# The Controversy over Prostate Cancer Screening

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"Relax, Mr. Fuerte, it's just a simple prostate examination!"

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# Agenda

- **PSA: A History**
- The Controversy
- Impact of PSA Screening
- Screening Smarter: PSA Derivatives
- Screening Smarter: Additional Testing
- What to do?

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# PSA: A History

## PROSTATE CANCER

- Most common solid cancer in men
- Mean age at diagnosis is 66
- New cases 180,000 this year (ACS Estimate)
- 1 in 7 men diagnosed in lifetime
- Deaths:  26,120
  - Down from over 40,000 in the mid 1990's
  - Second to lung cancer
  - 1:39 men will die of prostate cancer

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# PSA: A History

## PROSTATE CANCER: Risk Factors

- African Americans have higher incidence— 275/100k vs. 173/100k Caucasian
- BRCA gene mutation
  - Lifetime risk of prostate cancer is 33%
- FH of prostate cancer in father/brother before 65
- All associated with earlier onset prostate cancer and more aggressive disease

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# PSA: A History

## PROSTATE CANCER SCREENING

- A combination of History, Rectal exam (DRE), and PSA blood test

- Who?
  - Generally men 45-75 years of age
  - Life expectancy over 10 years
  - High risk start earlier—not before age 40
  - **Shared Decision Making discussion**

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# PSA: A History

- Albin credited with discovery in 1970

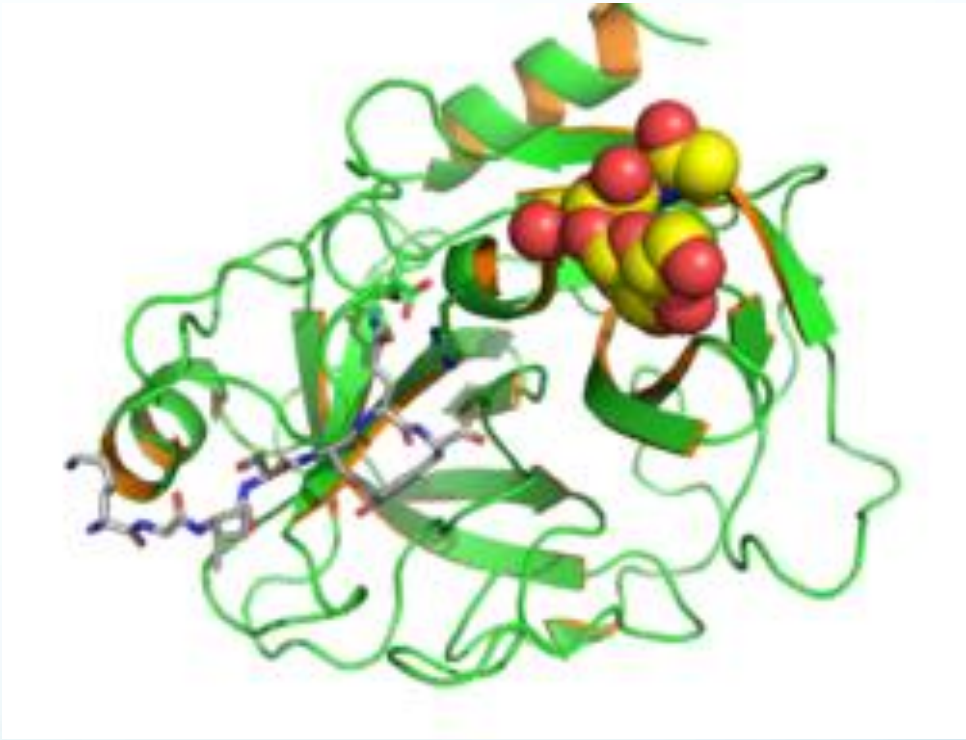
- Also known as gamma-seminoprotein or kallikrein-3 (KLK3)

- Secreted by the epithelial cells of the prostate gland

- Serine protease that lyses seminal clot and dissolves cervical mucous

- Hybritech Tandem-R PSA test first commercially available in 1986

- Before its discovery, the only way to diagnose Prostate Cancer was by detecting palpable disease (DRE)



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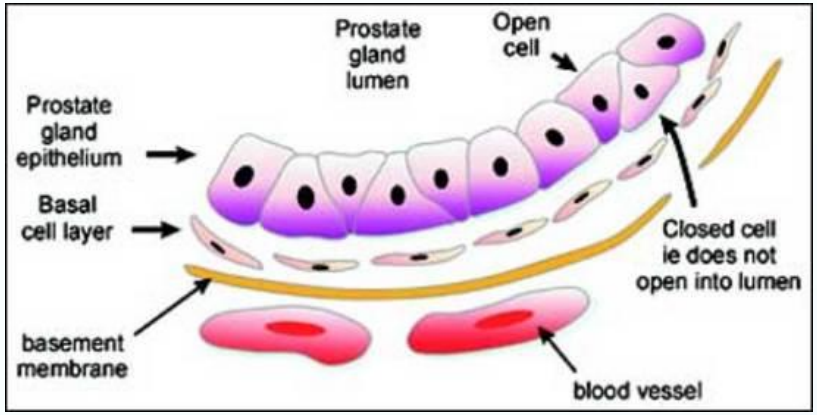
# PSA: A History

- Derangement of the gland's cellular architecture results in an elevation in serum PSA

- Glandular luminal secretion impaired

- May be due to a variety of factors (benign growth, infection, inflammation, trauma, malignancy)

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# PSA: A History

- Reference Range – First defined as a discrete “cutoff” test: 4.0 ng/mL
  - 99% of 472 healthy male volunteers had a total PSA level below 4 ng/mL
  - **Prior to 2004, this simplified version of a PSA cutoff taught in American medical schools**

# PSA: A History

- However…
- 15% of men with a PSA less than 4.0 ng/mL found to have prostate cancer
  - 6.6% of men with a PSA < 0.5 ng/mL
  - 26.9% of men with a PSA between 3.1 ng/mL and 4.0 ng/mL
  - 20% of these cancers are high grade (Gleason score > or = 8)[1]
- No clear "cutoff value" – a continuous variable
- There is no way to optimize the AUROC without major concessions
  - As PSA upper limit rise, it's screening utility falls off
  - As the lower limit drops, false-positives soar

[1]Thompson IM. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng/mL. NEJM 350: 2239-46.

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# The Controversy

- US Preventive Services Task Force (USPTF)
  - 2008: Recommend against PSA screening for patients over age 75
  - 2012: Recommend against PSA screening for all
  - **Screening: PSA/DRE**
  - Treatment: Active Surveillance/Radical Prostatectomy/Radiation Therapy

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# The Controversy

"Prostate-specific antigen-based screening **results in small or no reduction in prostate cancer-specific mortality** and is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary."[2]

[2]Chou R, et al. "Screening for Prostate Cancer - A Review of the Evidence for the U.S. Preventive Services Task Force". United States Preventive Services Task Force.http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm.

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# The Controversy

- USPTF identified and reviewed 2 “fair-quality” studies, as defined by their internal reviewers
  - **European Randomized Study of Screening for Prostate Cancer (ERSPC)**
  - **Prostate, Lung, Colon and Ovarian Cancer Screening Trial (PLCO)**

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# The Controversy

- ERSPC[3]
  - Initiated in the Early 1990s
  - Intention: Evaluate the effects of PSA screening on death rates from prostate cancer
  - 182,000 men (50-74 years old)
  - 2 cohorts
    - A) Offered a PSA test every 4 years
    - B) No such screening

[3]Schroder FH, et al. Screening and prostate-cancer mortality in a randomized European study. NEJM 333: 1401, 2009.

# The Controversy

- ERSPC
  - 13-year follow-up
  - Screened Cohort
    - 7,408 cancer cases diagnosed
    - 299 total deaths attributable to prostate cancer
  - Unscreened Cohort
    - 6,107 cancer cases diagnosed
    - 462 total deaths attributable to prostate cancer

# The Controversy

- ERSPC
  - **<u>Screening reduces the risk of cancer-specific death by 27%</u>**
  - Screening reduces the risk of metastatic disease by 40%
    - Results in a high degree of over-diagnosis and overtreatment
  - 781 men screened/27 men treated to save 1 life
  - **Cross contamination – some in the unscreened cohort underwent screening
  - Modeling a longer-term follow-up at 25 years
    - **98 men screened/5 men treated to save 1 life**

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# The Controversy

- PLCO[4]
  - 1993-2001
  - Intention: Assess the general effectiveness of prostate cancer screening using PSA and DRE
  - 76,693 men
  - 2 cohorts
    - A) Annual PSA for 6 years/DRE for 4 years
    - B) “Usual care” (some screening)

[4]Andriole G, et al. "Mortality results from a randomized prostate-cancer screening trial.". *N Engl J Med* **360**: 1310–9.

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# The Controversy

- PLCO
  - 7-10 year follow-up
  - **Rate of prostate cancer deaths in both groups were very low/almost indistinguishable**
  - Screened Cohort
    - 2820 cancer cases
    - Incidence of cancer-specific death: 2 cases/10,000 patient years
  - Unscreened Cohort
    - 2322 cancer cases
    - Incidence of cancer-specific death: 1.7 cases/10,000 patient years

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# The Controversy

- PLCO
  - Considered to be a “deeply flawed study”
  - Initiated during a time when PSA screening was becoming widely adopted
  - **74% of men in the “usual care” arm were screened at least once**
  - Over 90% of the prostate cancers found in the "control" arm were stage T1 or T2 (typically detected with screening)
  - PLCO authors themselves later admit that the PLCO should not be interpreted as a trial of screening vs. no screening, but rather as **a trial of *annual* screening vs. so-called *opportunistic* or ad-hoc screening**[5]

[5]Pinsky P, et al. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial". *Clin Trials* **7**: 303–11.

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# The Controversy

- Goteborg, Sweden randomized population-based prostate cancer screening trial
  - 20,000 men aged 50-64
  - 14 year follow-up

  - **44% risk of prostate cancer mortality**
    - 139 men screening & 13 treated to save 1 life

  - Why was this study so definitive?
    - Younger population
    - True control group (no screening in Sweden at that time)
    - Lower PSA threshold used for biopsy
    - Longer follow up period

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# The Controversy

- USPTF Identified Harms:

- Within PLCO
  - False-positive PSA values resulting in unnecessary biopsies
  - Bleeding/Pain from DRE: 0.3 events/10,000 screened
  - Venipuncture bruising/fainting: 26 events/10,000 screened
  - Biopsy Complications: 68 events/10,000 screened

- Within ERSPC
  - 5802 biopsies performed (76 % negative for malignancy)
  - 200 fevers
  - 20 episodes of urinary retention
  - 27 hospitalizations for prostatitis and/or urosepsis

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# Consequences of USPSTF

- Numerous reports of (1) decreased incidence of early stage prostate cancer (by 3-10%) and
  (2) lower rates of PSA screening since 2012 USPSTF recommendations
- Shift toward tumors being higher grade and stage upon detection
- Rise in incidence of metastatic disease at diagnosis
- Metastatic disease is incurable and death rate will invariably increase

Hu JC et al: Increase in Prostate Cancer Distant Metastases at Diagnosis in the United States. JAMA Oncol 2017; 3(5): 705-707.

Jemal A et al: Prostate cancer incidence and PSA testing patterns in relation to USPSTF Sreening Recommendations. JAMA 2015; 314(19); 2054-2061.

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- Screening Smarter: PSA Derivatives
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# Impact of PSA Screening

- Does PSA have any value?

  Profound Stage Migration – the majority of men diagnosed with prostate cancer will have clinically-localized disease[6]

[6]Galper, S.L., Chen, M.H., Catalona, W.J., et al: Evidence to support a continued stage migration and decrease in prostate cancer specific mortality. J Urol, 175: 907, 2006

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# Impact of PSA Screening

- 1991: 20% of men found to have bony metastases at the time of diagnosis
  - 2011: **4%**
- 1990: 38.6 prostate cancer deaths per 100,000 men
  - 2014: **19.1 deaths per 100,000 men**
- 40 - 70% decrease in number of deaths attributable to prostate screening (NCI)[8]

[8]Prostate Cancer Discovery: The Jame Buchanan Brady Urological Institute. Johns Hopkins University, 2012

# Impact of PSA Screening

- Prior to 1987 (pre-PSA era—DRE is only test)
  - 35% of patient's with presumed **clinically-localized** disease were found to have positive lymph nodes at surgery[9]
  - 65% of these patients were found to have **pathologically-advanced** disease
- PSA-era (post 1991)
  - 48% of cases diagnosed today are T1c (biochemically-present, non-palpable disease)
  - 75% of tumors are organ-confined (</= pT2c)
    - Eligible for nerve-sparing
    - Decreased risk of needing adjunctive therapy—lower cost, lower morbidity

[9]McLaughlin, A.P., Saltzstein, S.L., McCullough, D.L., et al: Prostatic carcinoma: incidence and location of unsuspected lymphatic metastases. J Urol, 115: 89, 1976

# Impact of PSA Screening: Limitations

- False positives:
  - Enlarged prostate, inflammation, infection, urinary retention, instrumentation
  - PSA>4.0: 30-35% chance of prostate cancer
  - **Empiric treatment with antibiotics of no benefit**

- False negatives:
  - About 20% prostate cancer had only abnormal DRE
  - **5 alpha reductase (-) lower levels by 50%**
  - Finasteride and Dutasteride

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# Impact of PSA Screening

- The PSA-Era “Bottom Line”
  - Pathologic stage migration to organ-confined prostate cancer is a tangible result of PSA screening
  - Death rates have dropped due to earlier diagnosis and treatment
  - Are we diagnosing more indolent tumors that pose no imminent risk to the patient?
  - **How do we reconcile the coincident anxiety and morbidity of over-diagnosis and over-treatment with improved disease-specific survival?**

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# Screening Smarter: PSA Derivatives

- **Age Specific PSA**
  - Reflects prostate gland growth as men age

| Age | PSA Threshold |
|---|---|
| 50 | <2.5 |
| 60 | <3.5 |
| 70 | <4.5 |
| 80 | <6.5 |

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# Screening Smarter: PSA Derivatives

- **PSA Velocity** – rate of rise in PSA/unit time
  - slope calculated from at least 3 measured values over 18 months
  - Increases detection of prostate cancer in younger men and those with PSA < 4.0 ng/mL

# Screening Smarter: PSA Derivatives

- **Free/Bound PSA Ratio**
  - Serum PSA exists in two forms – protein-bound (complexed) and free
  - Benign tissue has more free PSA than prostate cancer tissue
  - F/T ratio <10% higher risk (>50% find cancer)
  - F/T ratio >25% considered lower risk <10% have cancer)[10]
  - Applicable for patients with PSA of 2.5-10

[10]Lee R. A meta-analysis of the performance characteristics of the free prostate-specific antigen test. Urology, 67:762, 2006.

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# Screening Smarter: PSA Derivatives

- **PSA Density** – Unit Measure of PSA/$cm^3$ gland
  - Larger prostate glands produce more PSA
  - Higher PSA density has been shown to correlate with increased pathologic upstaging at prostatectomy (as compared to initial biopsy)[11]
  - **High PSAD = poor candidate for active surveillance**

[11]Babaian R. Comparative analysis of prostate specific antigen and its indexes in the detection of prostate cancer. J Urol, 156:432, 1996.

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# Screening Smarter: Additional Testing

## PCA3

- Non-coding prostate tissue-specific RNA over-expressed in Prostate Cancer
- Post-DRE (prostate massage) urine specimens
- Not specific enough for first biopsy
- May reduce repeat biopsies by 50%
- 90% negative predictive value
- **FDA approved for patients with rising PSA after negative biopsy**

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# Screening Smarter: Additional Testing

## Prostate Health Index (PHI)

- Combination TPSA, fPSA and proPSA
- Avoid 36% of biopsies miss 2.5% high grade disease
- FDA Approved for patients with PSA between 4-10

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# Screening Smarter: Additional Testing

## 4K Score

- tPSA, fPSA, Human kallikrein 2 and intact PSA, age, DRE and prior biopsy
- Reports % likelihood finding high grade disease (> or = Gleason 7)
- One study allowed 58% biopsies averted
- Not FDA approved (a Lab developed test)
- Cannot be used with DRE within 96 hrs, 5ARI or recent prior prostate surgery (6mo)
- ****NO specific cutoff threshold has been established for this test**

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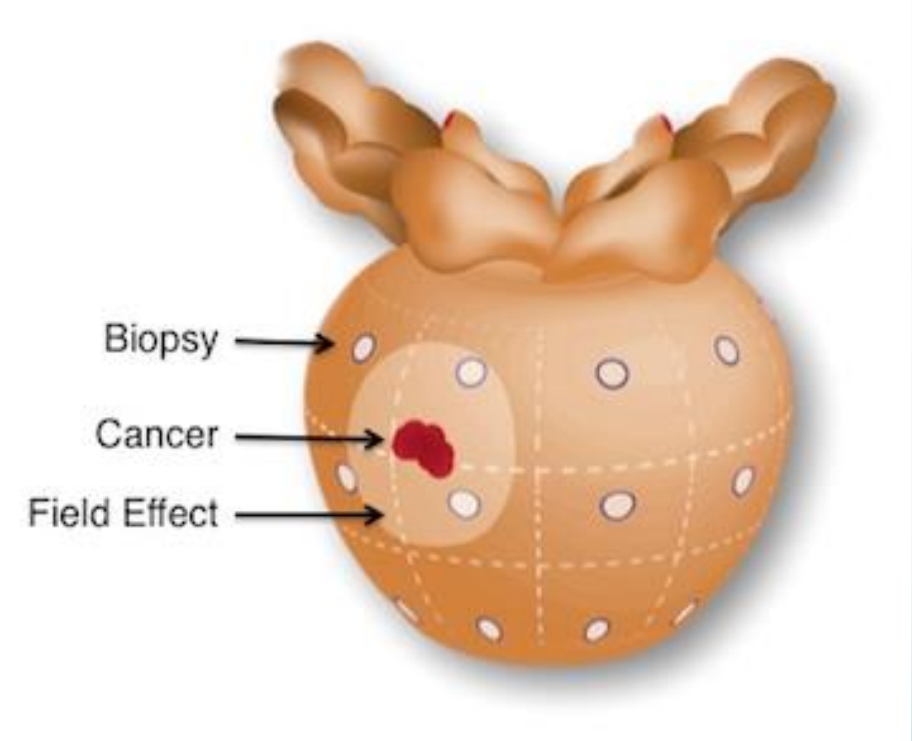
# Screening Smarter: Additional Testing

## Confirm MDx

- Uses previous biopsy tissue
- Multiplex Epigenetic assay
- Hyper-methylation of promoter regions
- “Field Effect” changes around tumor
- 90% Negative predictive value
- A Laboratory Developed Test—Clinically validated but not FDA approved

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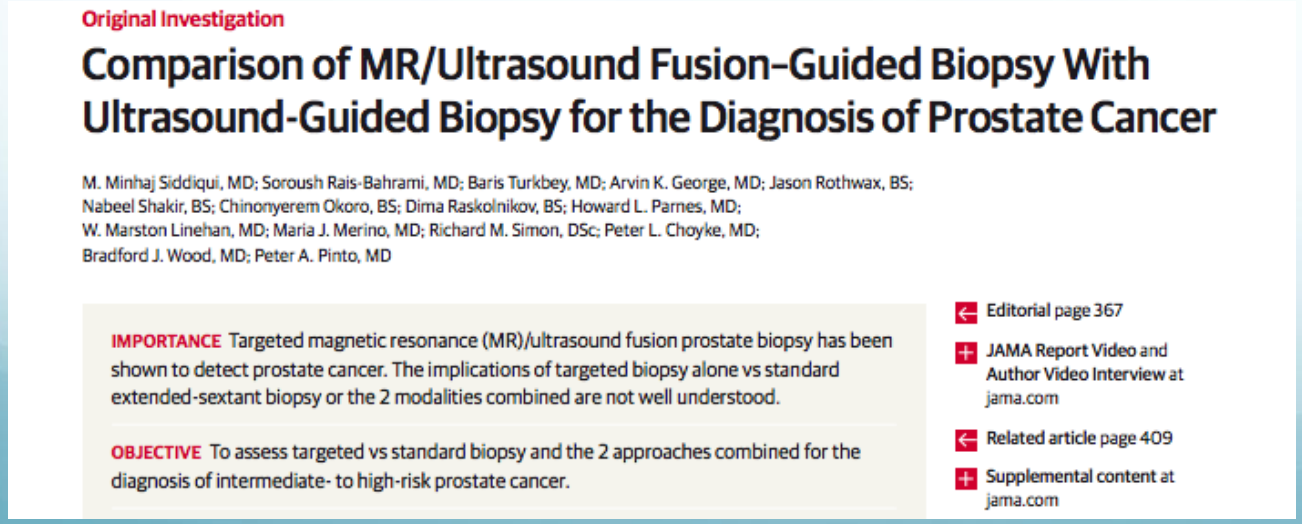
# Screening Smarter: Additional Testing

## Multiparametric Prostate MRI

- First imaging modality to “see” prostate cancer
- PIRADS system 1-5.  3, 4, 5 increasing risk finding high grade clinically significant CaP
- MRI Fusion biopsy:  merges stored MRI images with real-time US image
- Increases detection of clinically significant, higher risk disease while lowering detection of lower risk disease



Original Investigation

**Comparison of MR/Ultrasound Fusion–Guided Biopsy With Ultrasound-Guided Biopsy for the Diagnosis of Prostate Cancer**

M. Minhaj Siddiqui, MD; Soroush Rais-Bahrami, MD; Baris Turkbey, MD; Arvin K. George, MD; Jason Rothwax, BS; Nabeel Shakir, BS; Chinonyerem Okoro, BS; Dima Raskolnikov, BS; Howard L. Parnes, MD; W. Marston Linehan, MD; Maria J. Merino, MD; Richard M. Simon, DSc; Peter L. Choyke, MD; Bradford J. Wood, MD; Peter A. Pinto, MD

**IMPORTANCE** Targeted magnetic resonance (MR)/ultrasound fusion prostate biopsy has been shown to detect prostate cancer. The implications of targeted biopsy alone vs standard extended-sextant biopsy or the 2 modalities combined are not well understood.

**OBJECTIVE** To assess targeted vs standard biopsy and the 2 approaches combined for the diagnosis of intermediate- to high-risk prostate cancer.

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# ACS Guidelines

- Men have a chance to make an **informed decision** with their health care provider about whether to be screened for prostate cancer. The decision should be made after getting information about the uncertainties, risks, and potential benefits of prostate cancer screening. Men should not be screened unless they have received this information. [12]

- age 50 for men who are at average risk of prostate cancer and are expected to live at least 10 more years.

- age 45 for men at high risk of developing prostate cancer. This includes African Americans and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65).

- age 40 for men at even higher risk (those with several first-degree relatives who had prostate cancer at an early age), BRCA positive.

[12]http://www.cancer.org/Cancer/ProstateCancer/MoreInformation/ProstateCancerEarlyDetection/prostate-cancer-early-detection-acs-recommendations

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# Other Guidelines

- AUA, NCCN similar
- USPSTF 2017 Draft Recommendation Statement
  - Age 55-69 recommend clinicians inform patients re: potential benefits and harms of PSA Screening.
  - Rationale for draft recommendations
    - Reductions in CaP mortality in a screened population
    - Increased utilization of Active Surveillance for low risk disease
- When interpreted appropriately, PSA provides important information with respect to the diagnosis, pre-treatment staging or risk assessment and monitoring of prostate cancer patients[13]

[13]http://www.auanet.org/content/press/press_releases/article.cfm?articleNo=262

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# Smarter Treatment

- Active Surveillance for low risk disease
  - Clinical stage T1-T2a
  - PSA < 10
  - Gleason = 6
  - PSAD < or = 0.15
  - 3 or fewer cores with prostate cancer
- PSA/DRE q 6 months
- Biopsy q 18-24 months
- Consider mpMRI instead of biopsy
- ~40% of low risk disease managed with AS

Cooperberg MC et al: Trends in Management for patients with localized prostate cancer. JAMA 2015;314(1): 80-82.

# Smarter Treatment

- ProtecT trial (Prostate Testing for Cancer and Treatment)
  - 82k men aged 50-69 underwent PSA screening
  - 1,643 of 2,664 diagnosed with localized disease were randomized
  - At 10 years, no difference in mortality
  - 2.5x higher risk of developing metastatic disease

The NEW ENGLAND JOURNAL of MEDICINE

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10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

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# What to do?

- Prostate Health Screening with serum PSA should be an **informed decision** made **collaboratively** by the patient and clinician
- PSA results should be interpreted in the context of the patient's age, physical findings, family history and other pertinent individual characteristics (including co-morbid conditions)
- A total PSA value should be interpreted against a background of other associated parameters
- PSA screening has reduced prostate cancer mortality & is being refined by oncologic community to reduces associated risks
- Low risk disease can be managed with active surveillance

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