Breakthroughs In Prostate Cancer Detection and Risk Assessment

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Boulder Medical Center

Boulder Community Health

Prostate Cancer

Boulder Community Health

#1 cancer

Estimated New Cases

		Males
Prostate	248,530	26%
Lung & bronchus	119,100	12%
Colon & rectum	79,520	8%
Urinary bladder	64,280	7%
Melanoma of the skin	62,260	6%
Kidney & renal pelvis	48,780	5%
Non-Hodgkin lymphoma	45,630	5%
Oral cavity & pharynx	38,800	4%
Leukemia	35,530	4%
Pancreas	31,950	3%
All Sites	**970,250**	**100%**

#2 killer

Estimated Deaths

		Males
Lung & bronchus	69,410	22%
Prostate	34,130	11%
Colon & rectum	28,520	9%
Pancreas	25,270	8%
Liver & intrahepatic bile duct	20,300	6%
Leukemia	13,900	4%
Esophagus	12,410	4%
Urinary bladder	12,260	4%
Non-Hodgkin lymphoma	12,170	4%
Brain & other nervous system	10,500	3%
All Sites	**319,420**	**100%**

Siegel RL, CA Cancer J Clin. 2021 Jan;71:7-33.

Topics to Cover

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- Risk factors for prostate cancer
- Understanding the prostate specific antigen (PSA)
- Prostate cancer detection guidelines
- Noninvasive pre-diagnostic testing
  - Multiparametric MRI
  - Genomic tests
- What to do next with a new prostate cancer diagnosis.

Where is the Prostate?

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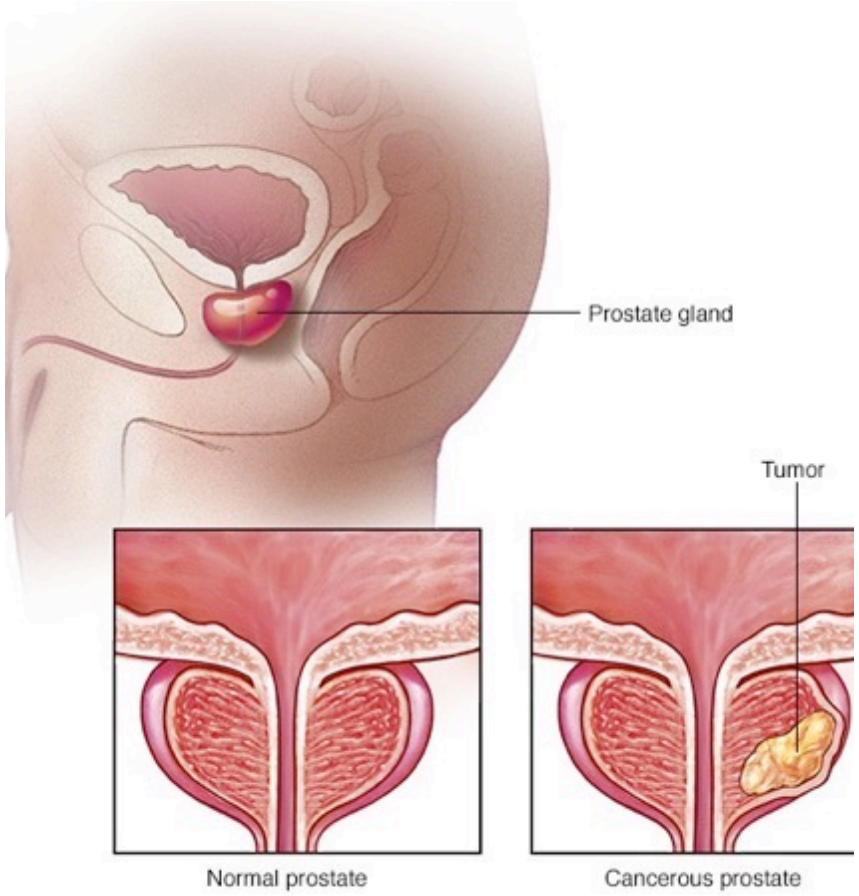

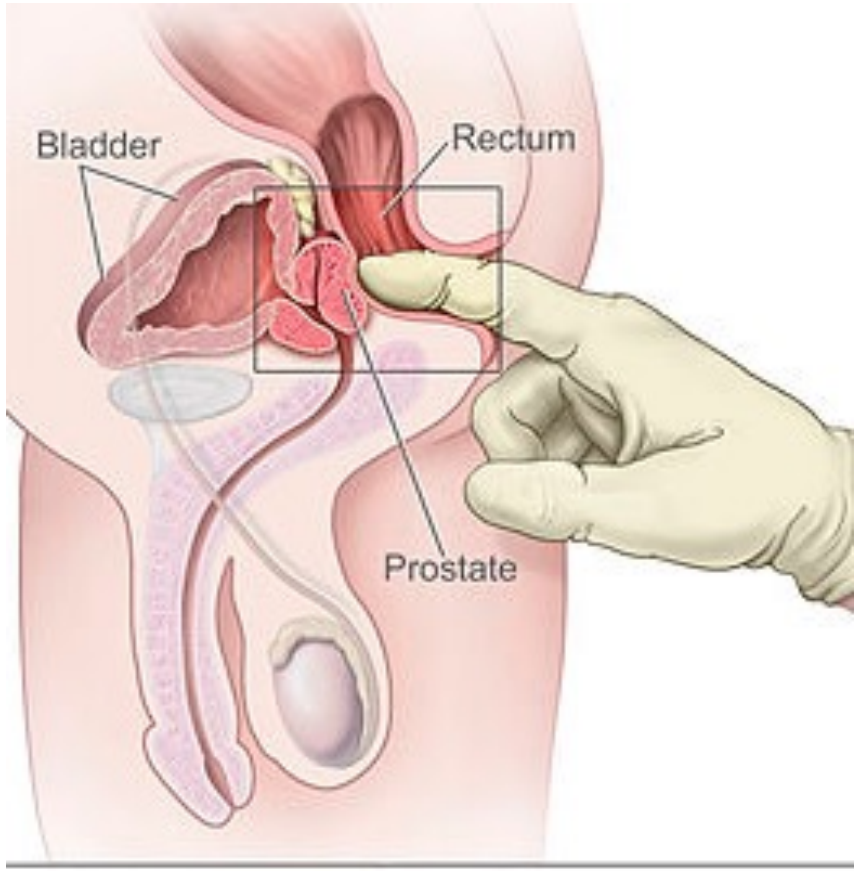

Risk factors for prostate cancer

Risk Factors

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- Male gender and older age
- Ethnicity
  - African Americans 1.6 x more likely to have disease
  - African Americans 2.2 x more likely to die of disease
- Family history
  - Father w prostate ca 2x more likely
  - Brother w prostate ca 4x more likely
  - Father and brother w prostate ca 8x more likely

Risk Factors

Boulder Community Health

- **African American**
  - Higher incidence prostate cancer
  - Increased mortality from prostate cancer
  - Earlier age at diagnosis
  - ? Genetics vs access to health care
  - Begin shared decision making about prostate cancer screening at age 40yr

Risk Factors

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- **Family history of cancers**
  - Metastatic prostate cancer
  - Ovarian cancer
  - Male or female breast cancer
  - Colorectal
  - Endometrial cancer
  - Pancreatic cancer

Risk Factors

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- Germine Mutations
  - *BRACA2 or HOXB13*
    - Strong association with prostate cancer before age 65
    - Associated with death from prostate cancer
    - Begin PSA screening at age 40

Genetic Risk Factors

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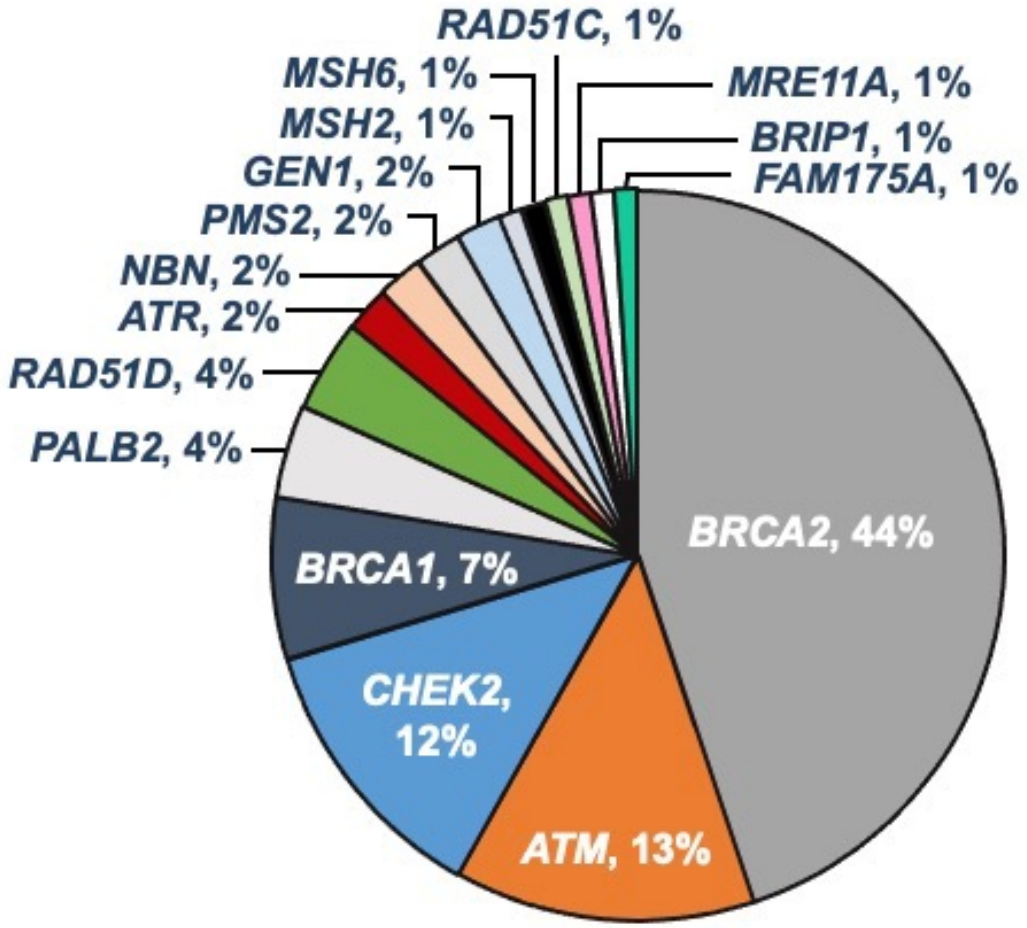
- DNA repair gene mutations:
  - 11.8% metastatic prostate cancer
  - 6% localized high-risk prostate cancer
  - 2% low-to-intermediate-risk prostate cancer

- Why important? Possible new treatment options with PARP inhibitors and platinum-based chemotherapy in metastatic disease.



Albright F et al, Prostate 2015;75:390-398; Bratt O, et al., J Natl Cancer Inst 2016;108; Jansson J Clin Oncol 2018:JCO2017766907; Pritchard CC,et al, N Engl J Med 2016;375:443-453; Abida W; JCO Precis Oncol 2017;2017. Incorporating genomic testing into your practice, AUA 2021 summer series

Germline Testing Recommended

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- Family history germline mutations
- Ashkenazi Jewish ancestry
- Family history prostate cancer
- Multiple cancers in family

Risk Factors

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- Taking 5 α reductase inhibitors
  - Finasteride (Proscar)
  - Dutasteride
- Cut the PSA in half, so must always double PSA if on these medications.
- Example - If taking finasteride, and PSA is 2.5, then the real PSA is 5.0.
- Associated with higher risk of aggressive prostate cancer.

Prostate specific antigen (PSA)

Incidence of Prostate Cancer

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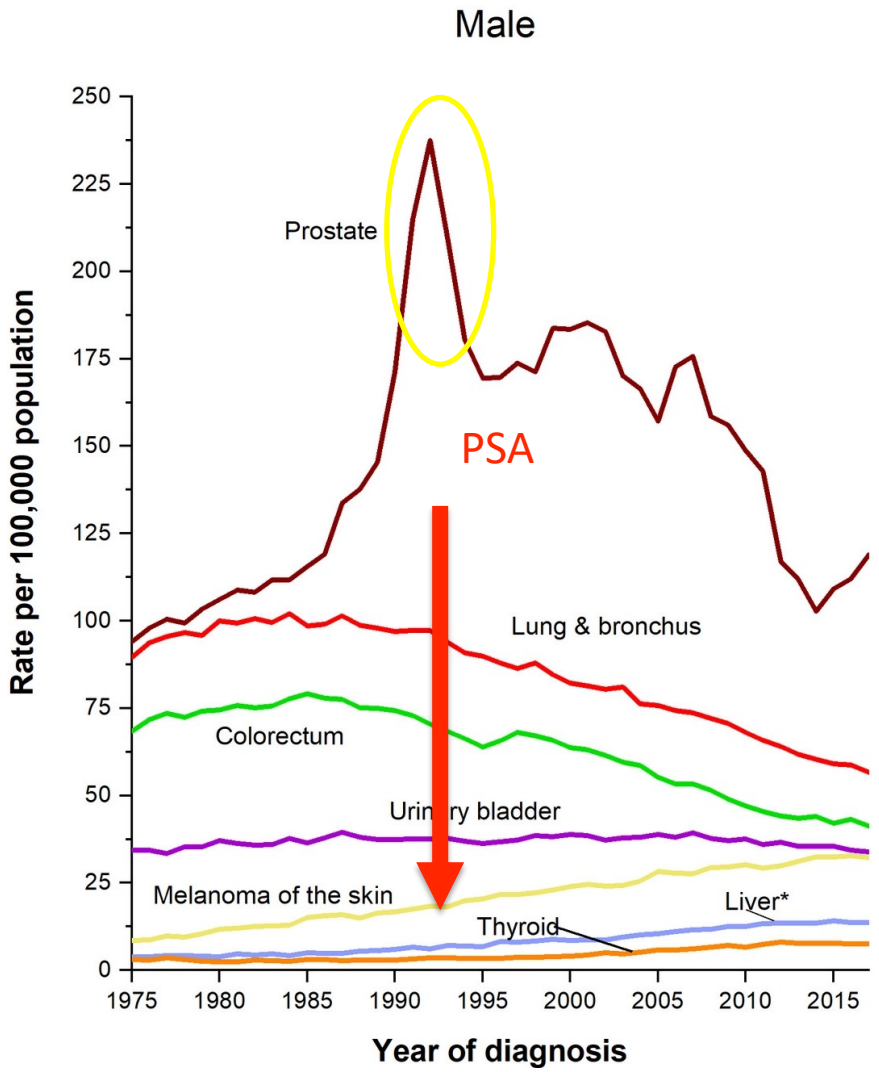

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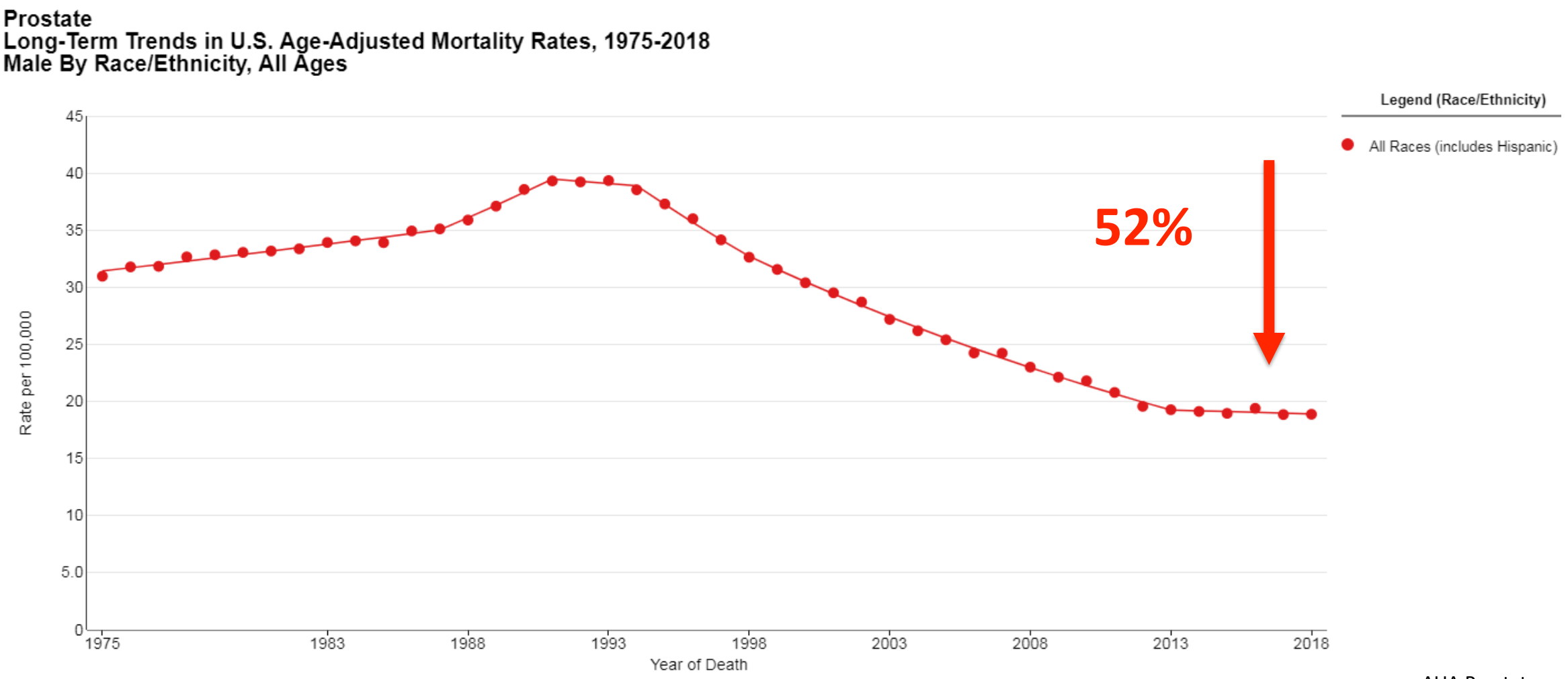
Mortality from prostate cancer



AUA Prostate cancer updates 2021

PSA not a Prostate Cancer-Specific Marker

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- PSA can be higher
  - Large prostates (Benign Prostate Hyperplasia)
  - Infections (prostatitis, urinary tract infections, epididymitis)
  - Recent ejaculation
  - Trauma
  - Recent urinary catheterization
  - Recent biking
  - Prostate cancer

PSA not a Prostate Cancer-Specific Marker

Boulder Community Health

- Only 25% of men with PSA 4 - 10 ng/mL have a subsequent positive biopsy.
  Catalona et al, JAMA 1998;279:1542-1547.

- If an abnormally high PSA is observed, then repeat the test
  - PSA measured by different commercial assays are not necessarily interchangeable
  - 25% of men with initial PSA levels between 4 and 10 ng/mL had normal PSA values upon repeat testing.
  - Lavallee LT, et al, Mayo Clin Proc 2016;91:17-22.

- Still, men with low PSA values have a significant risk of prostate cancer
  - Some prostate cancers don't make PSA.

PSA not a Prostate Cancer-Specific Marker

Boulder Community Health

- 15% of men with a PSA level of 4.0 ng/mL or less and a normal DRE had prostate cancer.
  - Thompson IM, et al, N Engl J Med 2004;350:2239-2246.
- 30% to 35% of men with PSA 4 to 10 ng/mL range will be found to have cancer.
- PSA levels >10 ng/mL have >67% likelihood of prostate cancer.
  - Catalona et al. N Engl J Med 1991;324:1156-1161.

Early detection →Over treatment

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- Unnecessary side effects from unnecessary treatments.
- Some prostate cancers are not lethal and do not threaten quality of life.
- Anxiety.
- Increased health care expenditures.

Response to overtreatment:

U.S. Preventive Task Force Recommendations

US Preventative Task Force 2008-2012

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- Discouraged use of PSA
- Task force is a panel of 16 experts:
  - family medicine
  - general internal medicine
  - nurses
  - obstetrician-gynecologists
  - occupational medicine physicians
  - pediatricians

- **PANEL DID NOT INCLUDE UROLOGISTS OR CANCER SPECIALISTS**

Incidence of Prostate Cancer

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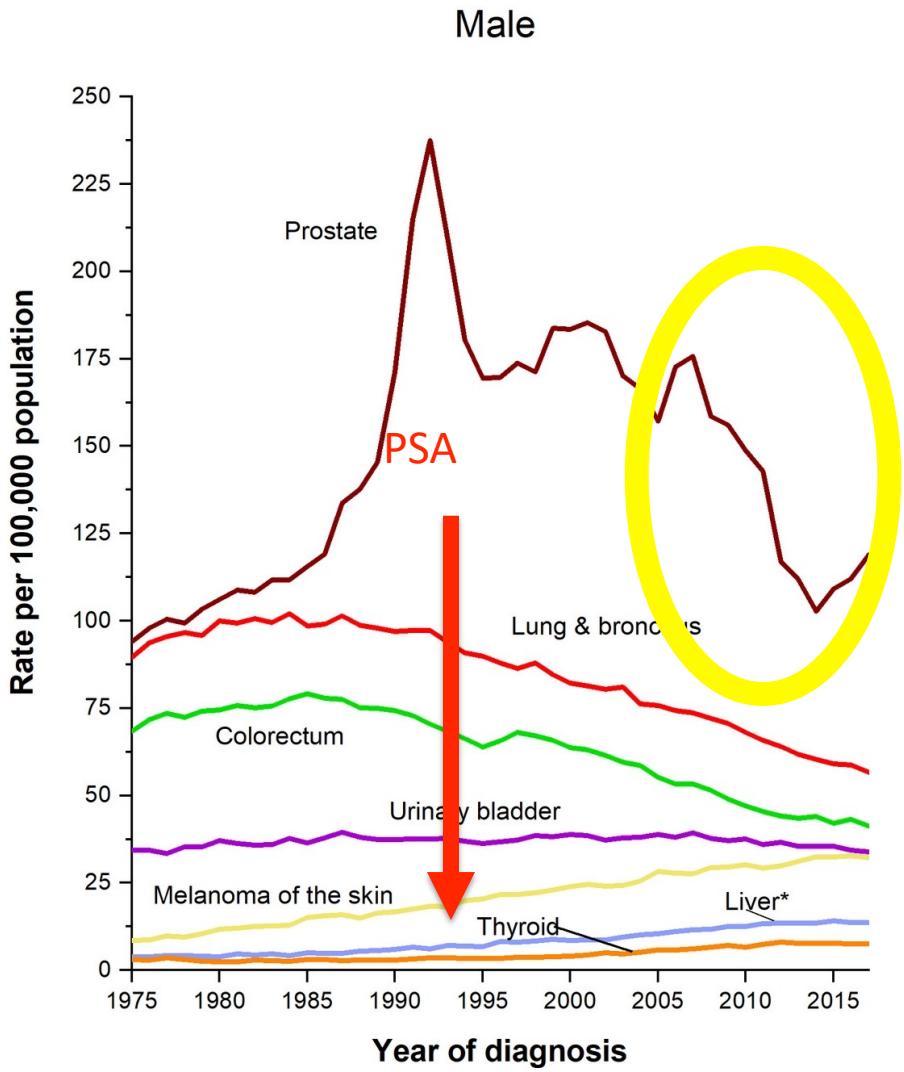

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Relative 5 year Survival by Stage

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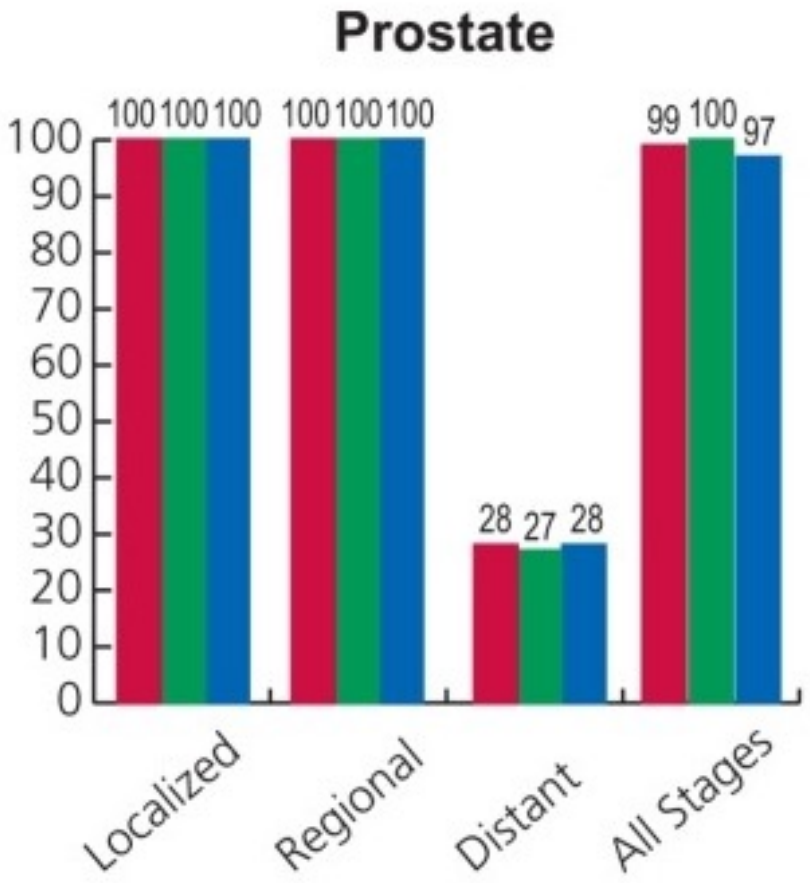
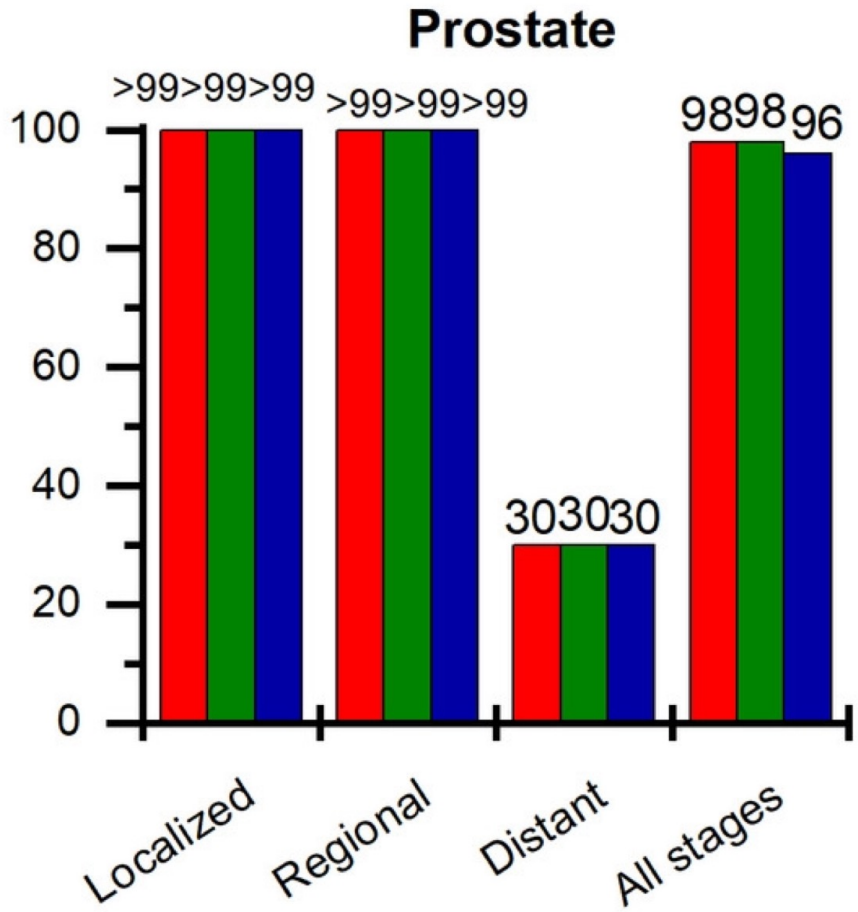
2003-2009



Siegel RL, CA Cancer J Clin. 2014 Jan;64:9-29.

2010-2016



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Cancer Stage Distribution at Diagnosis

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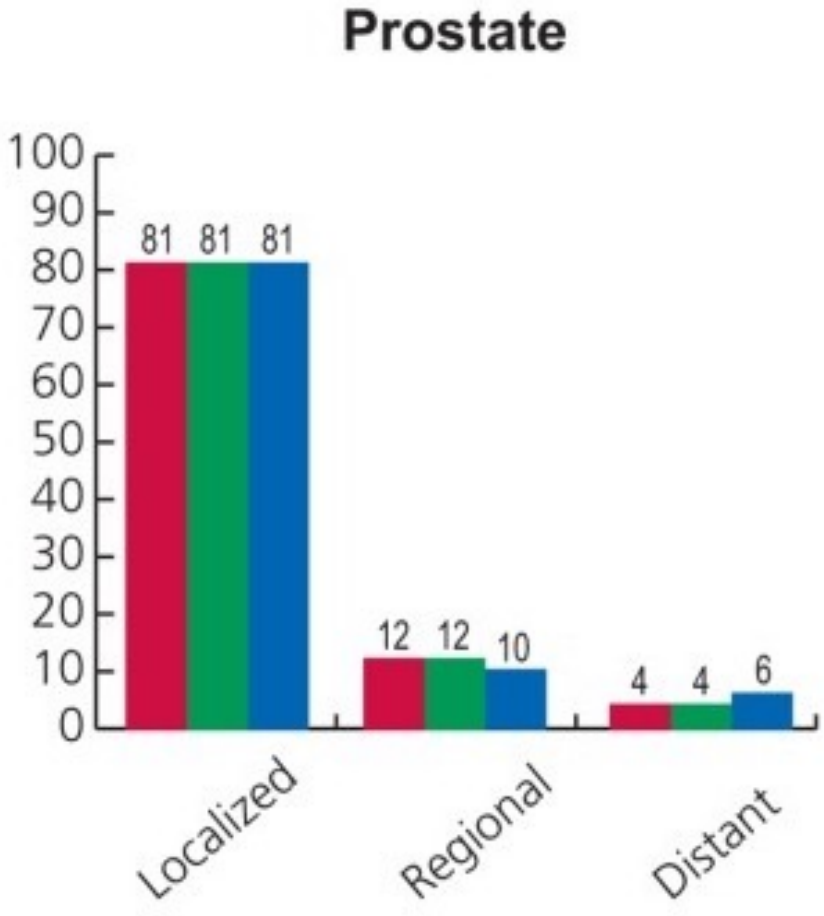
2003-2009



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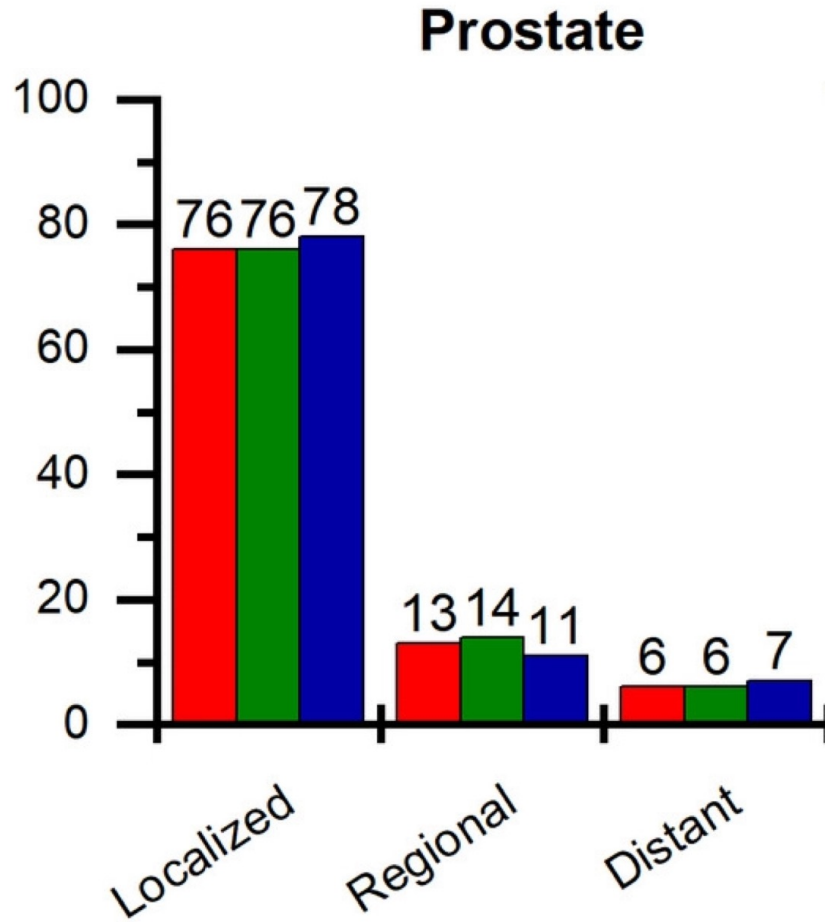

Siegel RL, CA Cancer J Clin. 2021 Jan;71:7-33.

Outcome from Task Force

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- **MORE DEATHS FROM PROSTATE CANCER**
  - Prostate cancer deaths increased in 2018 for the first time in two decades from an estimated 26,730 in 2017 to 29,430 in 2018.

Siegel et al, Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.

  - Death from prostate cancer, which had been in decline for two decades, has stabilized since 2012.

Negoita S et al. Cancer 2018.

Revised Task Force Recommendations

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For men > =70yrs

- USPTF continues to recommend against PSA testing.

- **SHARED DECISION MAKING**

American Urological Association (AUA) Guidelines (2013) on Early Detection

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Guideline Statement: Age 40-54 Years

- Screening as a *routine* is not recommended, unless risk factors.

Why?

- The evidence for benefit is marginal
- The evidence for harm is high

- Doesn't apply to high-risk populations or men with risk factors.

AUA Guidelines Early Detection

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Guideline Statement: Age 55-69 Years

- **Shared Decision Making** and proceeding based on a patient's values and preferences.

- This is the population with greatest benefit.
- Weigh the benefit of preventing 1 prostate cancer death per 1,000 screened over a decade vs the harms of screening and treatment.

AUA Guidelines Early Detection

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Guideline Statement: Age 70 Years and Above

- Recommend against *routine* PSA-based screening in men age 70+ years, **or** in any patient with less than a 10-15yr life expectancy.

- Some men over age 70yrs who are in excellent health may benefit from prostate cancer screening.

Individualized Decision Making

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- Maximize detection of lethal prostate cancer in patient with life expectancy of >10-15yrs.
- Accurately characterize the biology of the tumor.
- Risk stratification of the cancer
  - Minimize immediate treatment (over-treatment) of indolent cancers.
  - Proceed with treatment of potentially lethal prostate cancers.

Initial Evaluation

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- Digital rectal exam (DRE) + PSA
- PSA and DRE should be done on men 50+ years and earlier if risk factors.
- A DRE should be done in all men with an abnormal PSA.

- If abnormal DRE and elevated PSA —
  - Positive predictive value for prostate cancer is 48.6% vs 22.4% for men elevated PSA and a normal DRE.

Gosselaar et al, European urology 2008;54:581-588.

Abnormal DRE, Normal PSA

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- Some prostate cancers do not make PSA.
- Positive predicative value of an abnormal DRE in men with normal PSA only 4%– 21%.
- BUT an abnormal DRE should be evaluated!!

NON-INVASIVE
Pre-diagnostic tests

Noninvasive Pre-diagnostic Markers

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- Men want to avoid a biopsy if possible.
- A prostate biopsy is still considered "gold standard".
- BUT non-invasive options to determine if biopsy is needed are mainstream.
- These tests are an additional out-of-pocket expense.

Goal - NOT just find prostate cancer but find potentially lethal prostate cancer.

Pre-diagnostic Tests

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- After PSA and rectal exam but before biopsy

- Multiparametric MRI prostate
- PCA3
- 4Kscore
- Phi (prostate health index)
- Select MDX
- ExoDX

Prostate MRI

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- Multiparametric(mp) MRI of the prostate
  - Anatomic evaluation
  - Diffusion weighted imaging
  - Dynamic contrast enhanced MRI
- Needs to be with and without gadolinium contrast
- Helps to:
  - determine who needs a prostate biopsy
  - characterize suspicious lesions felt on DRE
  - evaluate elevated PSA but prior benign biopsy (Did we miss a lesion on the random biopsy?)
  - active surveillance of men diagnosed with very low/low/favorable intermediate risk prostate cancer
  - perform **targeted biopsy** of a suspicious lesion

mpMRI PI-RADS score

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Prostate Imaging – Reporting and Data System version 2

PI-RADS classification	Definition	Total T2 + DWI + DCE score	Total T2 + DWI + DCE + MRS score
I	Most probably benign	3 - 4	4 - 5
II	Probably benign	5 - 6	6 - 8
III	Indeterminate	7 - 9	9 - 12
IV	Probably malignant	10 - 12	13 – 15
V	Most probably malignant	13 - 15	17 - 20

PI-RAD IV and V should have targeted biopsy

Fusion Prostate Biopsy

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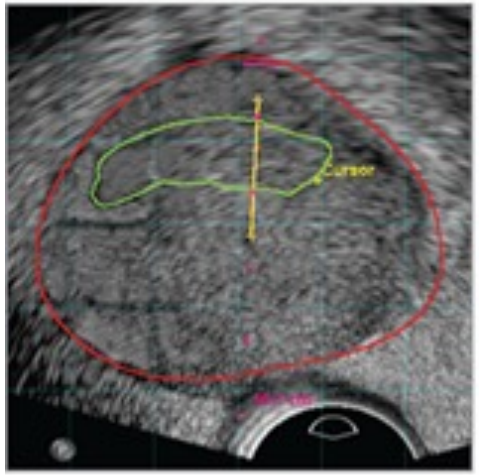
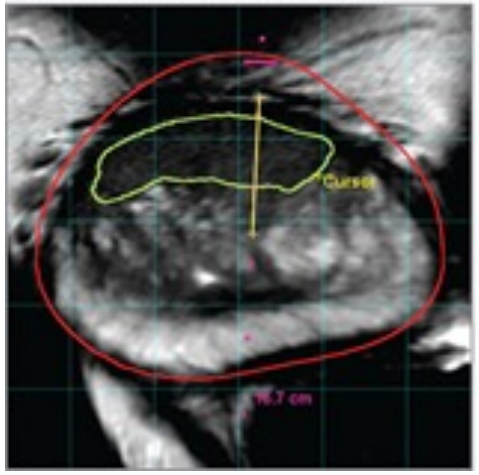
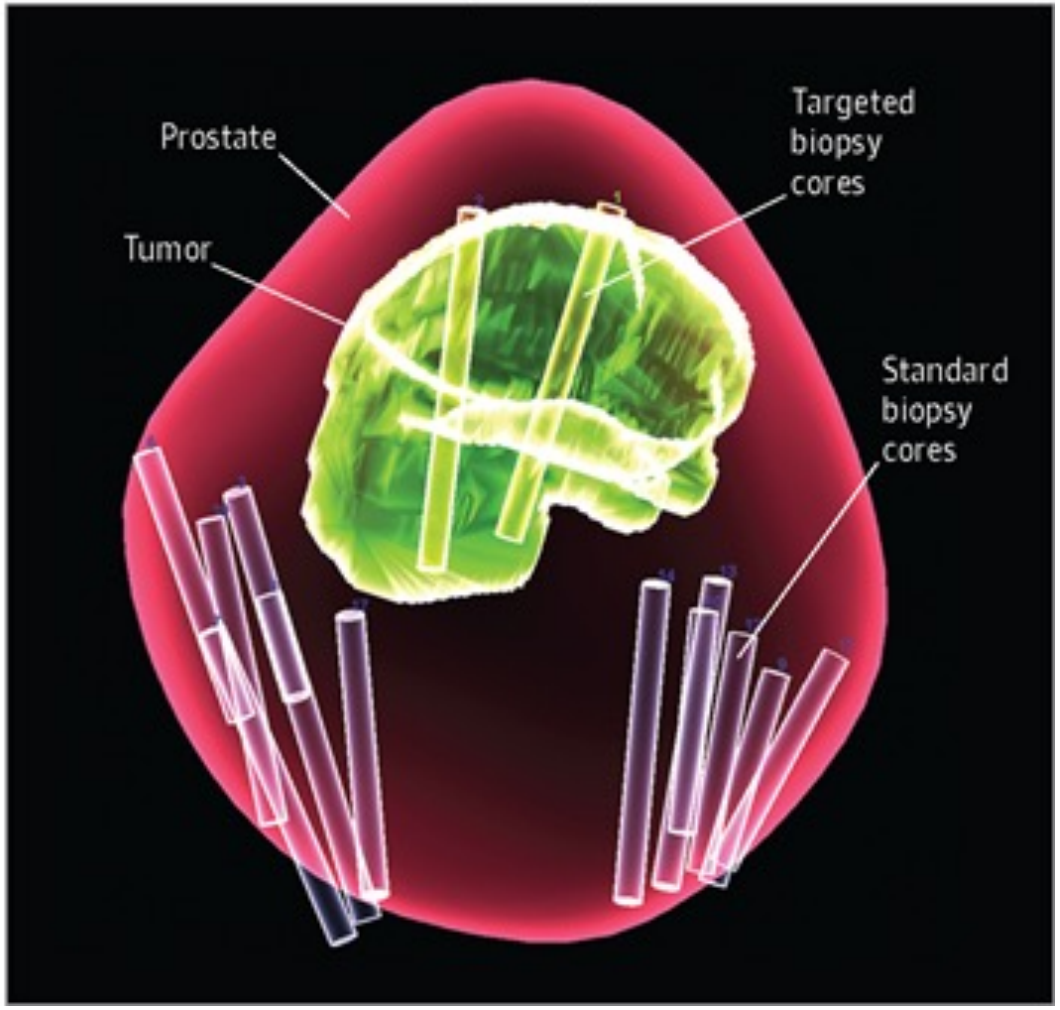
Real-time axial transrectal ultrasound



Correlated T2-weighted MRI



Reconstructed 3-dimensional map of the prostate



Benefit of Prostate MRI

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- Prospective study 223 biopsy naïve men
- All had standard biopsy and MRIs
  - If MRI PIRAD 3-5, then also fusion prostate biopsy.
- Reduced biopsy rate by 36% by not doing a biopsy of benign lesions (PI-RADS 1 and 2 lesions)
- Reduce the identification of low-risk prostate cancer by 87%
- Increase finding intermediate/high-risk tumors by 18%
- But miss 6.7% of cancers.

- Pokorny et al,. Eur Urol 2014;66:22-29.

MRI Before Biopsy

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- PROMIS trial
  - 27% of patients could avoid a primary biopsy
  - diagnosis of 5% fewer clinically insignificant cancers.
  - TRUS-biopsies after mpMRI
    - up to 18% more cases of clinically significant cancer might be detected compared with the standard prostate biopsy.
  - But this MRI before biopsy approach could miss 24% of potentially lethal prostate cancers.

Ahmed et al. Lancet 2017; 389:815

Prostate MRI

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- Not perfect (no test is).
- Interobserver variability
  - One radiologist scores prostate lesions one way and another radiologist scores the lesion another way.
  - Multiple studies addressing this problem.
  - Boulder Community Health radiologists read all my scans
    - Two Boulder Community Health radiologists always read each MRI

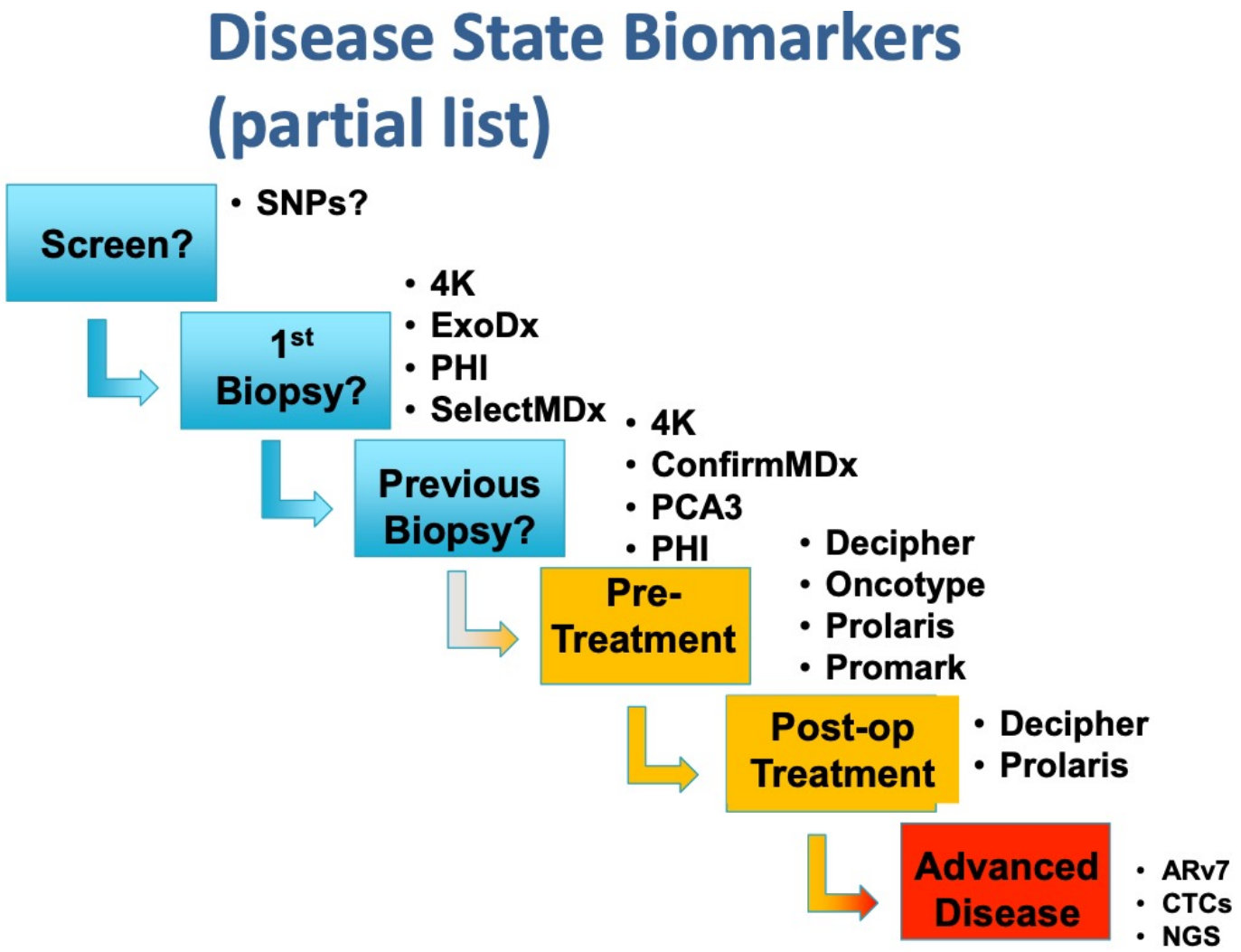
Genomic testing

Genomic Tests

Boulder Community Health

- Detect a substance or process that indicates the presence of cancer.
  - a molecule secreted by a tumor.
  - a specific response of the body to the presence of cancer.
- **However, genomic tests are not perfect and will miss some cancers.**

Why is genomic testing important?



Incorporating genomic testing into your practice, AUA 2021 summer series

Prostate Cancer Biomarkers

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- Give a probability of finding cancer before proceeding with biopsy.
- Decrease unnecessary biopsies.
- Increase the specificity of cancer detection, without missing a potentially lethal prostate cancers.

Prostate Health Index

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- Blood test - Combines tPSA, fPSA, and proPSA
- FDA approved 2012 for PSA 4 - 10 ng/mL.
- Area under the curve (AUC) of 0.72 for discrimination of high-grade (Gleason ≥7) cancer from low-grade cancer or negative biopsy.
  - Catalona WJ, et al, J Urol 2011;185:1650- 1655.
- 36% of biopsies avoided.
- Approximately 2.5% of high-grade cancers missed.
  - de la Calle C, et al, J Urol 2015;194:65-72.

PCA3

Boulder Community Health

- Prostate tissue-specific RNA found in urine after "prostate massage."
- Negative predictive value (NPV) of 90%
  - a sensitivity of 78%, specificity of 57%, Positive predictive value of 34%.
    - Gittelman et al,The Journal of urology 2013;190:64-69.

–Not a good predictor of high-grade disease.

–Not used much in practice anymore as goal is to find potentially lethal prostate cancer, not just prostate cancer.

Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 supplement PSA in the early detection of prostate cancer? J Clin Oncol 2014;32:4066-4072.

4Kscore

Boulder Community Health

- Algorithm patient's age, family history, race, digital rectal exam, and previous biopsy status
- Panel of 4 known markers
  - total PSA
  - free PSA
  - intact PSA
  - hK2
- Gives percent likelihood of finding potentially lethal cancer on biopsy
- Biopsies can be avoided, high-grade cancer detected, but 5-10% cancers are missed in reported trials.

Select MDx

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- Urine assay for RNA
- Urine collected after digital rectal exam
- *DLX1* and *HOXC6* mRNA
- DLX1 and HOXC6 have been associated with prostate cancer aggressiveness.
- Improves the identification of men with clinically significant prostate cancer prior to biopsy, thereby reducing the number of unnecessary biopsies.
  - 53% prostate biopsies can be avoided

Select MDX

Boulder Community Health

- Prospective multicenter trials
- AUC of 0.76
- Sensitivity of 91%
- Specificity of 36%
- NPV of 94%, and a PPV of 27% for the prediction of Gleason score ≥7 prostate cancer.
- When combined with PSA levels, PSAD, DRE results, previous negative prostate biopsies, age, and family history in a multimodal model, the overall AUC was 0.90 in the training set and 0.86 in the validation set (95% CI, 0.80–0.92).
  - Van Neste L, et al, Eur Urol 2016;70:740-748.

ExoDX

Boulder Community Health

- Urinary exosomal RNA
- At home urine test
- No rectal exam required
- For high-grade disease
  - NPV 97.5% and PPV 34.5%

–JAMA Oncol. 2016;2(7):882-889

ConfirmDx

Boulder Community Health

- If prostate biopsy comes back benign.
- Improve the stratification of men with prior negative biopsy being considered for repeat prostate biopsy.
  - Who needs to be followed more aggressively?
- Hypermethylation of the promoter regions of *GSTP1, APC,* and *RASSF1* is assessed in core biopsy tissue samples.
- Biopsy samples < 30mo of age.

ConfirmDx

Boulder Community Health

- In two clinical trials
  - The NPV was 90% (95% CI, 87%–93%)
    - Stewart et al, J Urol 2013;189:1110- 1116.
  - The NPV was 88% (95% CI, 85%–91%)
    - Partin et al, J Urol 2014;192:1081-1087.

New Prostate Cancer Diagnosis

Boulder Community Health

- Now what??
- Treatment?
- Active surveillance?
- Use genomics to assess risk.

Prostate Cancer Risk Stratification

	AUA Risk Category	NCCN Risk Category
Very Low	—	PSA ≤ 10 ng/mL, Gleason score ≤ 6, clinical stageT1c, < 3 positive biopsy cores, ≤ 50% in each core, and PSA density < 0.15 ng/mL/g
Low	PSA ≤ 10 ng/mL, Gleason score ≤ 6, and clinical stageT1c or T2a	PSA < 10 ng/mL, Gleason score ≤ 6, and clinical stageT1-T2a
Intermediate	PSA > 10-20ng/mL or Gleason score 7, or clinical stage T2b	PSA 10-20 ng/mL, Gleason score 7, or clinical stageT2b-T2c
High	PSA > 20ng/mL or Gleason score 8-10, or clinical stage ≥T2c	PSA > 20ng/mL or Gleason score 8-10, or clinical stage T3a
Very High	—	Clinical stage T3b-T4

Prostate Cancer Risk Stratification

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Low	PSA ≤ 10 ng/mL, Gleason score ≤ 6, and clinical stageT1c or T2a	PSA < 10 ng/mL, Gleason score ≤ 6, and clinical stageT1-T2a
Intermediate	PSA > 10-20ng/mL or Gleason score 7, or clinical stage T2b	PSA 10-20 ng/mL, Gleason score 7, or clinical stageT2b-T2c
High	PSA > 20ng/mL or Gleason score 8-10, or clinical stage ≥T2c	PSA > 20ng/mL or Gleason score 8-10, or clinical stage T3a
Very High	—	Clinical stage T3b-T4

New Prostate Cancer Diagnosis

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- **Genomics adds helpful information.**
- Each tumor is unique.
- What is the REAL RISK of harm by not doing treatment?
- Can you wait and follow the tumor and decide later to do treatment?
- Tumors can get upstaged or downstaged.
- Overall survival "gold standard".....BUT…

New Prostate Cancer Diagnosis

Boulder Community Health

- **Metastasis free survival** is the STRONGEST surrogate for OVERALL survival in localized prostate cancer.

J Clin Oncol 35, 3097-3104, doi:10.1200/JCO.2017.73.9987 (2017)

Decipher

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- Genomic test
- Predicts metastasis in a prostate biopsy
- Developed at Mayo Clinic
- Use RNA, 22 genes across 7 cancer pathways
- Divides the results into high, intermediate and low risk category
- DECIPHER outperforms all other clinical risk factors for predicting metastasis
  - Better than PSA, stage, Gleason score, NCCN risk categories

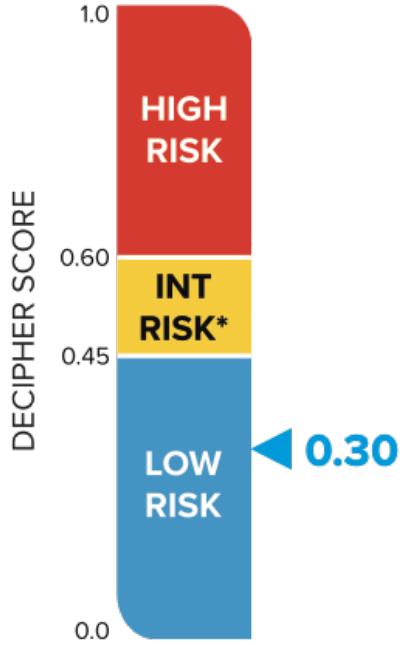
Decipher Result

Boulder Community Health

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

Specimen: **Needle Biopsy**
Clinical Stage: **T1c**
Most Recent PSA: **4.9 ng/mL**
Gleason Score: **3+4**
NCCN Risk Category: **Intermediate**

DECIPHER GENOMIC RISK RESULTS



GENOMIC RISK IS: LOW

0.5%	1.2%	2.4%	14.6%
5-year	*10-year*	*15-year*	*At RP*
Risk of Metastasis with RT† or RP‡		**Risk of Prostate Cancer Mortality** with RT or 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.

Decipher Result

Boulder Community Health

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Specimen: **Needle Biopsy**
Clinical Stage: **T1c**
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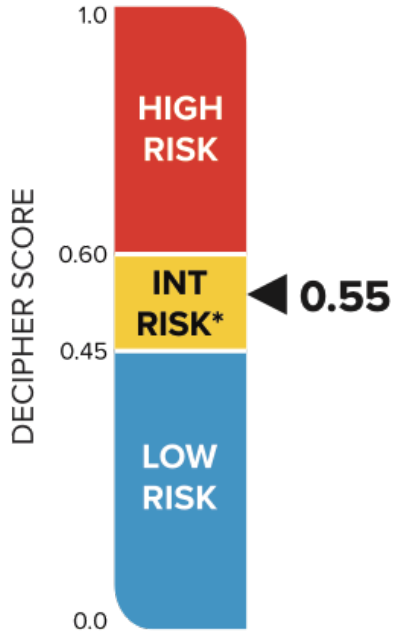
DECIPHER GENOMIC RISK RESULTS



GENOMIC RISK IS: INTERMEDIATE

1.1%	2.7%	4.6%	28.4%
5-year	*10-year*	*15-year*	*At RP*
Risk of Metastasis with RT† or RP‡		**Risk of Prostate Cancer Mortality** with RT or RP	**Risk of Adverse Pathology**

Clinical studies have shown that Decipher intermediate-risk patients have an average clinical risk and prognosis. Depending on life expectancy and overall health status:

- These patients may not be ideal candidates for active surveillance.[1-3,6]
- These patients may benefit from definitive therapy.[2-5,9]

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Decipher Result

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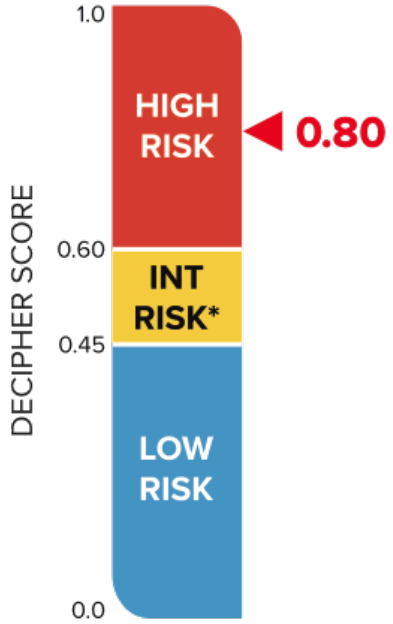
Gleason Score: **3+4**
NCCN Risk Category: **Intermediate**

DECIPHER GENOMIC RISK RESULTS



GENOMIC RISK IS: HIGH

2.6%	6.5%	8.8%	48.1%
5-year	*10-year*	*15-year*	*At RP*
Risk of Metastasis with RT† or RP‡		**Risk of Prostate Cancer Mortality** with RT or RP	**Risk of Adverse Pathology**

Clinical studies have shown that Decipher high-risk patients have an unfavorable prognosis.

- These patients may benefit from treatment intensification with multimodal therapy.[2-5,9,10]
- These patients may not be ideal candidates for active surveillance.[1-3,8]

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.

Decipher Result

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- Decipher can also help guide:
  - If treatment with radiation, does patient need radiation treatment along with hormone therapy?
  - And what is the duration of hormone therapy?

Additional Post-biopsy Genomic Tests

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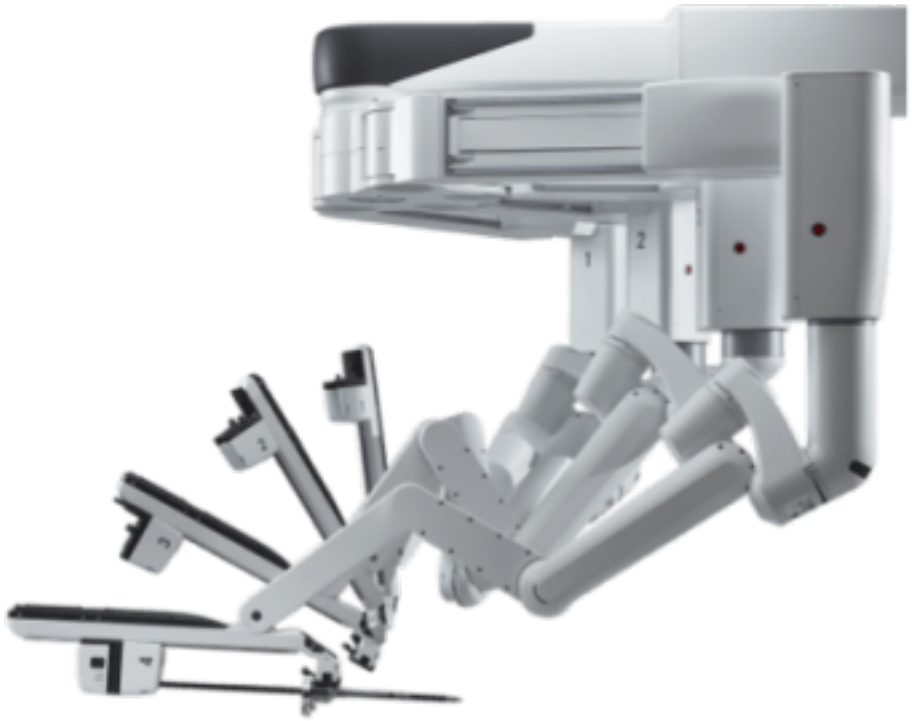
- Oncotype DX
- Prolaris
- ProMark (for low grade tumors)

Da Vinci Xi Robotic-Assisted Surgery

Boulder Community Health

- Sharper 3D-HD visuals (10 times greater than the human eye)
- Four robotic arms that can move in virtually any direction
- Articulating instruments outfitted with technology to minimize blood loss and pain.
- Greater, more intuitive range of motion



Take Home Messages

Boulder Community Health

- **Take control of your health care decisions.**

- PLEASE get your PSA checked.
- PLEASE ask your health care provider to do a rectal exam.
- Request the use of novel tests for detection of prostate cancer to assess YOUR RISK FOR LETHAL PROSTATE CANCER.

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