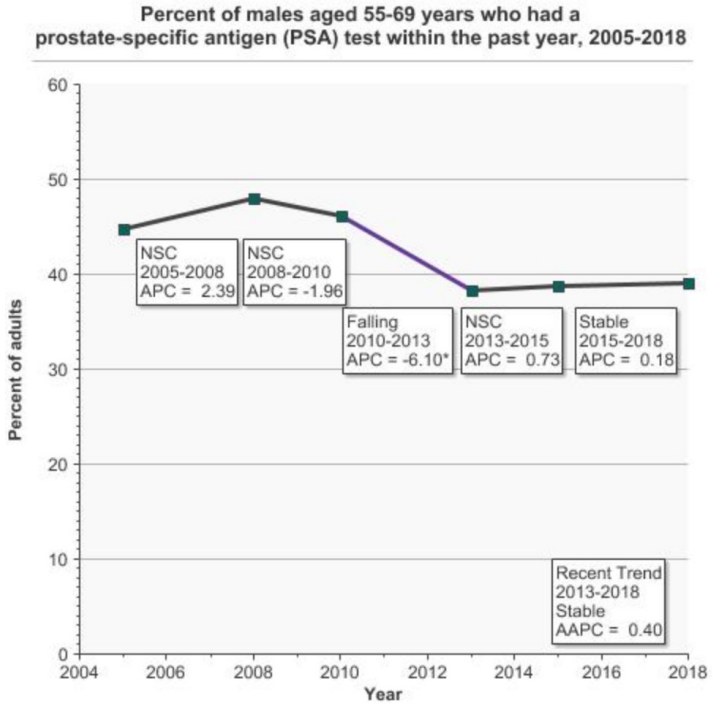
Game Changers in Prostate Cancer Diagnostics: Imaging Probably Wins the Most

John W. Davis, MD, FACS


Right Decision
Wrong Decision
EXCUSES
PROGRESS

PSA Screening—what happens?

- Earlier detection of disease
- Modest gain in mortality
- Risks of diagnostic testing, treatment
- Overdetection of low grade disease



NCI Cancer Progress Report 2022

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Prostate Cancer Screening Trials

	PLCO	ERSPC	CAP
Total Population	76,693	162,243	419,582
Age	55-74	55-69 (50-74)	50-69
PSA testing interval	Annual for 5-6 years	q2-7 yr	Single invitation
Biopsy threshold (ng/mL)	4	3	3
Prostate cancer mortality	**Equivocal**	**Benefit to screening**	**Equivocal**
Limitations	**Contamination**	**Variable intervals**	**Lead time**

Hugosson J, Roobol MJ, Mansson M, Tammela TLJ, Zappa M, Nelen V, et al. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. Eur Urol. 2019;76(1):43-51.
Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. JAMA. 2018;319(9):883-95.
Pinsky PF, Miller E, Prorok P, Grubb R, Crawford ED, Andriole G. Extended follow-up for prostate cancer incidence and mortality among participants in the Prostate, Lung, Colorectal and Ovarian randomized cancer screening trial. BJU Int. 2019;123(5):854-60

Prostate Cancer Screening Trials

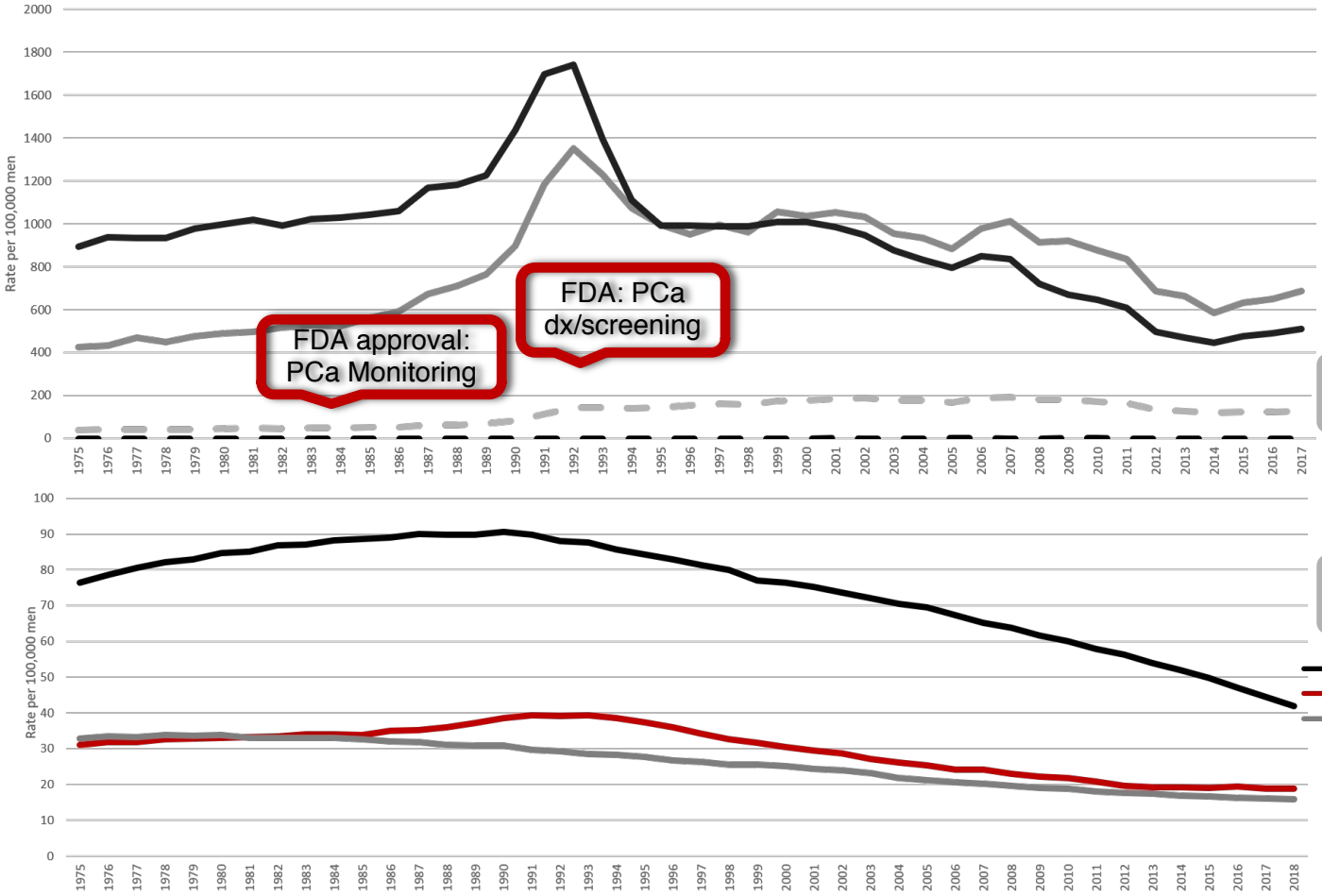
	PLCO	ERSPC	CAP

Take home points

- **Some data suggests benefit, but still concern for many being overtreated**
- **Other data shows no benefit**
- **Most data shows**
  - **In the first round of screening a cohort we detect many untreatable/aggressive cancers which may dilute the CSS benefit**
  - **Screening leads to overdiagnosis of many clinically insignificant cancers**

Hugosson J, R 19;76(1):43-51.
Martin RM, D domized Clinical Trial. JAMA. 2
Pinsky PF, Miller E, Prorok P, Grubb R, Crawford ED, Andriole G. Extended follow-up for prostate cancer incidence and mortality among participants in the Prostate, Lung, Colorectal and Ovarian randomized cancer screening trial. BJU Int. 2019;123(5):854-60

PCa Screening: Trials, Reducing Overdiagnosis, and Improving Utilization



Prostate Cancer in low PSA

PCA possible whenever a needle passed

PSA level	Prevalence of Prostate Cancer	High-Grade Disease
3.1 - 4.0	26.9%	25.0%
2.1 - 3.0	23.9%	19.1%
1.1 - 2.0	17.0%	11.8%
0.6 - 1.0	10.1%	10.0%
<0.5	6.6%	12.5%

Thompson et al, JAMA 294:66-70, 2005.

Thompson et al, NEJM 350:2239-46, 2004.

2012 Media Sound Bites—Mostly Against Screening

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Experts explain why PSA test is not w

By Liz Szabo, USA TODAY

Comment Recommend 120 Tweet 18 +1 0

A government panel issued a recommendation Monday that health
screened for prostate cancer with the PSA test. USA TODAY aske

By Michael A. Schwarz, USA TODAY

Cancer isn't necessarily always deadly, says Otis Brawley, chief medical officer at the American Cancer Society. Up to 60% of prostate cancers never need to be found, he says.

Q: Why should men skip the

A: Men are unlikely to be helped
Virginia Moyer, a pediatrician an
U.S. Preventive Services Task F
recommendation. Researchers
in overall survival between men
get a PSA and other men.

STORY: PSA harmful, study finc
MORE: PSA screening twitter ch

Q: Will the PSA still be available?

A: Yes. Men concerned about prostate cancer can still ask for the PSA, says Ian Thompson, a urologist and spokesman for the American Urological Association. The task force's recommendation notes that doctors should "understand the evidence but individualize decision-making to the specific patient or situation," such as men with a strong family history of prostate cancer.

Q: Why not get a PSA just in case it helps?

Q: What are the risks of treating prostate cancer?

A: Prostate cancer surgery increases a man's risk of urinary incontinence by 28 percentage points, from 21% among men who didn't have surgery to 49% among men who had surgery, according to the evidence review in *Annals of Internal Medicine.*

Prostate cancer surgery increases a man's risk of erectile dysfunction by 36 percentage points, from 45% among men who haven't had surgery to 81% among men who have had surgery.

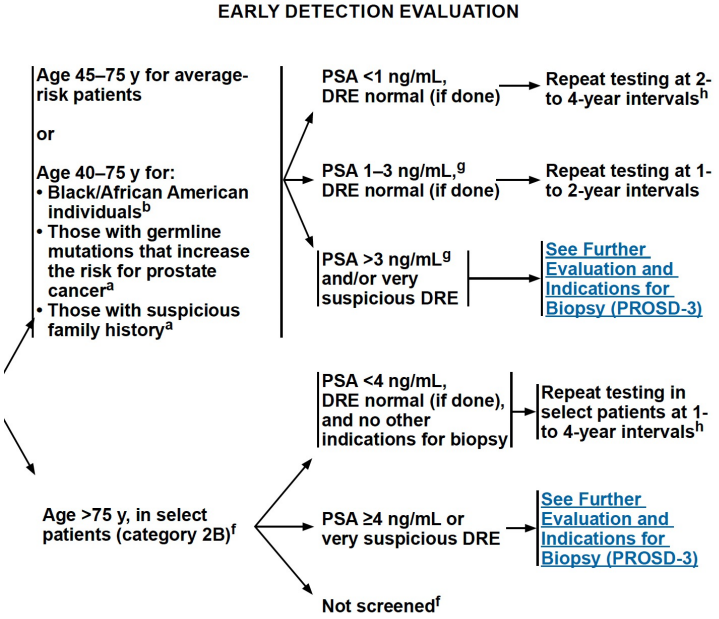
Up to one in 200 men die from prostate cancer surgery, Moyer says.

2012 Screening Guidelines

- When
  - Starting age 40 for baseline
  - Consider stopping or slowing age 75
- Who
  - Properly counseled patients
  - Higher risk groups
  - Higher baseline PSA's; any abnormal DRE
- How
  - NCCN or other guidelines/algorithms on how to trigger a biopsy, secondary testing, additional biopsies
- Frequency?
  - A few reports of decreased screening since guidelines, but likely will continue in some form and add better markers

2022 Updates--NCCN

- Baseline Evaluation
  - Family history, germline mutations
  - PSA and related history
  - Ethnicity
  - Medications
  - Environmental exposures
- Risk/benefit discussion on detection
  - Baseline PSA
  - DRE discussion
- Age/PSA based initial algorithm



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PCA Early Detection Management

- Abnormal PSA—repeat it, DRE if not done, evaluate benign disease
- Two big changes:
  - Multiparametric MRI, “if available”—the latter I hope drops at some point!
  - Consider biomarkers that improve the specificity of screening
- High suspicion of clinically significant cancer: TRUS or TP biopsy with/without MRI targeting
- Low suspicion: follow-up in 6-12 mo with PSA/DRE

Management Footnotes

- PCPT levels of PSA correlate with PCA risk
- MRI targeted biopsy: increases detection of clinically significant, higher-risk GG>=3 PCA while lowering detection of GG1—lower volume GG2.
  - Targeted vs systematic inclusion approach—some high grade PCA unique in systematics—well referenced
- Negative MRI does not exclude possibility of cancer—consider PSA density or secondary biomarkers in deciding whether or not to avoid a biopsy

- Secondary biomarkers
  - Percent free PSA
  - PHI
  - Select MDx
  - 4k Score
  - ExoDx Prostate Test
  - MyProstateScore—MPS
  - Iso PSA
  - Extent of validation across diverse populations is variable
  - ***Not known if new tests could be applied in optimal combination with MRI***

Management Footnotes

- TP biopsy—associated with lower risk of sepsis; reduced need for antibiotics
- Persistent PSA increase and high PSA density with normal MRI—encourage biopsy

Back to 2012…USPSTF: 4 Point Evaluation

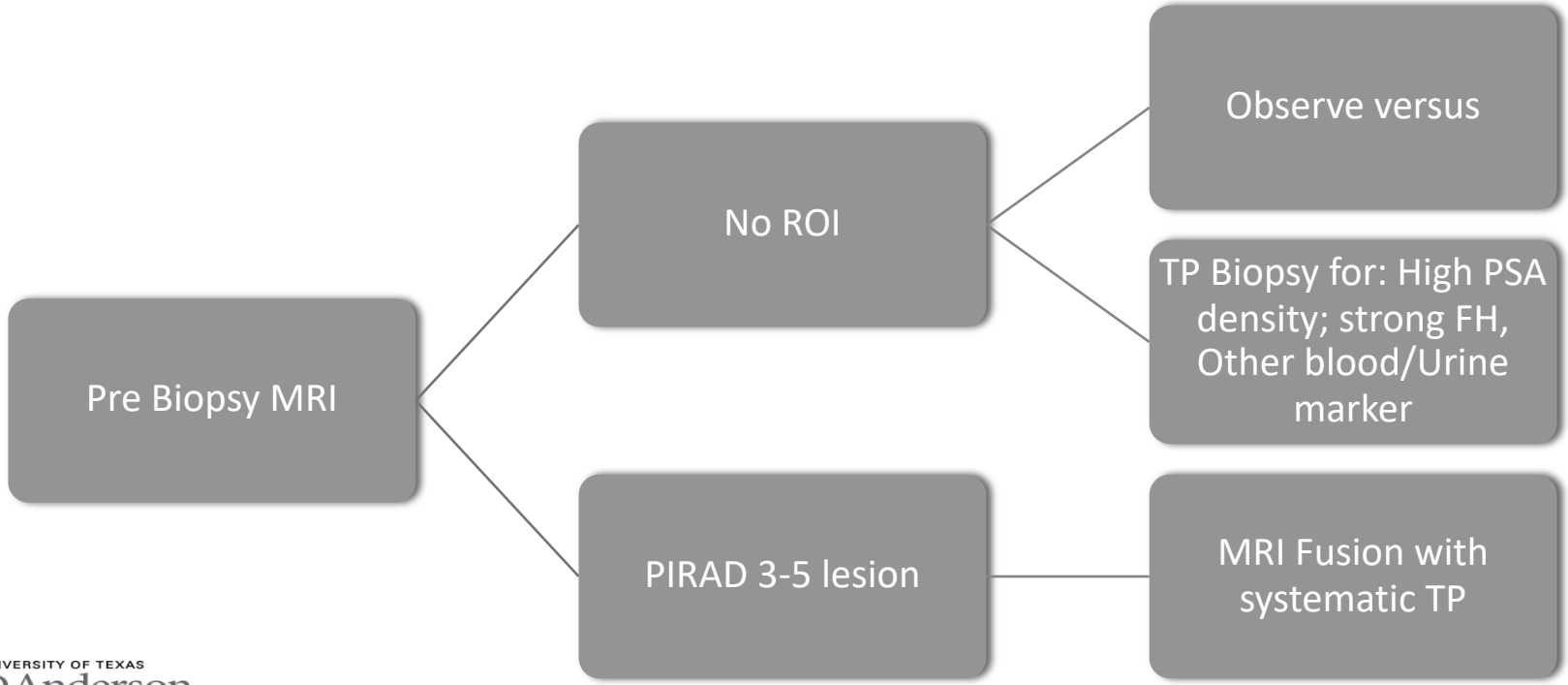
1. Benefits of Screening
   - 2 RCT's
2. Harms of Screening
   - Biopsy harms, PSA "itis"
3. Benefits of Treatment
   - PIVOT, Bill-Axelson, others
4. Harms of treatment
   - Mortality, complications, QOL

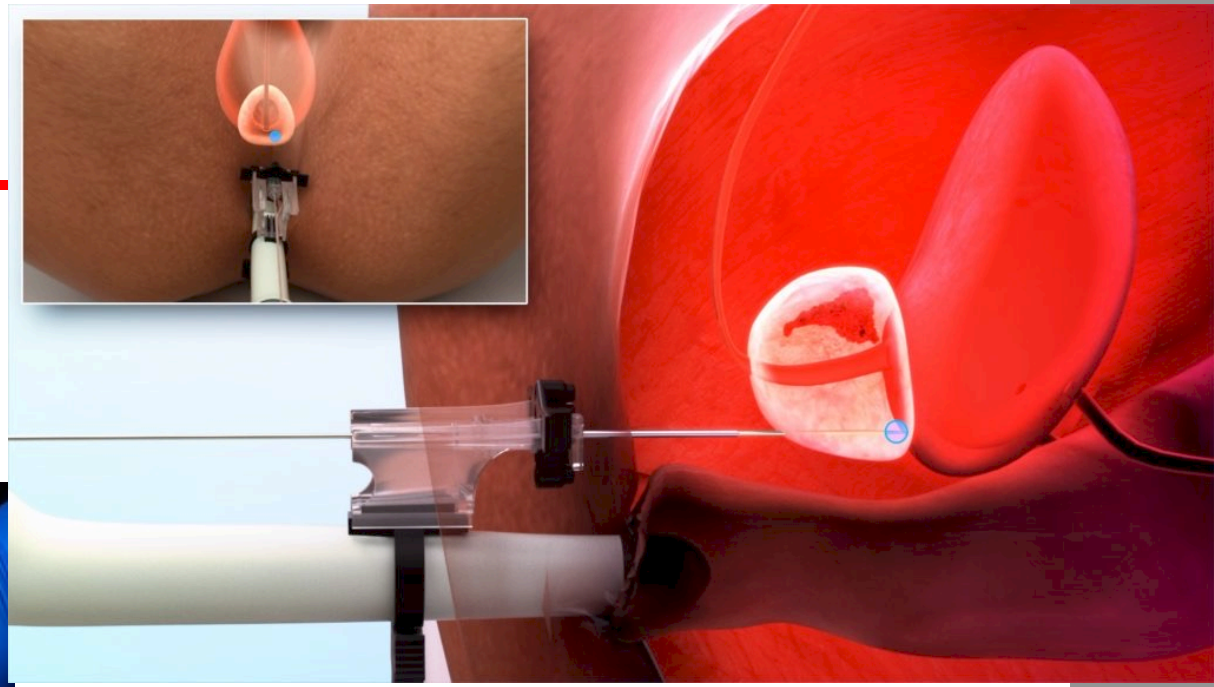
- ***By inference, this means that innovation and dissemination of improvements along any of these 4 categories will have a net improved effect on PSA screening***

2017 Premier Perspective Data

2008-2016	Open All	Open RH	RARP	LRP
Patients	26,253	21,110	84,186	1,002
Hosp Mortality	62 (0.234%)	46 (0.220%)	36 (0.042%)	3 (0.300%)
Post Discharge	17 (0.065%)	17 (0.081%)	27 (0.032%)	0
Overall Periop Mortality	79 (0.301%)	63 (0.300%)	63 (0.070%)	3 (0.300%)
Ratio 1 in __	332	333	1428	333

UCLA Algorithm





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Summary: Repeat TRUS—Fusion—TP

Clinically Significant Cancer

	Prior Neg Biopsy	Active Surveillance	N=
TRUS-BX	15%	16%	624
Transperineal	34%	33%	148
MR-Fusion Bx	31%	43%	530

BJUI Compass Catalog 2019-2022

Prostate Cancer Screening/Treatment

- Improved biopsy methods
  - TP has less infections with comparable cancer detection
  - Use of local anesthesia with TP biopsy
  - TP—selection for focal therapy
  - TP biopsy withs risk calculator validations
  - Pooled outcomes of PrecisionPoint TP access system
- Innovation
  - Single port retzius sparing technique

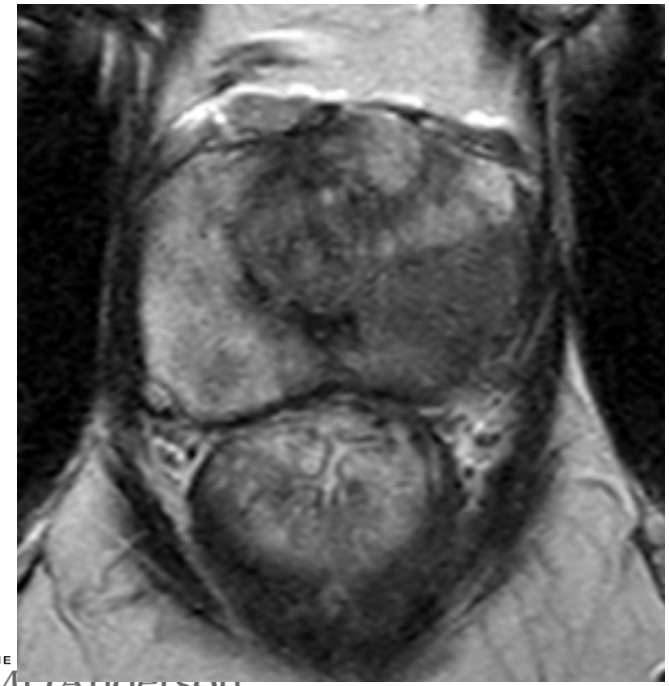
- Technical improvements to radical prostatectomy
  - Enhanced recovery
  - Methods to reduce incontinence
    - Slings vs not
    - Urethral length, bladder neck size
  - Online education re: ED
  - Selection for nerve sparing technique
  - Mobile APP to support pelvic floor exercises prior to RP
  - Detection and management of osteitis pubis

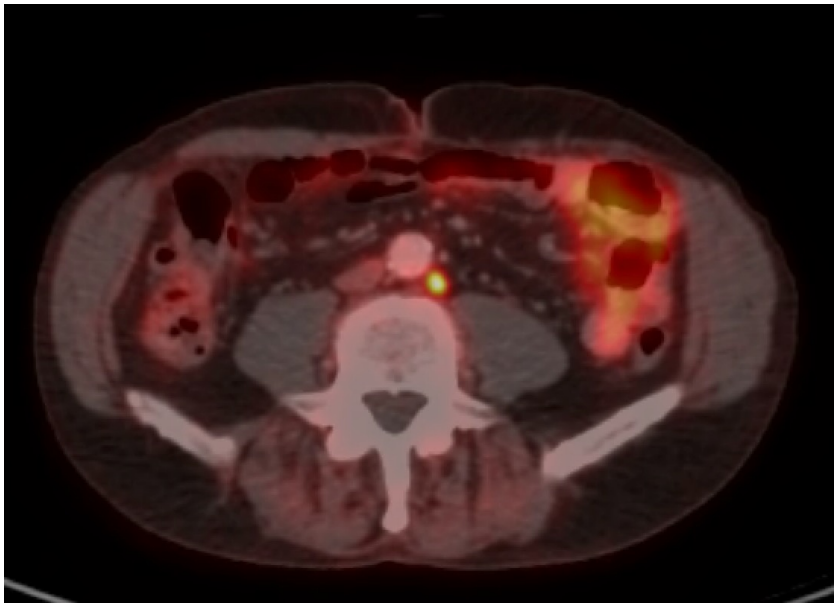
Conclusions: What are we doing better about PCA Screening?

- Better guidance:
  - When to screen and stop
  - Genetic, ethnic higher risk groups
  - mpMRI diagnostics
  - Secondary biomarkers
  - Longer term f/u on screening trials
- Techniques to reduce biopsy cost, morbidity, diagnostic failures
  - TP, fusion, local anesthesia
  - Risk calculators
- Acceptance of surveillance plus better guidance on how to select/conduct/monitor
- Treatment improvements
  - Minimally invasive surgery
  - Techniques to improve continence
  - RT techniques to improve results

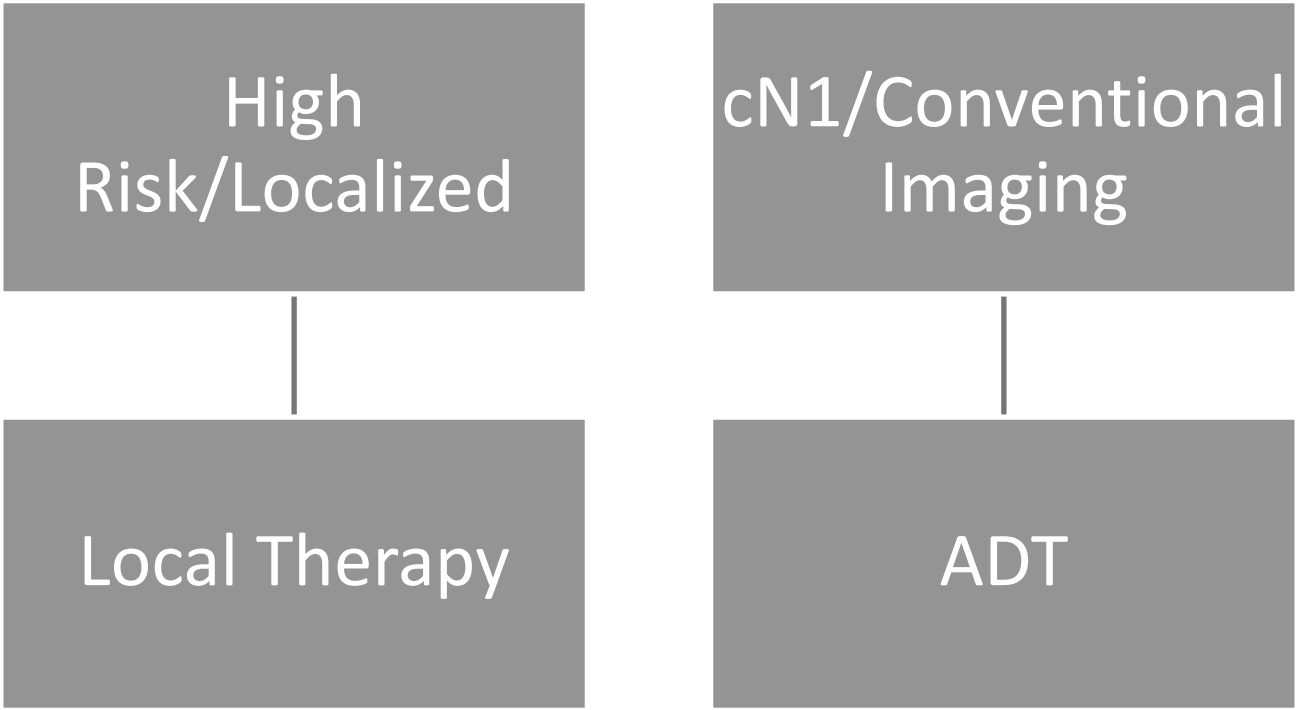
MRI—Large lesion—resectable

PSMA PET: 5 nodes including periaortic

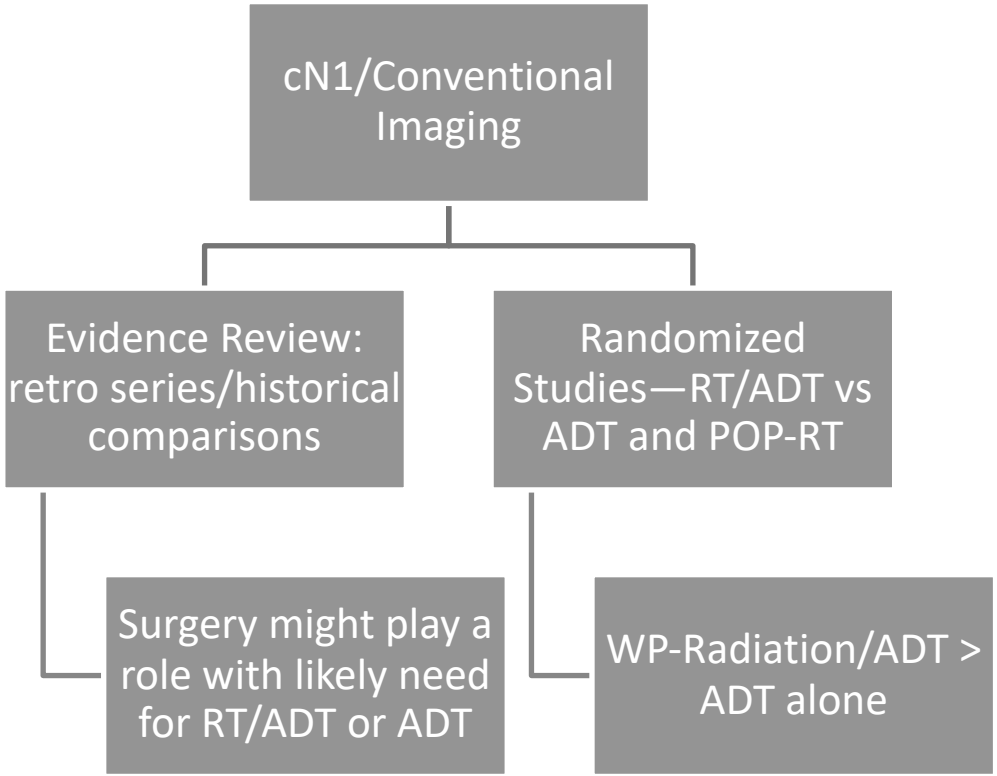




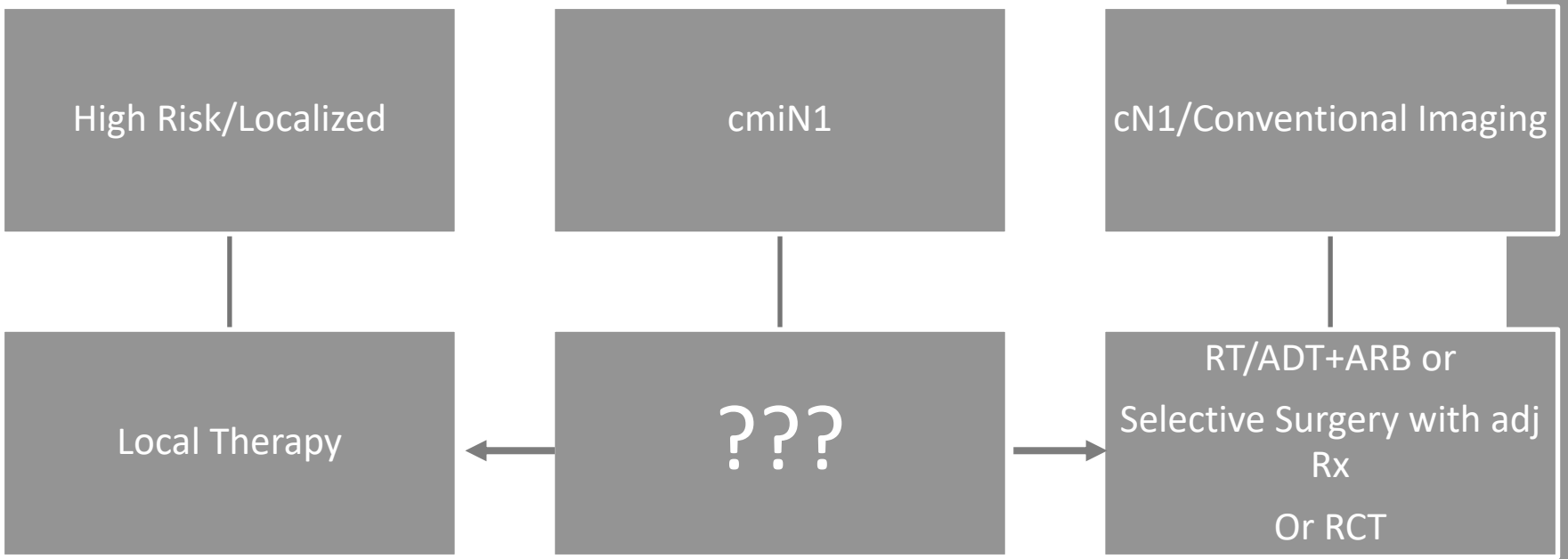
Historic Management of cN1 Disease



Updated Management of cN1 Disease



PSMA PET Era Management of cN1 Disease: c[mi]N1 (molecular imaging) vs cN1



Arguments

- We don’t know the staging implications of c[mi]N1 disease—so round it down to high risk cN0
- Control of the primary might be valuable
- Extent of pN1 disease is prognostic
- E-PLND might reduce ADT burden for limited N1 disease

Facts

- cN1M0 incidence 12% at presentation
- Surgical management 10-50% variance by country
- PSMA PET 40% sensitive, > 90% specific—false positive argument is there but 5-10%
- PSMA PET Positive—additional might be found

Rationale/Selection/Exclusions

- Provide local control, chance of cure, reduce metastatic progression and survival metrics
  - ADT alone cannot provide this
  - RT requires extended ADT—possible dual therapy. For some patients, same rationale for avoiding RT—logistics, ADT, inflammatory bowel disease, ? Cardiac risks
- Inclusion—minimal/equivocal cN1 disease, location in pelvis “in field” for eplnd, desire to avoid RT or ADT components
- Exclusions-Multiple sites, out of pelvis, out of field

PSMA PET Positive vs Negative

BJU Int 2023; **131:** 330–338 doi:10.1111/bju.15881

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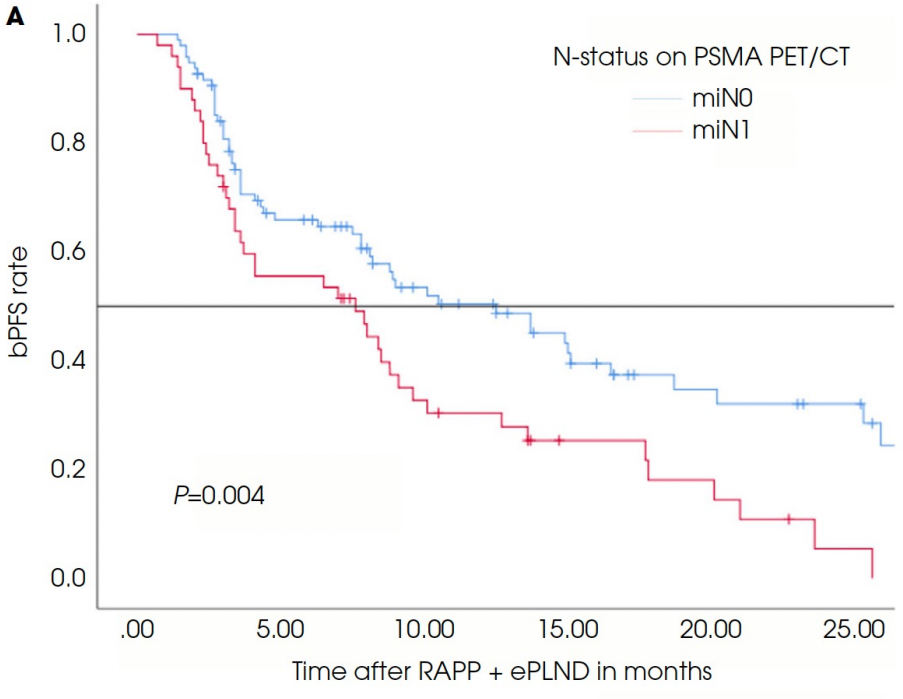
Original Article

The prognostic value of lymph node staging with prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and extended pelvic lymph node dissection in node-positive patients with prostate cancer

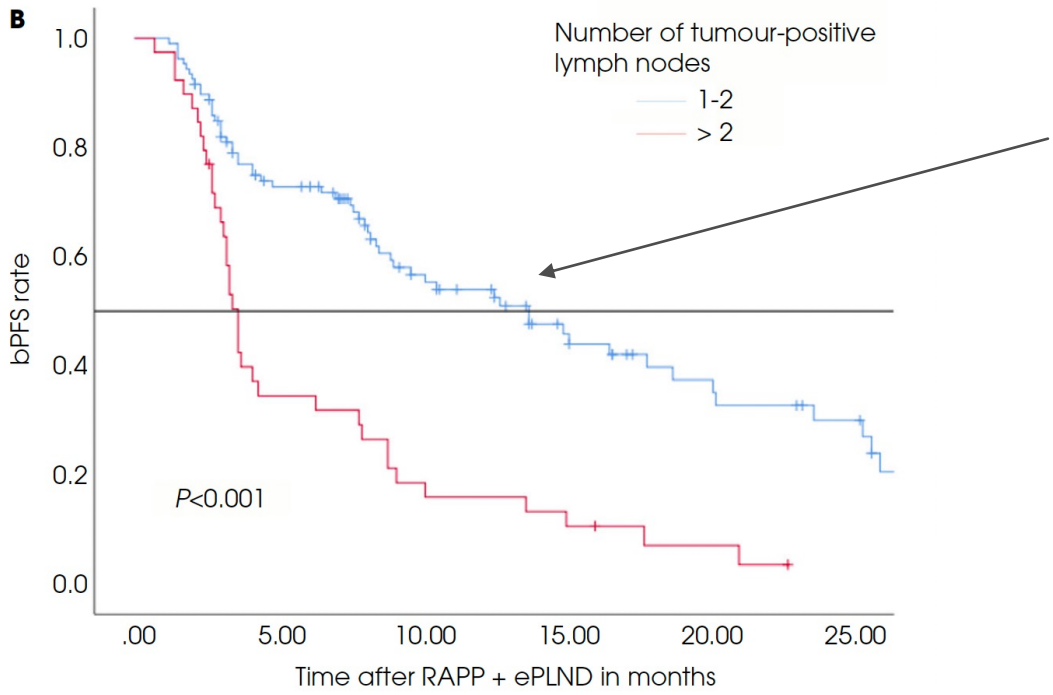
Dennie Meijer[1,2], Rosemarijn H. Ettema[1], Pim J. van Leeuwen[3], Theo H. van der Kwast[4], Henk G. van der Poel[3], Maarten L. Donswijk[5], Daniela E. Oprea-Lager[2], Elise M. Bekers[6] and André N. Vis[1,3]

Department of [1]Urology, Prostate Cancer Network Netherlands, Amsterdam University Medical Center and [2]Radiology & Nuclear Medicine, Cancer Center Amsterdam, Amsterdam University Medical Center, VU University, [3]Urology, Prostate Cancer Network Netherlands, [5]Nuclear Medicine, and [6]Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands and [4]Department of Pathology, University Health Network, Toronto, ON, Canada

PSMA PET Positive vs Negative



PSMA PET Positive vs Negative



- Inclusion criteria—looking for 1-2 nodes max
- In field—iliac chains
- And a little luck

Therapeutic or Diagnostic Bridge to Adjuvant Rx?

Effect of Extended Pelvic Lymph Node Dissection on Oncologic Outcomes in Patients with D'Amico Intermediate and High Risk Prostate Cancer Treated with Radical Prostatectomy: A Multi-Institutional Study

Felix Preisser, Roderick C. N. van den Bergh, Giorgio Gandaglia, Piet Ost,* Christian I. Surcel, Prasanna Sooriakumaran, Francesco Montorsi, Markus Graefen, Henk van der Poel, Alexandre de la Taille, Alberto Briganti, Laurent Salomon, Guillaume Ploussard and Derya Tilki,† on behalf of the EAU-YAUWP

0022-5347/20/2032-0338/0
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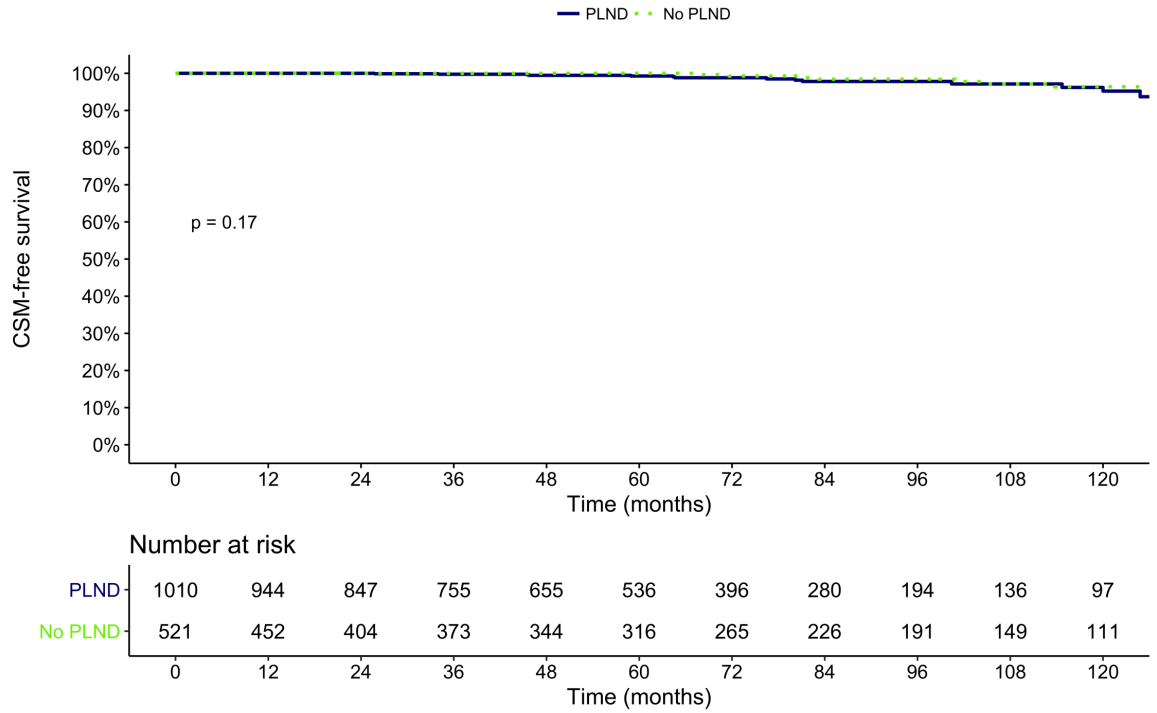
https://doi.org/10.1097/JU.0000000000000504
Vol. 203, 338-343, February 2020
Printed in U.S.A.

Therapeutic or Diagnostic Bridge to Adjuvant Rx?

Supplementary figure 3: Kaplan-Meier analysis depicting cancer-specific free survival forpatients who undergo PLND or do not undergo PLND at RP, after 2:1 propensity scorematching.



RP/PLND w/wo adj RT for pN1 Thiruthaneeswaran Clin Oncol 2020

Table 1
Prostatectomy ± adjuvant radiotherapy for pN1M0

Reference	*n*	Primary management	Median lymph node density*	Radiotherapy dose†	ADT	Outcome
[25]	250	RP + ePLND	2.5/16	CTVp = 59.4–70.2 CTVn = 55.8–72 (in 74% of patients)	All patients	10-year PCSS 72% (radiotherapy + ADT) versus 70% (ADT alone)
[26]	364	RP + PLND	2.4/13	CTVp = 55.8–72 Gy CTVn = 45–50.4 Gy	All patients	10-year CSS 86% (radiotherapy + ADT) versus 70% (ADT alone)
[27]	40	RP	NR	NA	ADT ($n = 18$)	CSS (85%) and overall survival (72.5%)‡
[28]	387 (total 1107)	RP + ePLND	1/15.8	NR	All patients	10-year CSM-free 84% (versus 87%)
[29]	7225	RP + PLND	NR	CTV = 68 Gy (WPRT in 53.7%, dose NR)	ADT ($n = 3239$)	5-year overall survival was 85.2% (observation), 82.9% (ADT), 88.3% (postoperative radiotherapy) and 88.8% (postoperative radiotherapy + ADT) ($P < 0.001$)
[30]	1652	RP + PLND	2.1/10	CTVp = 67 Gy	All patients	5-year overall survival 81% (ADT) versus 88% (ADT + radiotherapy) ($P = 0.007$)
[31]	1388	RP + PLND	NR	CTVp = 66–70 Gy CTVn = 45–50.4 Gy	ADT ($n = 1001$)	ADT versus ADT + radiotherapy (hazard ratio 0.46) Observation versus ADT + radiotherapy (hazard ratio 0.46)

- 7 retro studies in over 12,000 patients s/p RP/PLND and post Adj therapies
- Varying degrees of benefit of post RT/ADT vs ADT alone

RESEARCH ARTICLE

Optimizing patient's selection for prostate biopsy: A single institution experience with multi-parametric MRI and the 4Kscore test for the detection of aggressive prostate cancer

Sanoj Punnen[1]*, Bruno Nahar[1], Nachiketh Soodana-Prakash[1], Tulay Koru-Sengul[2], Radka Stoyanova[3], Alan Pollack[3], Bruce Kava[1], Mark L. Gonzalgo[1], Chad R. Ritch[1], Dipen J. Parekh[1]

PLOS ONE | https://doi.org/10.1371/journal.pone.0201384 August 9, 2018

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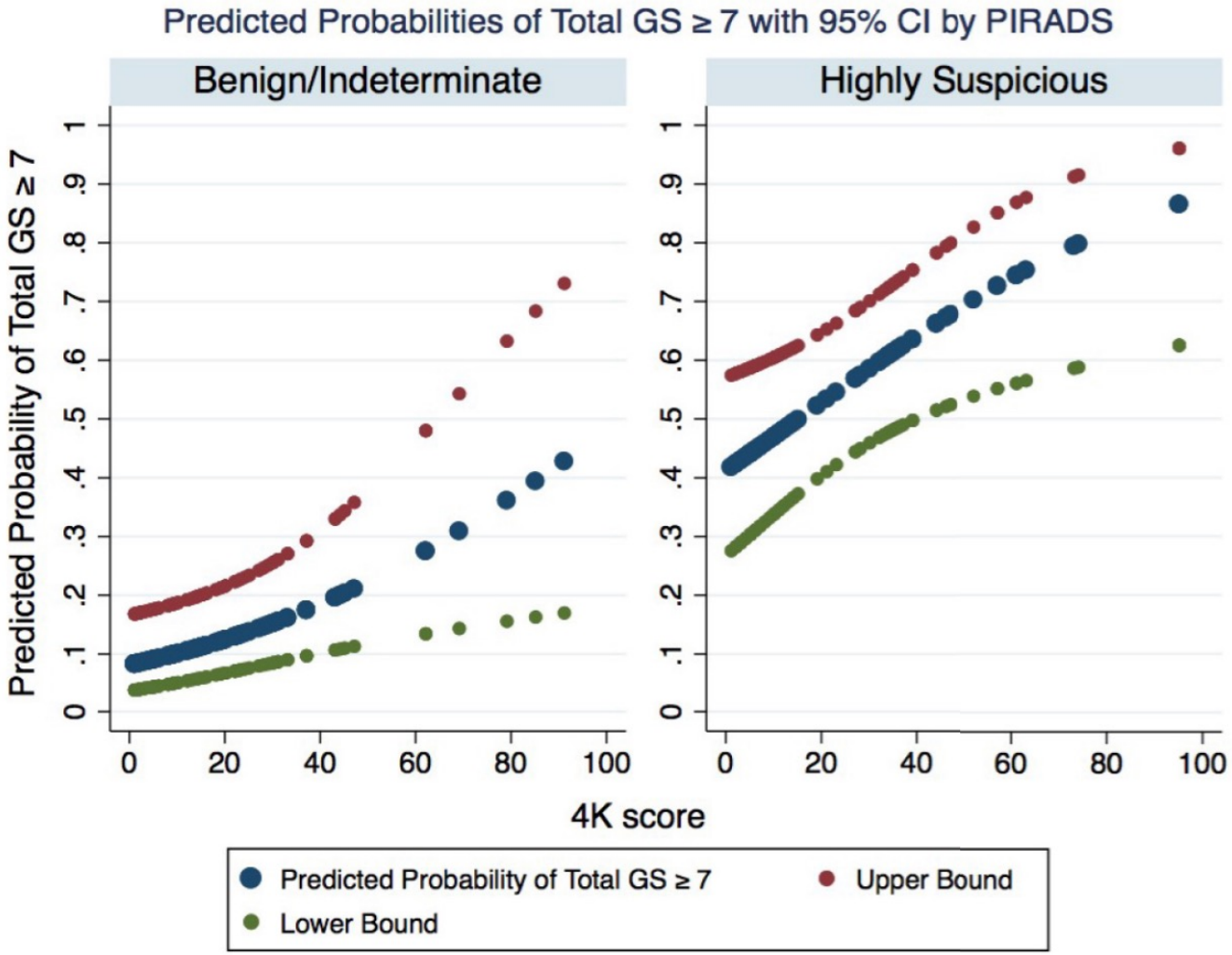


Table 2. The following table reports the impact of the following 5 strategies of using the 4Kscore and/or mpMRI to determine the need for a biopsy of the prostate among 149 men who had a 4Kscore, mpMRI and biopsy of the prostate.

Strategy	Biopsies Avoided	Any cancer detected	Any cancer missed	Gleason 7+ cancer detected	Gleason 7+ cancer missed
	N (%)	N (%)	N (%)	N (%)	N (%)
	N = 149*	N = 73*	N = 73*	N = 49*	N = 49*
Strategy 1	43 (29)	59 (80)	11 (20)	43 (88)	6 (12)
Strategy 2	81 (54)	49 (67)	24 (33)	38 (77)	11 (23)
Strategy 3	124 (83)	39 (53)	34 (47)	33 (67)	16 (33)
Strategy 4	23 (15)	69 (94)	4 (6)	48 (98)	1 (2)
Strategy 5	23 (15)	69 (94)	4 (8)	48 (98)	1 (2)

*149 men underwent a prostate biopsy, of which 73 had cancer, and 49 had Gleason 7 cancer

Strategy 1: Get a 4Kscore alone and perform a biopsy for any value above 7.5%

Strategy 2: Get an mpMRI alone and perform a biopsy for a positive MRI (PIRADS 4/5)

Strategy 3: Get a 4Kscore first and if less than 7.5%, do not biopsy. If greater than 7.5%, than do mpMRI and perform a biopsy only if it is positive.

Strategy 4: Get an mpMRI first. If it is positive, then biopsy, but if negative do a 4Kscore, and only biopsy if it is above 7.5%

Strategy 5: Getting both 4Kscore and mpMRI and doing a biopsy if either 4Kscore is above 7.5% or mpMRI is positive

https://doi.org/10.1371/journal.pone.0201384.t002

Imaging vs Biomarker

Comparison—Sanoj Punnen

mpMRI

- Pro
  - Level 1 evidence studies
  - Targeting—optimal grade, genomic testing
  - Definitive risk
  - Treatment planning
- Con
  - Variable access to high quality reads, targeting
  - Biopsy side effects—repeats over time

Biomarker

- Pro
  - Broader access
  - Improves specificity of psa
  - Risk estimate
- Con
  - Less level 1
  - Several products to compare
  - Non-targeted
  - Not a clear treatment planner

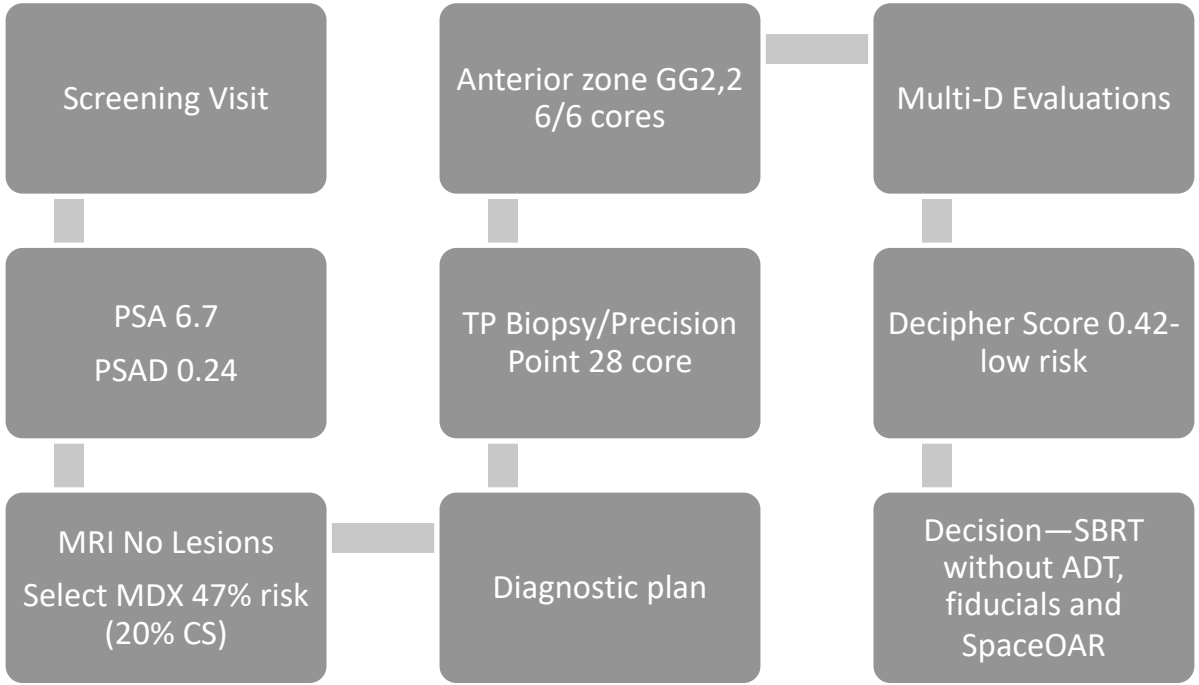
Tasks

- To patients/PCP's: Benefits of screening, if done properly
- 10 y progress in imaging, biopsy technology, secondary biomarkers, reduced morbidity
- Acquiring infrastructure and skills

Decisions

- MRI or secondary biomarkers to triage elevated PSA
  - My bias—age ranges—50-70 MRI next, > 70 markers next
- Fusion Platforms
- Microultrasound
- Genomic markers—likely GS 3+4

64 y/o AAM has SBRT for IR Prostate CA



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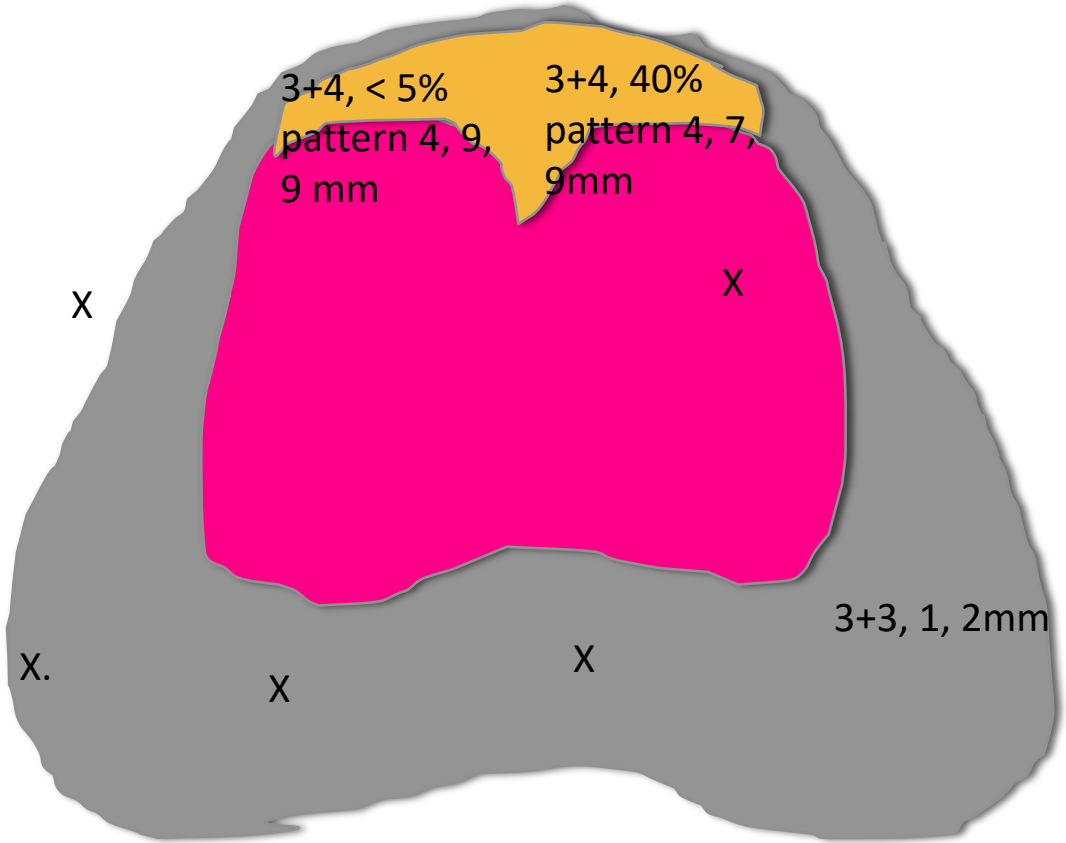
Results:

Right Basal
no tumor



Left Basal—
no tumor

Summary;
GS 3+4
Bilateral anterior
tumor
3/28 sites

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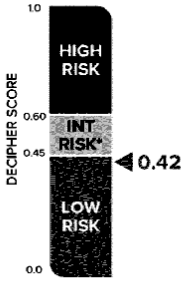
Decipher Score = 0.42—Low Risk

CLINICAL AND PATHOLOGY DETAILS For reference only, not used in calculation of genomic risk

Specimen: **Needle Biopsy** | Most Recent PSA: **8.9 ng/mL** | NCCN Risk Category: **Intermediate**
Clinical Stage: **T1c** | Gleason Score: **3 + 4**

DECIPHER GENOMIC RISK RESULTS



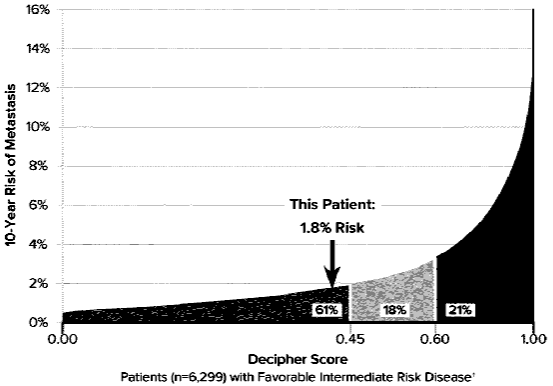
GENOMIC RISK IS: LOW			
0.7%	1.8%	3.3%	20.4%
5-year / *10-year* Risk of Metastasis with RT[1] or RP[2]		*15-year* Risk of Prostate Cancer Mortality with RT or RP	*At RP* Risk of Adverse Pathology

Clinical studies have shown that Decipher low-risk patients have a favorable prognosis.

- These patients may be ideal candidates for active surveillance.[1-3,6]
- Patients considering definitive treatment may have excellent oncologic outcomes when treated with local therapy alone.[2,5,9]

The Decipher score is determined solely by genomic characteristics of the tumor, independent of the NCCN risk category. No other clinical or pathologic parameters factor into the score.

RISK COMPARED TO PATIENTS WITH SIMILAR CLINICAL AND PATHOLOGIC FEATURES



Patients (n=6,299) with Favorable Intermediate Risk Disease[1]

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What did we learn?

1. Patient in the correct age for screening and had ethnic based higher risk, good survival odds, screening discussion
2. A full in house work-up; otherwise, our consult start with diagnostic optimization, i.e. MRI, path re reads, etc.
3. MRI first work-up—our practice is to use this for all; if contraindicated then primary TP biopsy if biopsy indicated, or some anesthesia work arounds
4. Use of secondary biomarkers to improve specificity

Conclusions

- PSA is the anchoring diagnostic test for prostate cancer—screening and clinical evaluation
  - And it was almost taken away!
  - Gamechangers: Extended f/u of screening trials—better understanding of at risk populations; multiple efforts to reduce diagnostic and treatment morbidity
- MRI and biopsy technique—gamechanger for treatment and AS
- Secondary biomarkers—more of an adjunct, specific case solution
- PSMA—gamechanger in high risk/locally advanced disease staging in addition to recurrent disease evaluation