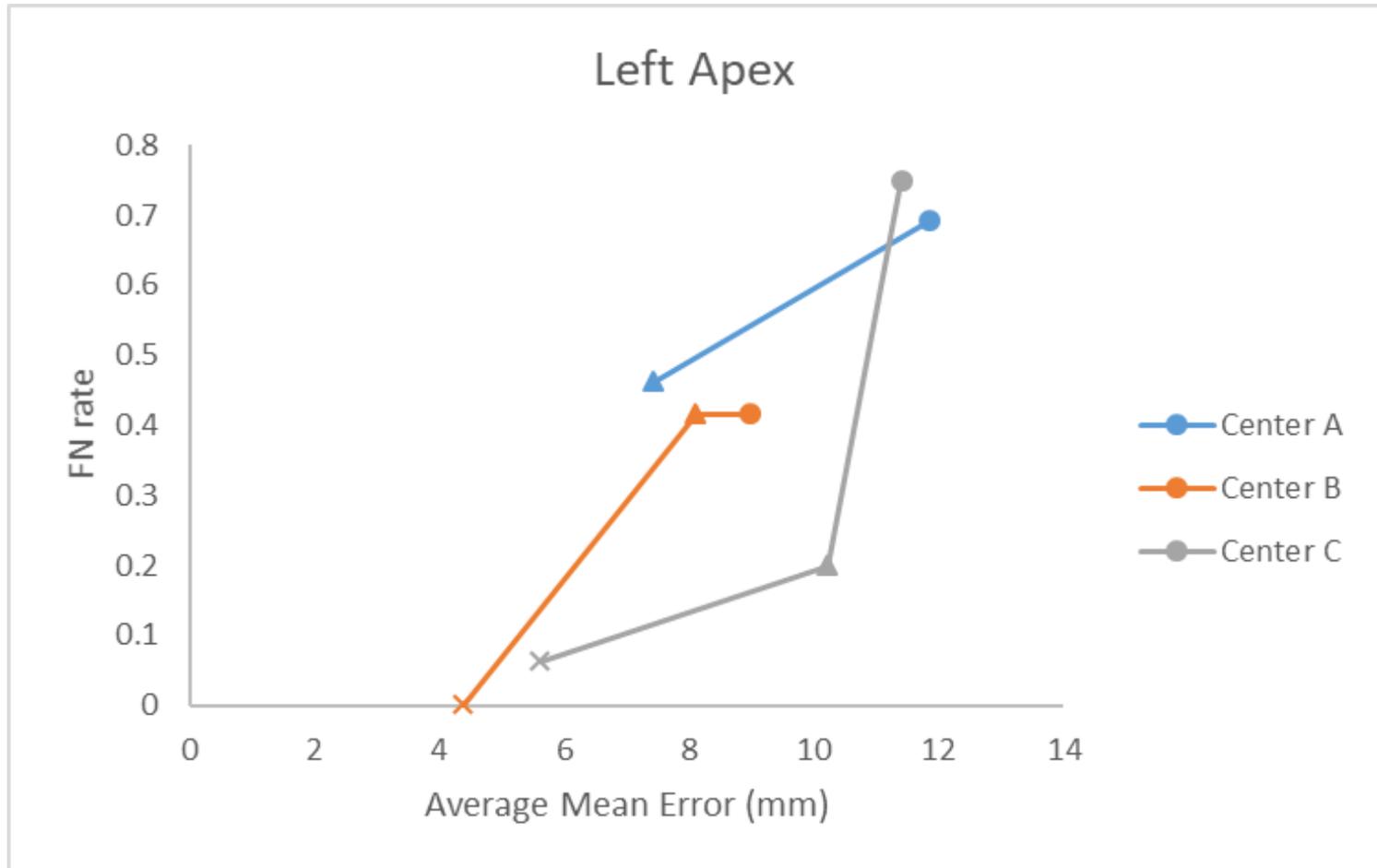
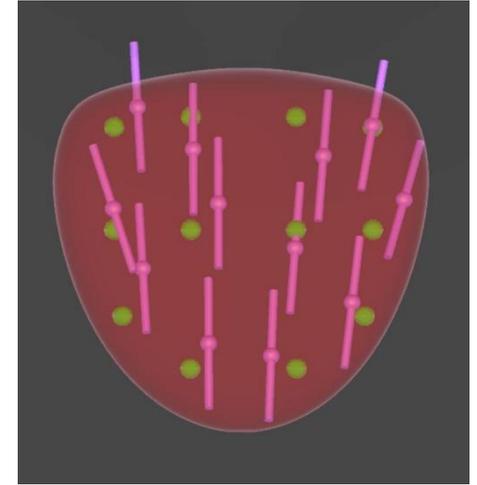# FN decreases with average mean error (p=0.0007) – Right Apex

Right Apex
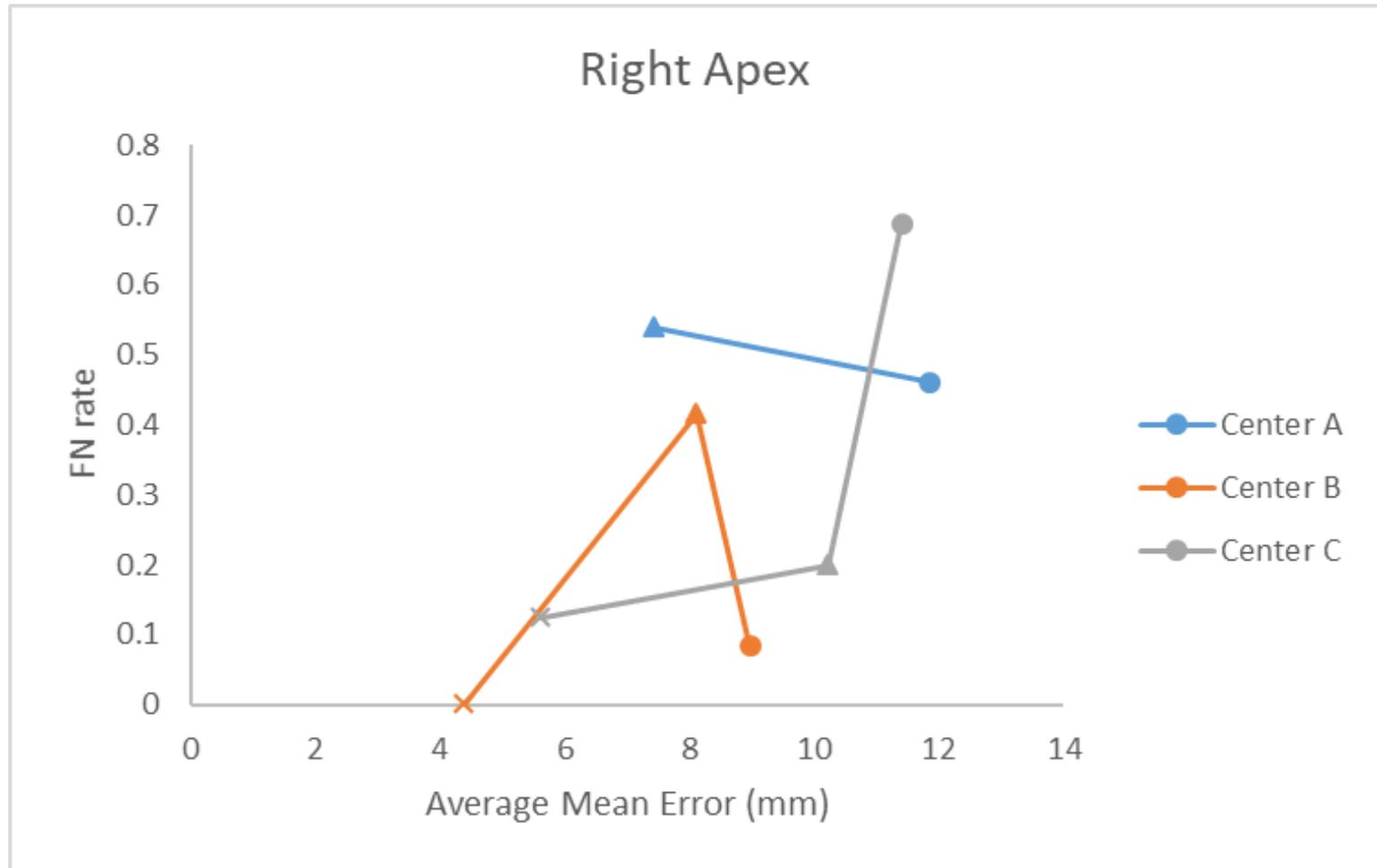
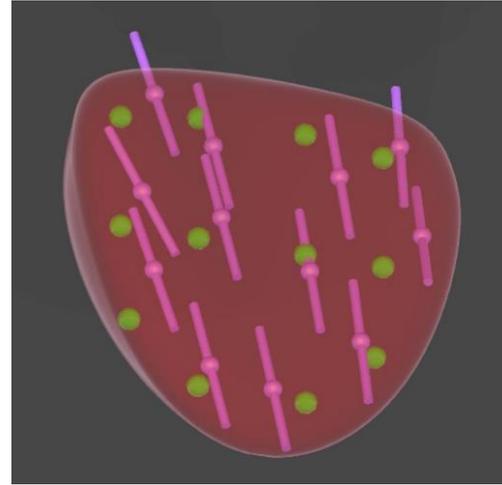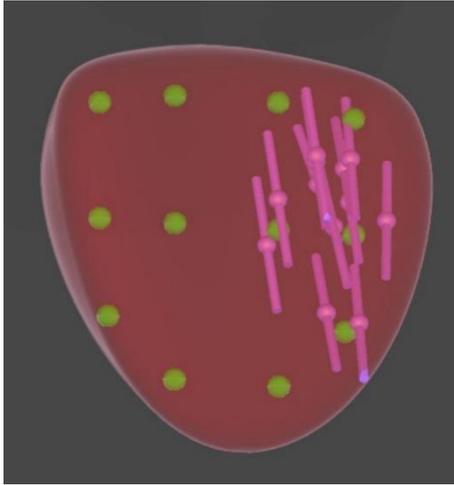- For all three centers, the false negative rate is increased by 20% with each 1 mm increase in mean average error.

False negative prostate biopsy
Biopsies (red) deviate from template (grey)

Improvement with simulator-based training – same trainee

- The number of 12 core sets needed to reach competency at Center B ranged from 1 to 10

Pitch-Neutral Systematic Prostate Biopsy Technique

- As far as we are aware,
  - no prostate biopsy simulator available prior to ours
  - no prostate biopsy technique existed or was taught

Future work

- Our lab developing a new precision prostate biopsy system for actual patient care, (not clinician training) that does not require MRI imaging

Take home messages

- PSA/DRE are useful screening tests and may help with early PCa detection

- Early PCa detection: improved odds of (a) survival and (b) retaining quality of life

- If your biopsy is negative for PCa, make sure to get a repeat PSA no later than 6 months after the biopsy

NCCN Prostate Cancer Early Detection Guidelines 2019

- **Between ages 45-49**, obtain a baseline PSA accompanied by DRE. If greater than 1, test at one year intervals; if less than 1, next test at age 50d

- **Between ages 50-70**, test PSA at one year intervals

- **Between ages 70-75**, test PSA in healthy individuals

- **Greater than age 75**, PSA screening only in the healthiest individuals

It's personal

- http://problemsolvingcare.org/sems-cancer-was-discovered-by-using-a-new-technology-to-target-the-tumor/

Questions?

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