



# Prostate Cancer: Guideline Recommendations and Emerging Therapies

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Manish Kohli MD  
Consultant, Professor of Oncology  
Department of Oncology  
Mayo Clinic, Rochester, MN  
[Kohli.manish@mayo.edu](mailto:Kohli.manish@mayo.edu)

# Overview

➤ **A:** PSA for Screening?      **YES**    **NO**    **MAYBE**    ??

➤ **B:** Emerging Therapeutic Developments

➤ Based on Novel Therapeutics

➤ Based on Novel Combinations of older drugs

➤ **C:** Guidelines on Genomic Biomarker applications  
in the Prostate Cancer Management

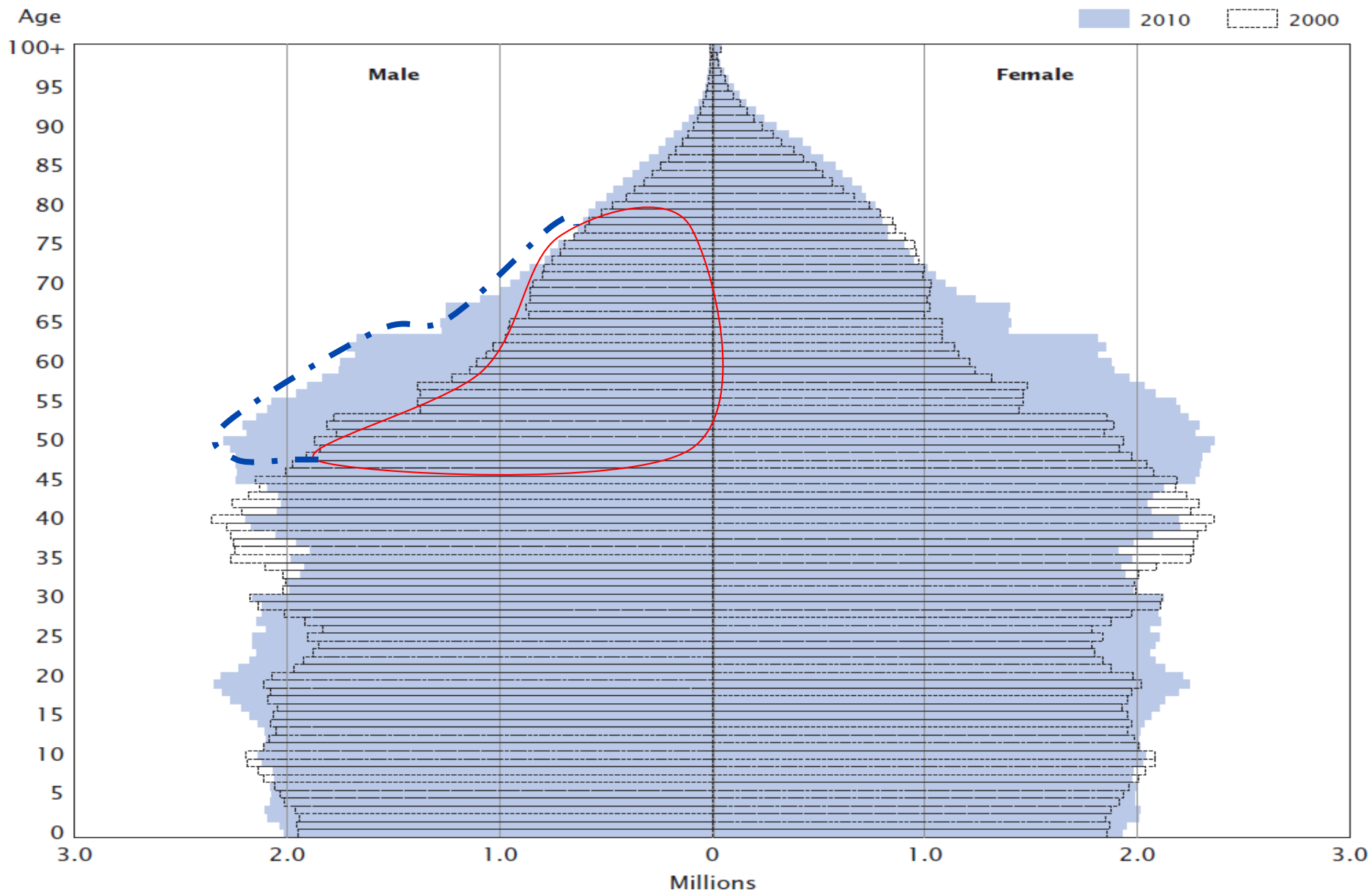
# A: PSA Based Screening

## US Census 2010

- Total Population: **308,745,538**
- Males – all ages: **151,781,326**
- Males: 65 years & above: **17,362,960**
  
- Known prevalence of prostate cancer cases in the US (2007-SEER): **2.23 million**
- **Lifetime risk in US males: 16%**
- **Risk of dying from prostate cancer: 2.9%**

# Population by Age and Sex: 2000 and 2010

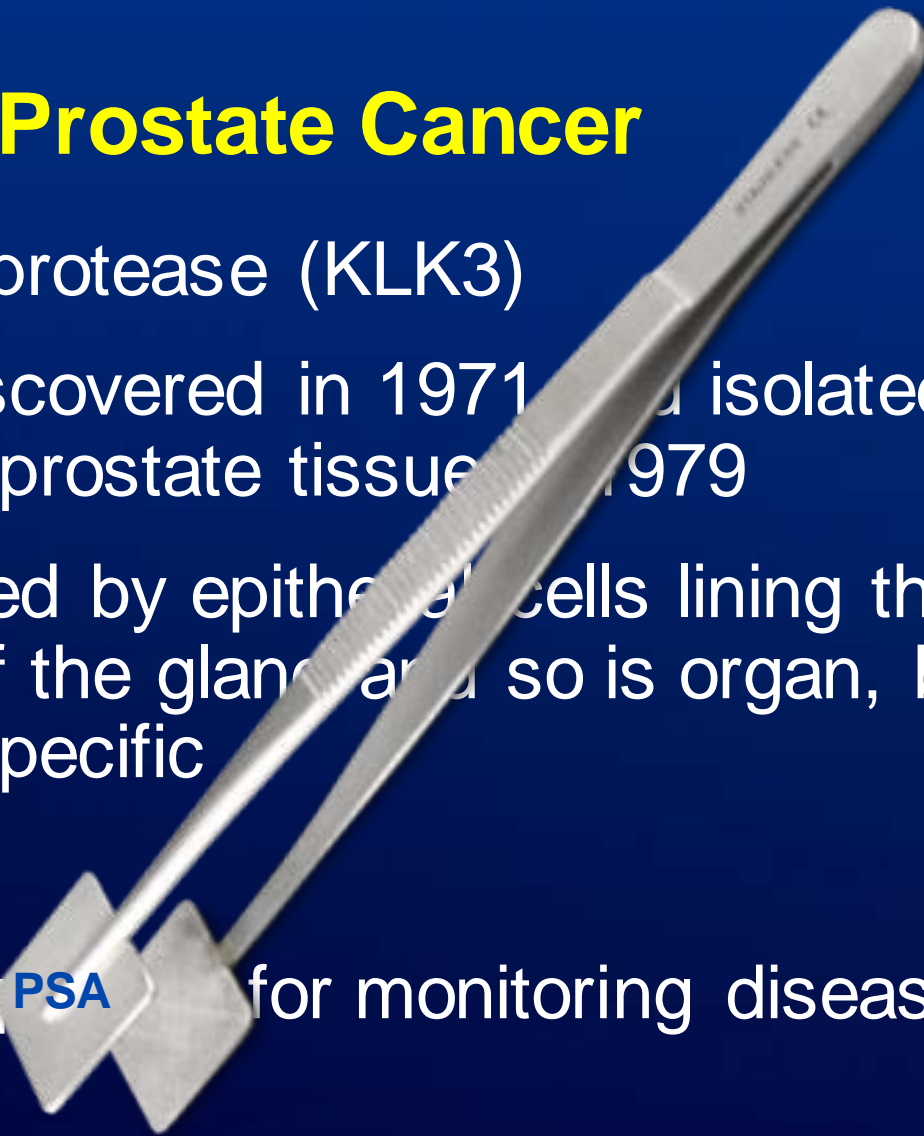
(For information on confidentiality protection, nonsampling error, and definitions, see [www.census.gov/prod/cen2010/doc/sf1.pdf](http://www.census.gov/prod/cen2010/doc/sf1.pdf))



Sources: U.S. Census Bureau, *Census 2000 Summary File 1* and *2010 Census Summary File 1*.

# PSA in Prostate Cancer

- Serine protease (KLK3)
- First discovered in 1971 and isolated from human prostate tissue in 1979
- Produced by epithelial cells lining the acini and ducts of the gland and so is organ, but not tumor specific
- FDA approved **PSA** for monitoring disease -1986



P94-16  
FOR IMMEDIATE RELEASE  
Aug. 29, 1994

Food and Drug Administration  
Sharon Snider (301) 443-3285  
Home (301) 622-0977

## FDA APPROVES TEST FOR PROSTATE CANCER

The Food and Drug Administration today approved the first blood test to help detect prostate cancer in men 50 and older. The test, a prostate specific-antigen (PSA) blood test, was approved for use in conjunction with a digital rectal exam.

The PSA test was initially approved by FDA in 1986 to aid in the care of patients who already had been diagnosed with prostate cancer. Today's approval expands the use to include helping to diagnose the disease.

The PSA test by itself cannot be relied on to determine whether a man has prostate cancer. It must be used in conjunction with other diagnostic procedures, including the digital rectal exam. The final diagnosis requires a biopsy.

"This test--used with other procedures--can help detect those men at risk for prostate cancer early on when more treatment options are available," said FDA Commissioner David A. Kessler, M.D. "But for the test to help, men must be aware of the importance of early check ups and get them on a regular basis."

FDA's approval of the test--the Tandem PSA Assay made by Hybritech Corp. of San Diego--is based on a review of clinical studies on safety and effectiveness submitted by the manufacturer and on the recommendation of FDA's Immunology Devices Panel. The tests were done in conjunction with a digital rectal exam.

-MORE-

Page 2, P94-16, Prostate Cancer Test

The firm's studies of more than 6,300 men showed that PSA testing when combined with a rectal exam was more effective in detecting prostate cancer than either a rectal test or PSA test alone.

While high levels of PSA may signal prostate cancer, they may also signal other common, non-cancerous prostate disorders.

# PSA Performance is Based on “Normal cut off ”

- **PPV:** the proportion of men with an “elevated” PSA value who have prostate cancer

PSA ( ng/ml)	PPV
> 4.0	30%
4.0-10	25%
>10	42-64%

- **NPV** is 85% i.e. <4.0 ng/ml 15 percent chance of having cancer

## Note: Lowering The “Normal Cut-off”

- Improves sensitivity but reduces specificity of test. The impact of this is:
  - **Greater** false positive rates;
  - **Greater** number of clinically indolent cases
  - **Increased** biopsies and increased rate of normal biopsies



# Relationship Of PSA Level To The Prevalence Of Prostate Cancer And High-grade Disease

**Table 2.** Relationship of the Prostate-Specific Antigen (PSA) Level to the Prevalence of Prostate Cancer and High-Grade Disease.\*

PSA Level	No. of Men (N=2950)	Men with Prostate Cancer (N=449)	Men with High-Grade Prostate Cancer (N=67)	Sensitivity	Specificity
		<i>no. of men (%)</i>	<i>no./total no. (%)</i>		
≤0.5 ng/ml	486	32 (6.6)	4/32 (12.5)	1.0	0.0
0.6–1.0 ng/ml	791	80 (10.1)	8/80 (10.0)	0.93	0.02
1.1–2.0 ng/ml	998	170 (17.0)	20/170 (11.8)	0.75	0.33
2.1–3.0 ng/ml	482	115 (23.9)	22/115 (19.1)	0.37	0.73
3.1–4.0 ng/ml	193	52 (26.9)	13/52 (25.0)	0.12	0.92

\* High-grade disease was defined by a Gleason score of 7 or greater. The population was restricted to men with a PSA level of 4.0 ng per milliliter or less throughout the study. Therefore, the definitions of sensitivity and specificity are restricted to cutoff values of less than 4.0 ng per milliliter (the cutoff values are equal to the lower value of the ranges in the PSA column [0.0, 0.6, 1.1, 2.1, and 3.1 ng/ml]). Sensitivity was defined as the proportion of men with cancer who had a PSA value above the cutoff among all men with cancer who had a PSA value of 4.0 ng per milliliter or less. Specificity was defined in a like manner.

# US Commission on Chronic Illness-1951

The **CC1 Conference** on Preventive Aspects of Chronic Disease, held in 1951, defined **screening** as:

*“... the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. **Screening tests** sort out apparently well persons who probably have a disease from those who probably do not...”*

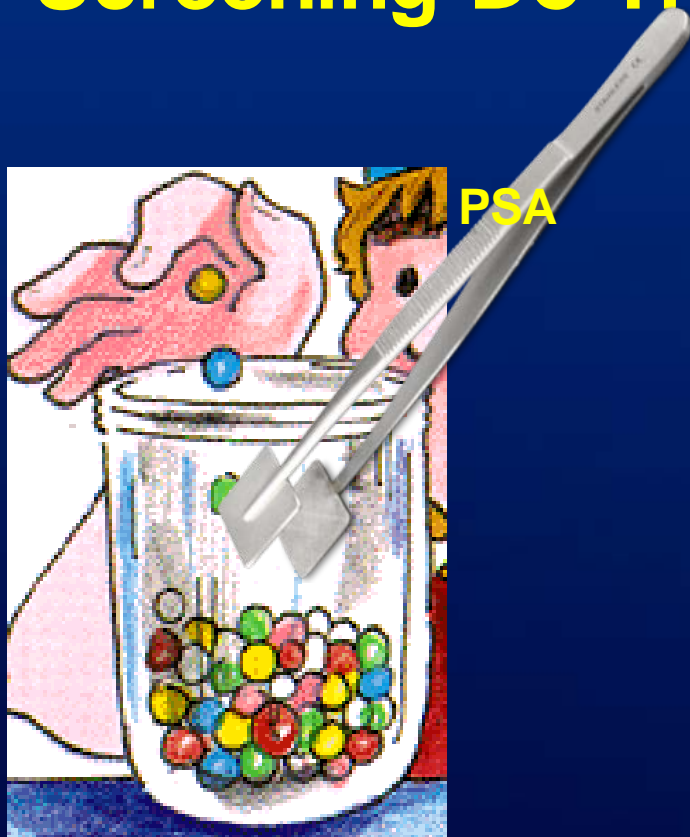
US proposed definition adopted by WHO

# PSA for Prostate Cancer Population Screening - Simple View !



•By population statistics the “prevalence” of prostate cancer is low

# 16% risk vs 3% Chance of Dying Can PSA for Prostate Cancer Population Screening Do This?



# Definition of a Screening Test and its Challenges

- Screening is a means of detecting disease in asymptomatic individuals, with the goal of decreasing morbidity and mortality **from the disease**
- Challenge is not simply detecting disease earlier, but showing that aggressive **treatment** of **screen-detected** disease will prevent disease specific mortality/morbidity and not survival

# 1992: ACS/AUA/ACR Position on PSA screening for Prostate Cancer

- “**All** men 50 years and above with an anticipated survival of 10 years or more based on presence of co-morbidities undergo an annual DRE and annual PSA for the purpose of detecting prostate cancer early”
- “It is **further** advised that annual screening being at age 40 years in African American males or men with a family history of prostate cancer “



## 1992: USPTF and Canadian Task Force for Periodic Health Examination Position

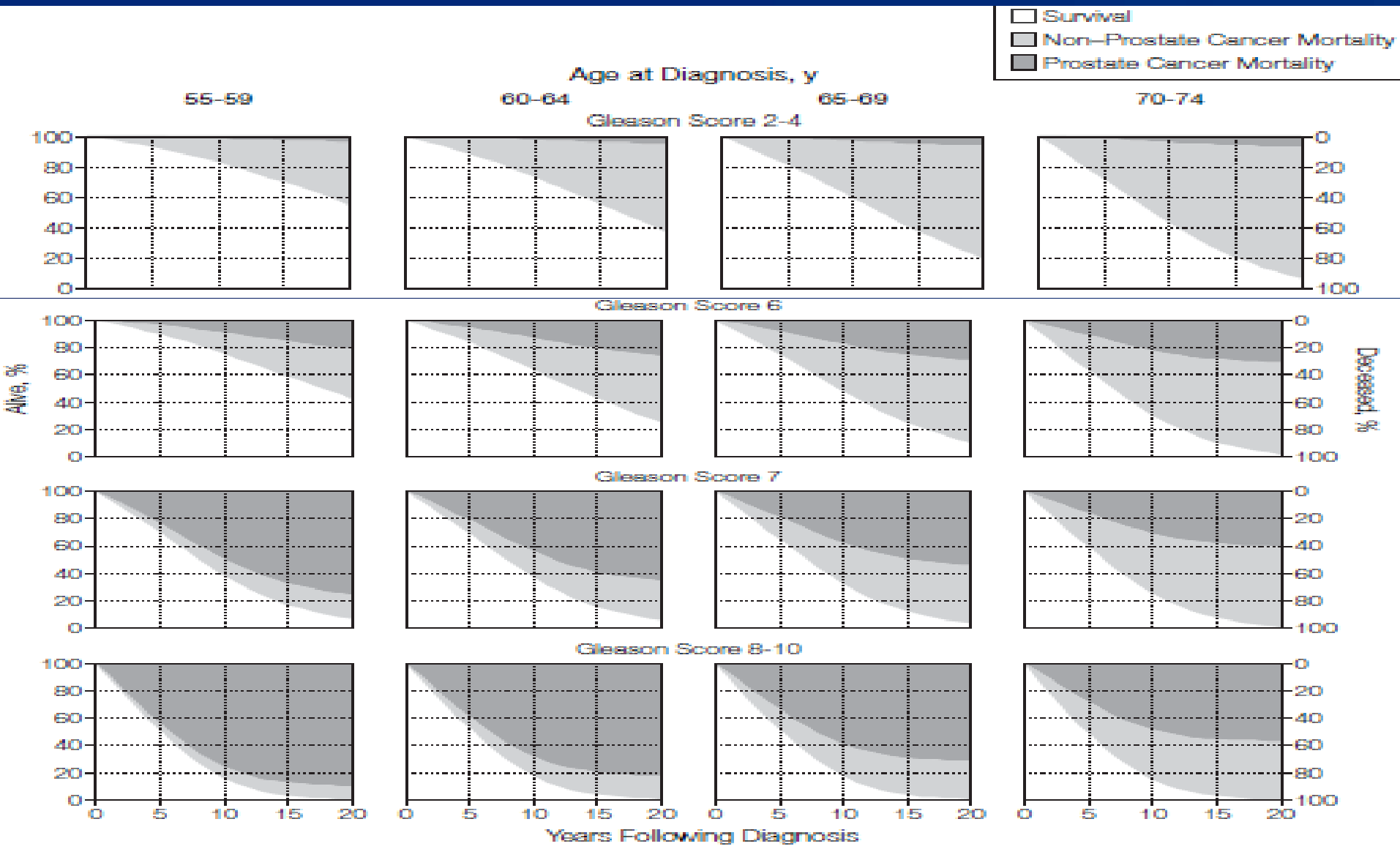
Recommend **against** annual screening with PSA

# Beyond PSA: Issues In Prostate Cancer Screening

- Long natural history
- Pathology = Aggressiveness (Gleason Scoring)
  - GS: 2-5                      Well differentiated tumors
  - GS: 6-7                      Moderately differentiated tumors
  - GS: 8-10                      Poorly differentiated tumors
- Give rise to biases in prostate cancer screening
  - **Lead time and Length time bias**

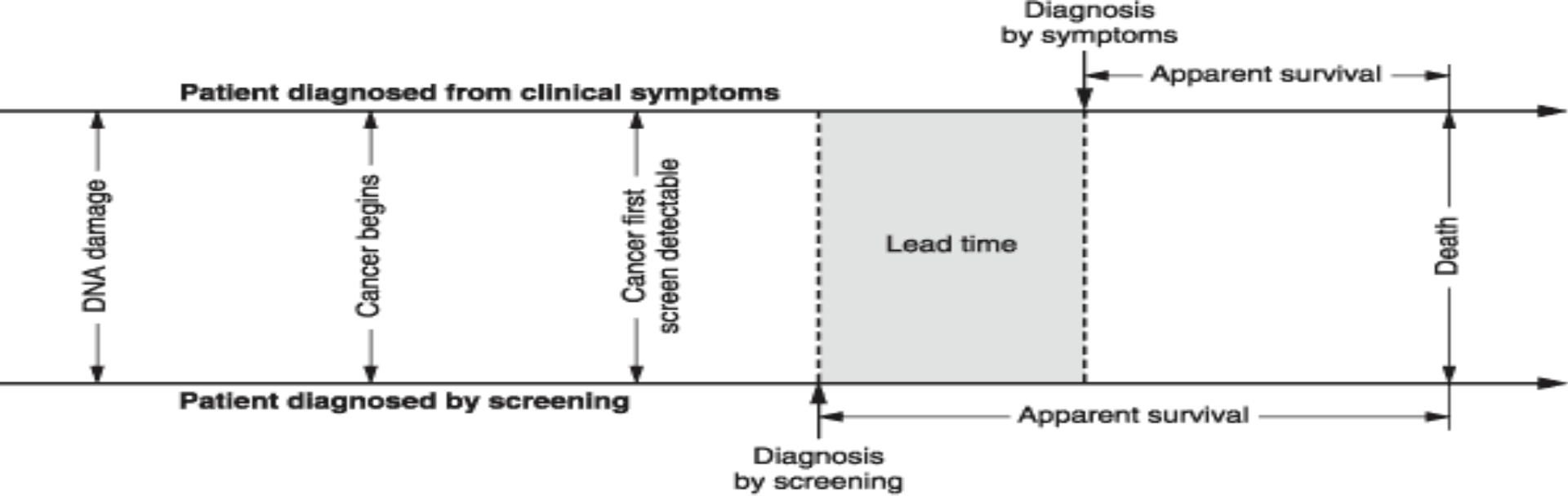


# 20-year Outcomes Of Clinically Detected Prostate Cancer *(JAMA.2005;293:2095-2101)*



# Length-Time Bias

- Screening tests diagnose slow growing tumors more easily than fast growing cancers
- Extreme form of length time bias is “**over diagnosis**” as the reservoir of slow growing tumors is large
- Patients are likely to die with the disease than of the disease



Source: Greenberg RS, Daniels SR, Flanders WD, Eley JW, Boring JR: *Medical Epidemiology*, 4th Edition: <http://www.accessmedicine.com>

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- Patient merely diagnosed earlier
- Survival “appears” increased, although life not prolonged
- Screening test prolongs time the subject is aware of diagnosis

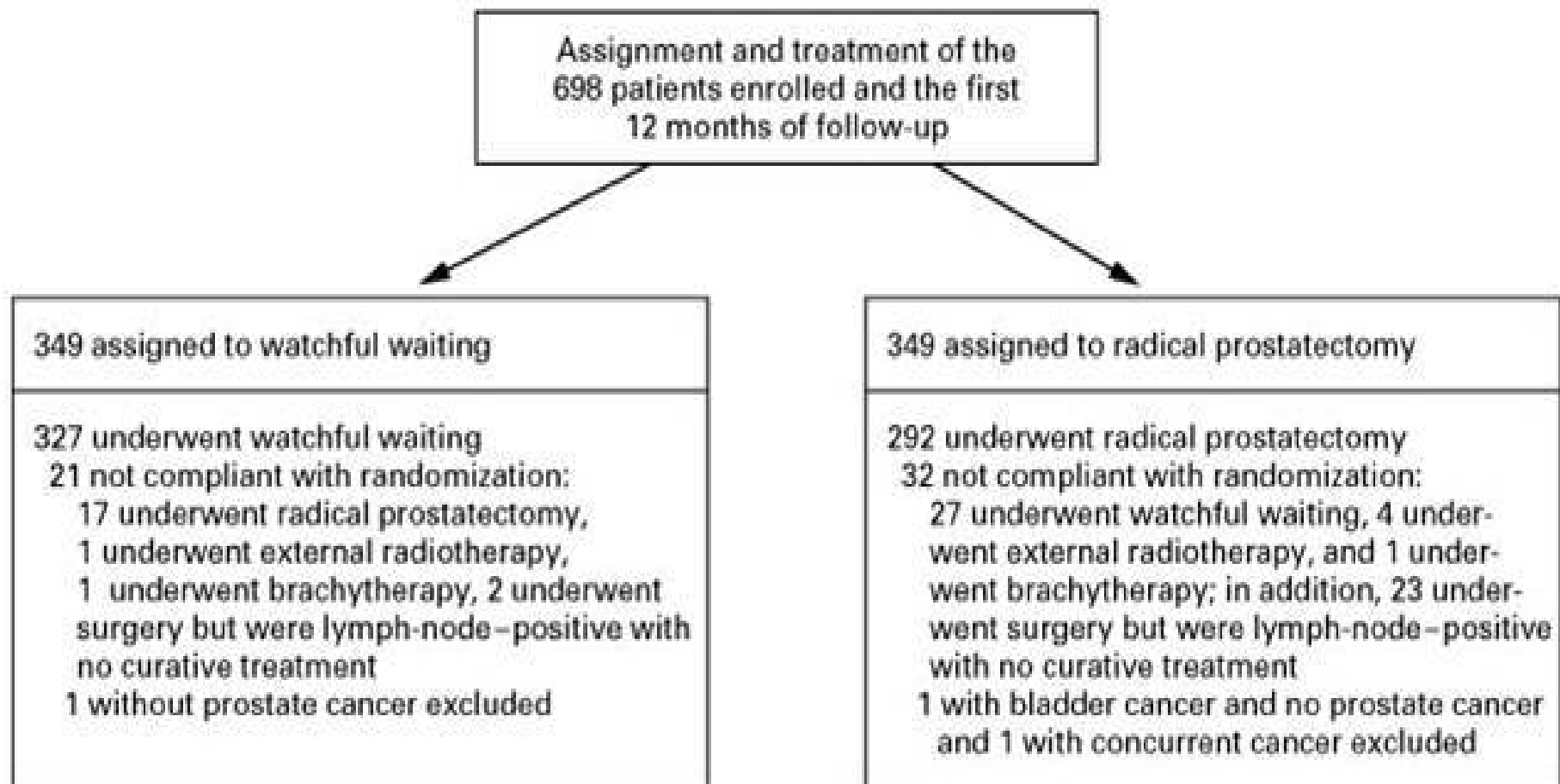
# Is There an Effective Treatment for Localized Prostate Cancer?

## Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Ph.D., et al. for the SPCG-4 Investigators

N Engl J Med  
Volume 364(18):1708-1717  
May 5, 2011

# Men With Prostate Cancer Diagnosed On The Basis Of Obstructive Urinary Symptoms (Rather Than Elevated PSA Levels)



# Cause Of Death Based on Treatment And Age At Diagnosis

**Table 2.** Cause of Death According to Treatment Group and Age at Diagnosis.\*

Cause of Death	Radical Prostatectomy (N=347)			Watchful Waiting (N=348)		
	All Men	<65 Yr of Age	≥65 Yr of Age	All Men	<65 Yr of Age	≥65 Yr of Age
				<i>number</i>		
Prostate cancer	55	28	27	81	49	32
Other cause	111	27	84	120	42	78
With metastases	6	2	4	16	5	11
Without metastases but with local progression or recurrence	12	2	10	26	8	18
With unknown status regarding metastases but with local progression	3	0	3	8	4	4
With no evidence of metastases or local pro- gression or recurrence	89	23	66	69	24	45
Within first month after randomization	1	0	1	1	1	0
Any cause	166	55	111	201	91	110

\* All events were evaluated by the independent end-point committee. [Bill-Axelsson A et al. N Engl J Med 2011;364:1708-1717](#)

# Nonfatal Surgical Complications within 1 Year after Radical-Prostatectomy

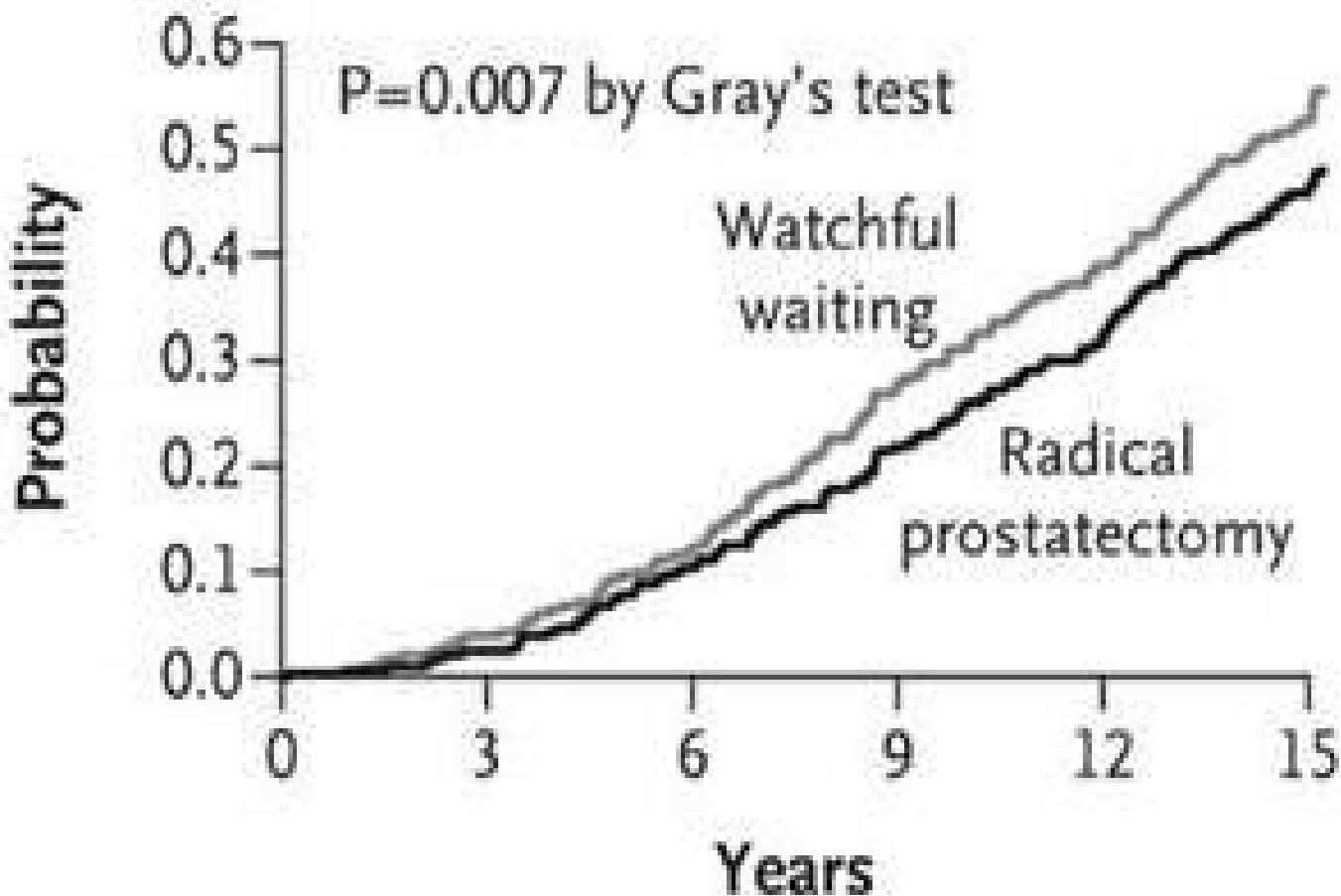
**Table 3.** Nonfatal Surgical Complications within 1 Year after Surgery among Men in the Radical-Prostatectomy Group.\*

Complication	No. of Events	1-Year Cumulative Incidence (95% CI)
Urinary leakage	93	32.2 (27.2–38.1)
Urinary obstruction	6	2.1 (0.9–4.6)
Impotence	168	58.1 (52.7–64.1)
Pulmonary embolism	4	1.4 (0.5–3.7)
Deep-vein thrombosis	3	1.0 (0.3–3.2)
Myocardial infarction	0	NA

\* A total of 289 men in the radical-prostatectomy group underwent surgery within the first year; 1 man died postoperatively. CI denotes confidence interval, and NA not applicable.

# A Death from Any Cause, Total Cohort

46.1% vs. 52.7%  
 (Absolute risk  
 reduction = 6.6%;  
 95% CI: 1.3-14.5)



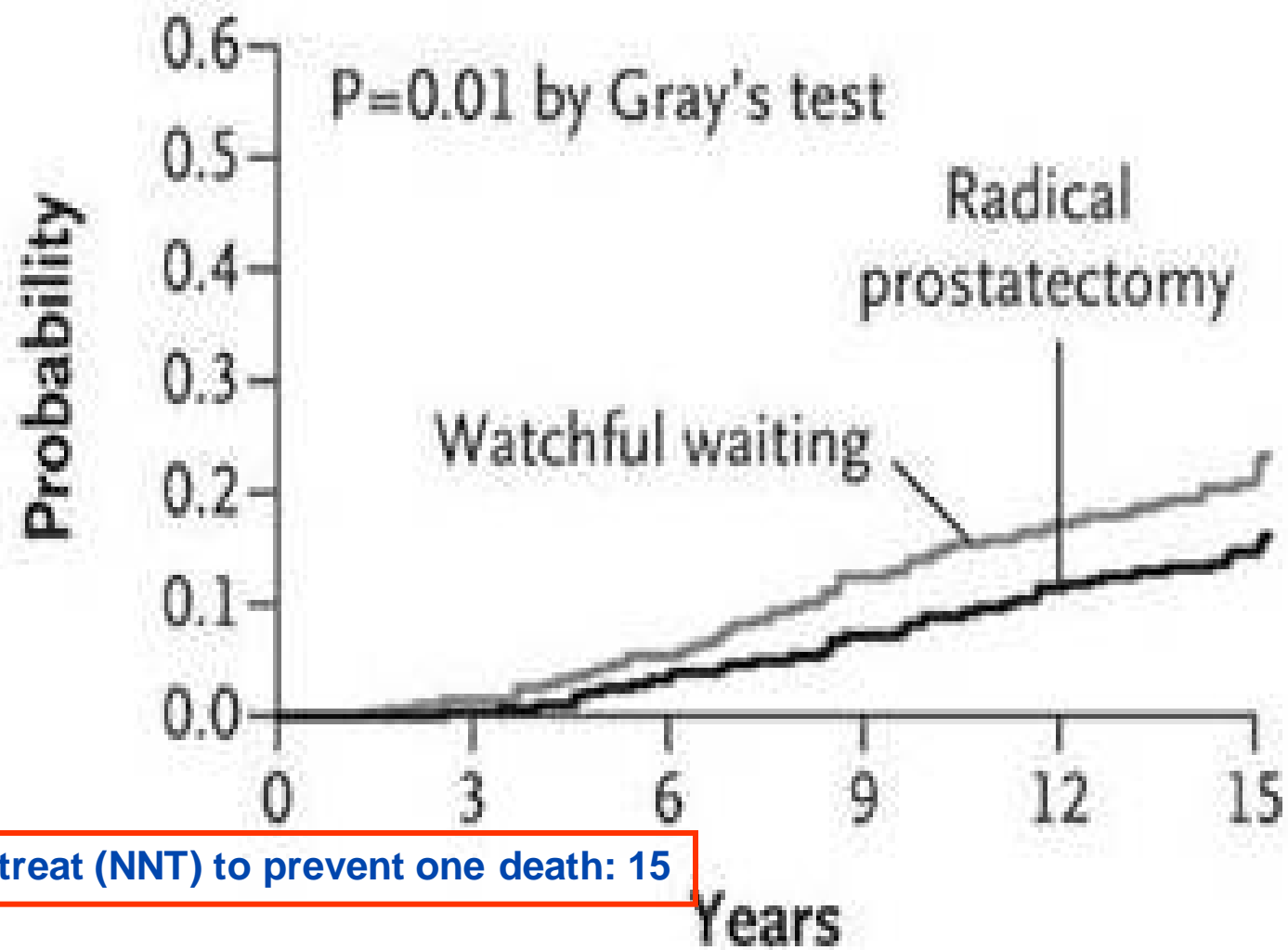
## No. at Risk

Radical prostatectomy	347	339	311	271	214	109
Watchful waiting	348	334	306	251	192	96



# B Death from Prostate Cancer, Total Cohort

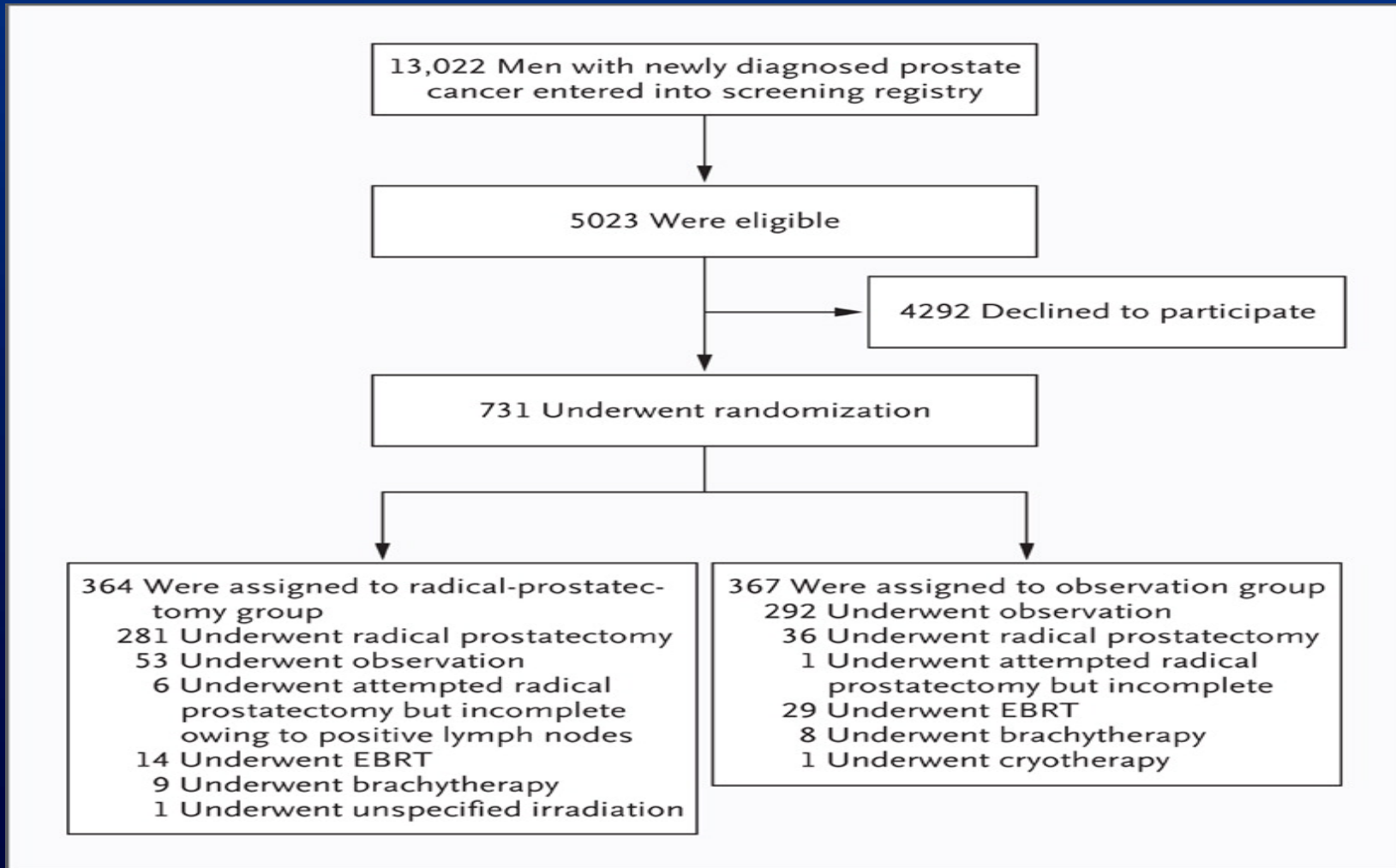
14.6 % RP group vs. 20.7% watchful waiting group



## No. at Risk

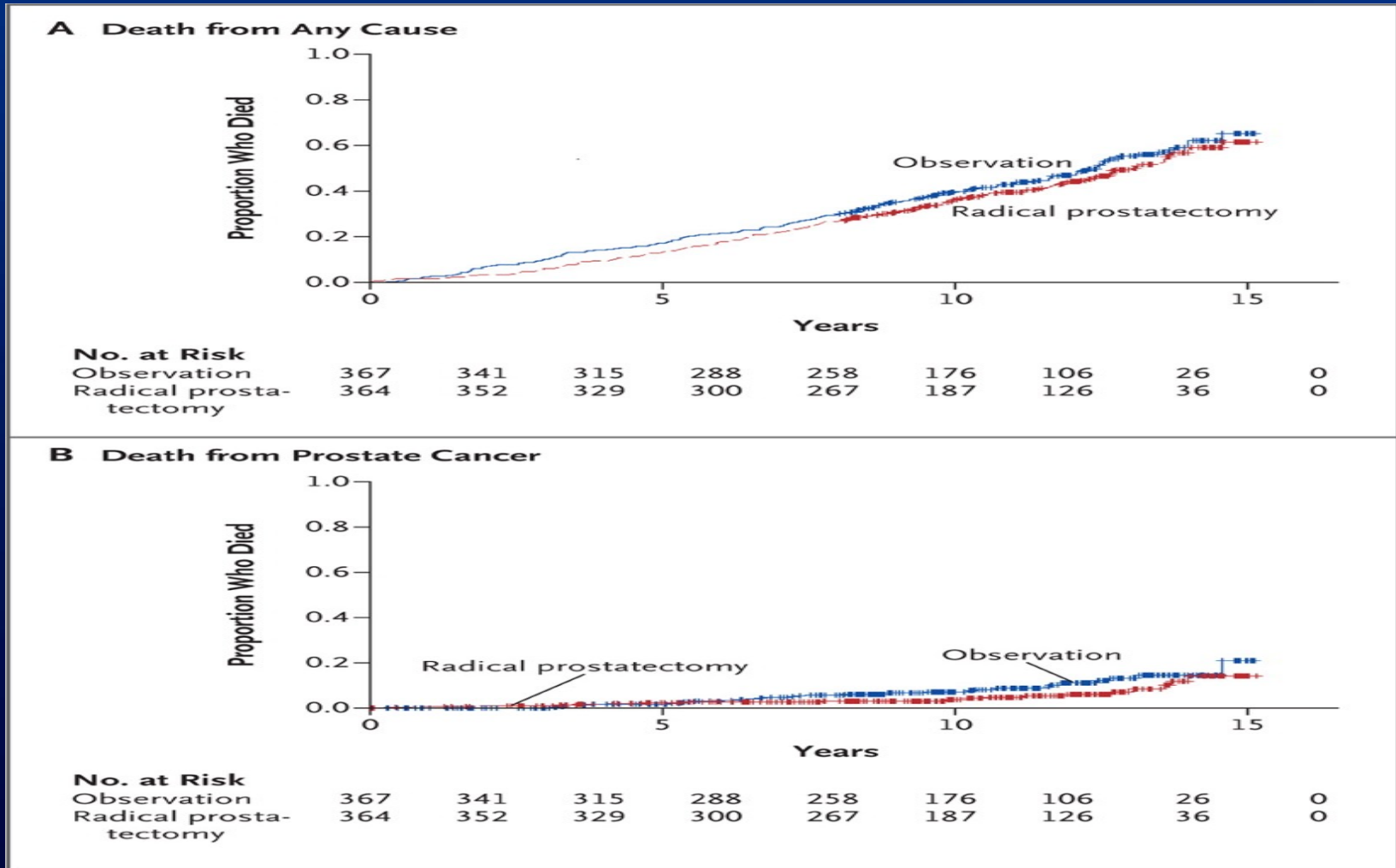
Radical prostatectomy	347	339	311	271	214	109
Watchful waiting	348	334	306	251	192	96

# PIVOT: Study Enrollment and Treatment



Wilt TJ et al. N Engl J Med 2012;367:203-213.

# PIVOT: Kaplan–Meier Plots of Mortality



Wilt TJ et al. N Engl J Med 2012;367:203-213.

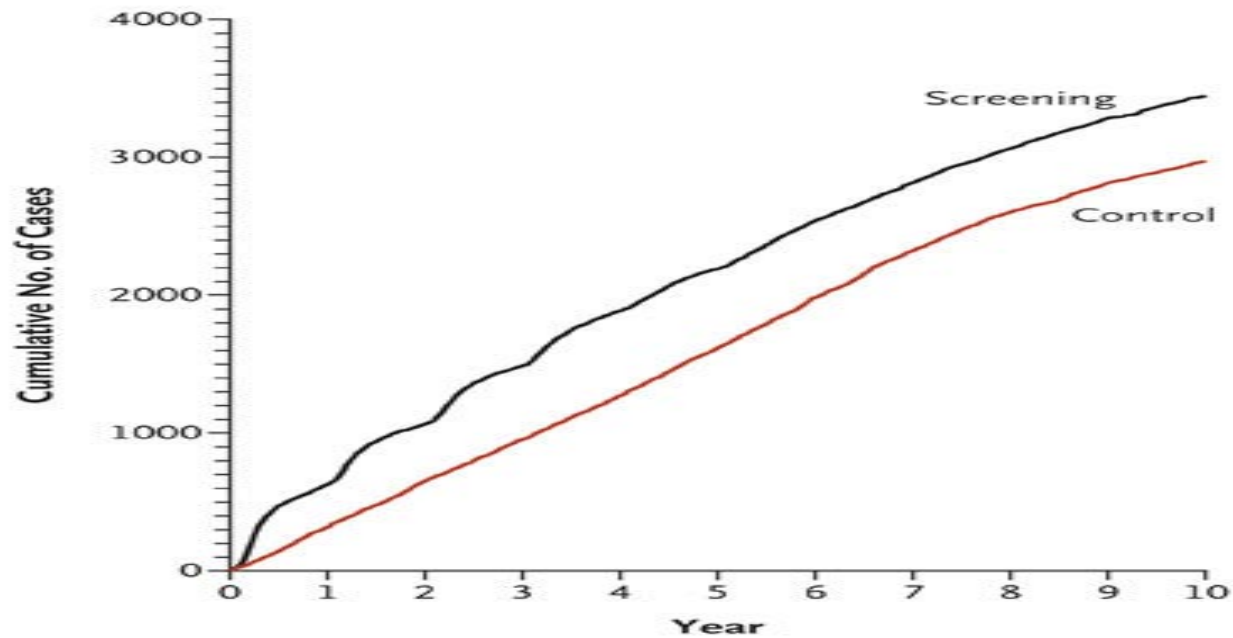
# 3 High Quality Randomized Controlled Trials Available

- The Prostate, Lung, Colorectal, and Ovarian Screening Trial (PLCO) 2009
- European Randomized Study of Screening for Prostate Cancer (ERSPC) 2009
  - Goterberg Trial 2010
- CAP 2018

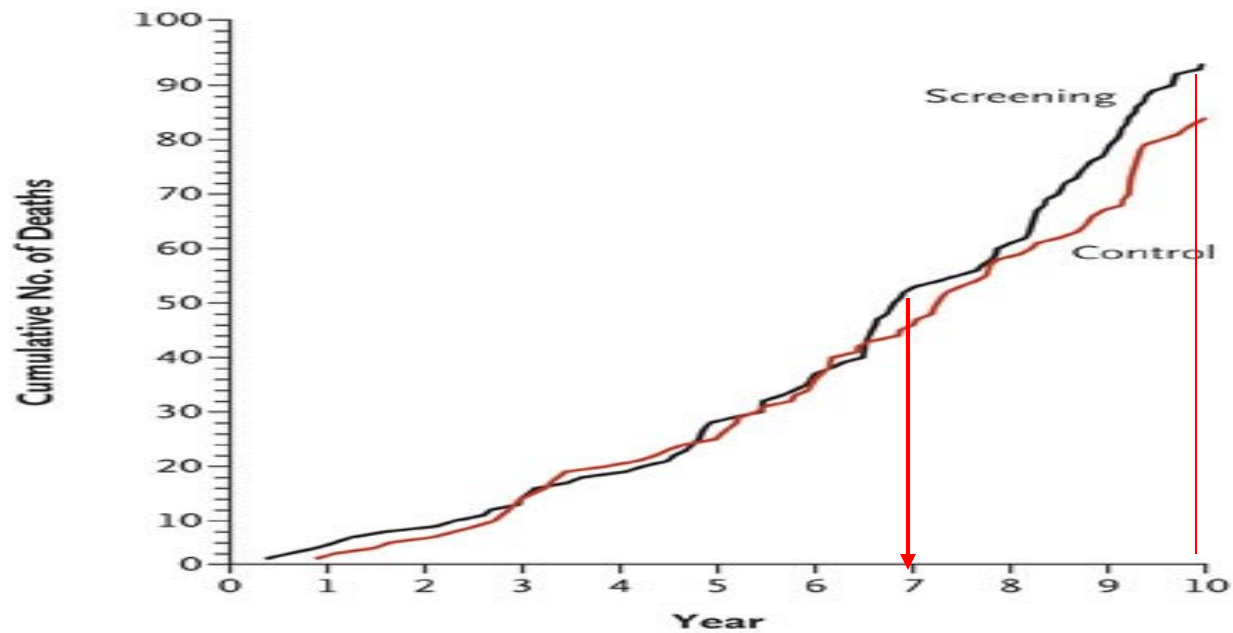
# PLCO

- Enrolled patients from 1993-2001 (10 US centers)
  - **Screening group:** Annual PSA/DRE for 6 years (PSA > 4.0ng/ml cut off for work up)
  - **“Usual care”** for the non-screening group
- **Primary Endpoint:** Cause specific mortality
- 7-year complete follow-up on death rate for **100%** and 10 year follow up for **67%**

### A Prostate Cancers



### B Prostate-Cancer Deaths



**Table 2. Tumor Stage, Histopathological Type, and Gleason Score for All Prostate Cancers at 10 Years, According to Method of Detection and Time of Diagnosis.\***

Variable	Screening Group					All Subjects (N=3452)	Control Group (N=2974)
	According to Method of Detection						
	Never Screened (N=154)	After Screening (N=875)	Outside of Screening Protocol (N=374)	Screen Detected at Baseline (N=549)	Screen Detected at Yr 1–Yr 5 (N=1500)		
Clinical stage							
I	1 (0.6)	5 (0.6)	8 (2.1)	2 (0.4)	2 (0.1)	18 (0.5)	15 (0.5)
II	138 (89.6)	838 (95.8)	347 (92.8)	516 (94.0)	1458 (97.2)	3297 (95.5)	2790 (93.8)
III	5 (3.2)	7 (0.8)	3 (0.8)	12 (2.2)	22 (1.5)	49 (1.4)	56 (1.9)
IV	10 (6.5)	20 (2.3)	9 (2.4)	19 (3.5)	15 (1.0)	73 (2.1)	79 (2.7)
Unknown	0	5 (0.6)	7 (1.9)	0	3 (0.2)	15 (0.4)	34 (1.1)
Histopathological type							
Adenocarcinoma							
Any	144 (93.5)	824 (94.2)	346 (92.5)	511 (93.1)	1375 (91.7)	3200 (92.7)	2802 (94.2)
Acinar	9 (5.8)	48 (5.5)	25 (6.7)	36 (6.6)	124 (8.3)	242 (7.0)	158 (5.3)
Other	1 (0.6)	3 (0.3)	3 (0.8)	2 (0.4)	1 (0.1)	10 (0.3)	14 (0.5)
Gleason score on biopsy†							
2–4	11 (7.1)	1.7 (1.9)	36 (9.6)	64 (11.7)	94 (6.3)	222 (6.4)	137 (4.6)
5–6	78 (50.6)	500 (57.1)	228 (61.0)	278 (50.6)	963 (64.2)	2047 (59.3)	1656 (55.7)
7	39 (25.3)	252 (28.8)	74 (19.8)	132 (24.0)	318 (21.2)	815 (23.6)	779 (26.2)
8–10	16 (10.4)	95 (10.9)	25 (6.7)	55 (10.0)	98 (6.5)	289 (8.4)	341 (11.5)
Unknown	10 (6.5)	11 (1.3)	11 (2.9)	20 (3.6)	27 (1.8)	79 (2.3)	61 (2.1)

\* Subjects with available data for tumor staging but not for nodal status or the presence or absence of metastasis were classified as having stage II disease. Percentages may not total 100 because of rounding.

† The Gleason score ranges from 2 to 10, with higher scores indicating more aggressive disease. **Andriole GL et al. N Engl J Med 2009;360:1310-1319**

**Table 4. Causes of Death at 10-Year Follow-up.\***

Cause	Screening Group	Control Group
	no. (%)	no. (%)
Any†	3953 (100.0)	4058 (100.0)
Cancer†	916 (23.2)	918 (22.6)
Ischemic heart disease	857 (21.7)	843 (20.8)
Stroke	107 (2.7)	109 (2.7)
Other circulatory disease	684 (17.3)	723 (17.8)
Respiratory disease	415 (10.5)	416 (10.3)
Digestive disease	141 (3.6)	133 (3.3)
Infectious disease	74 (1.9)	85 (2.1)
Endocrine or metabolic disease or immune disorder	155 (3.9)	188 (4.6)
Nervous system disease	128 (3.2)	113 (2.8)
Accident	238 (6.0)	235 (5.8)
Other	238 (6.0)	295 (7.3)

\* Causes of death were determined by death certificate.

† Causes of death from any cause and cancer do not include prostate, lung, and colorectal cancer.



# PLCO Prime Conclusion

- After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups
- At 14.8 years: PCSM had a RR of 1.8 (95% CI: 0.87-1.24)

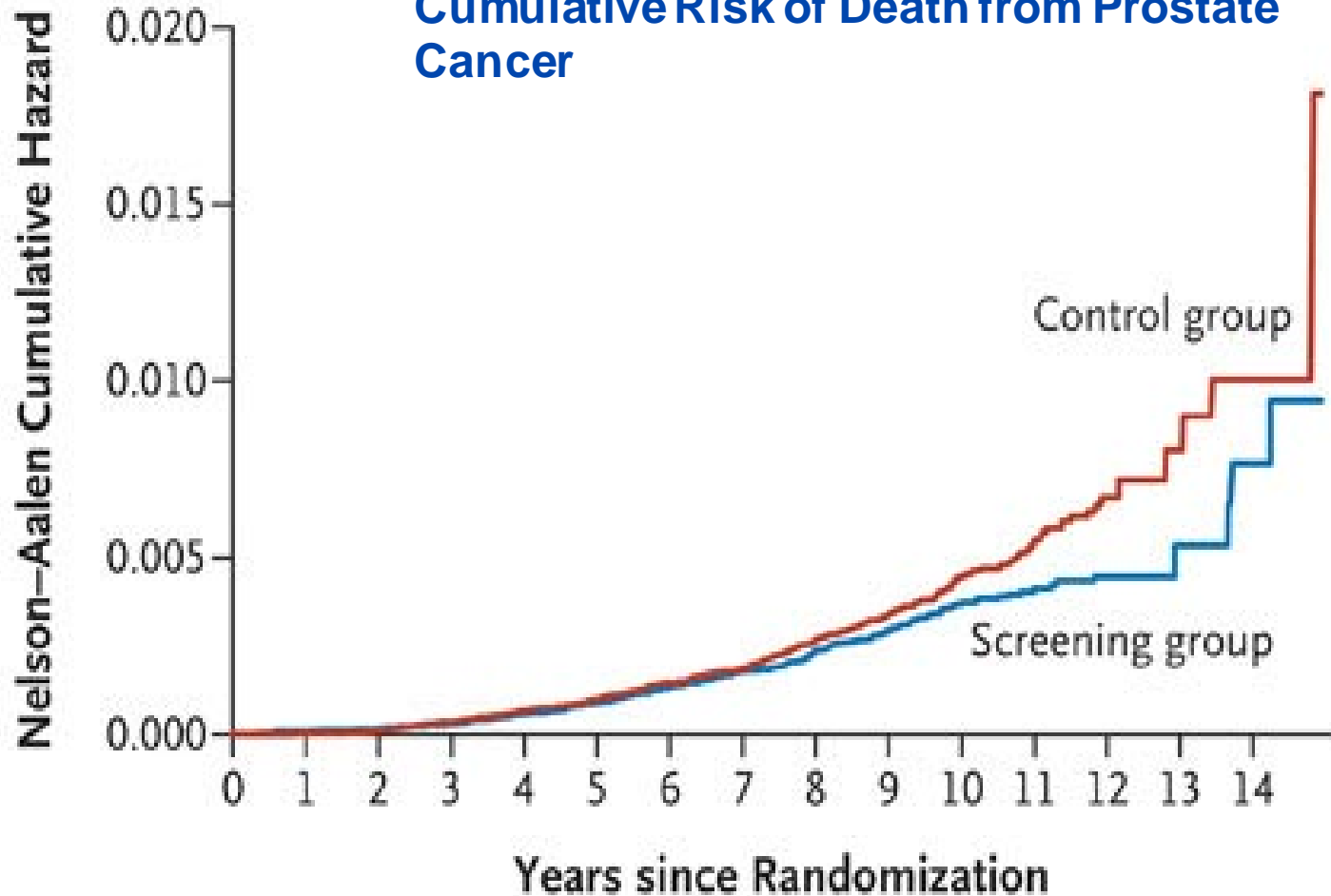
# Screening and Prostate-Cancer Mortality in a Randomized European Study (ERSPC)

N Engl J Med  
Volume 360(13):1320-1328  
March 26, 2009

# Study Overview

- PSA screening in 162,000 men between the ages of **55 and 69** years (core group) in seven European countries
- Primary endpoint: Death rate from prostate cancer
- Most centres used PSA cut off lower than US (3 ng/ml) for doing a biopsy
- Screening once every 4 years (6/7 centres)

## Cumulative Risk of Death from Prostate Cancer



### No. at Risk

Screening group

65,078 58,902 20,288

Control group

80,101 73,534 23,758

# ERSPC Conclusions

- PSA-based screening reduced the rate of death from prostate cancer by **20%** but was associated with a high risk of over diagnosis (PSA PPV of 24%)
- A significant reduction in prostate-cancer mortality was found after a median follow-up of 9 years
- Over diagnosis and overtreatment were important limitations of the screening program

# Gothenburg Randomized Population Based Prostate Cancer Screening Trial

(*Lancet Oncol*:v11;2010;p725.)

- PSA screening offered **once every two** years
- Initiated 1994 for target population **50-64** years

**N=20,000--1:1 randomization**

**9952 Screened**

**9952 Controls**

Urological work up initiated with PSA of **3.0ng/ml**

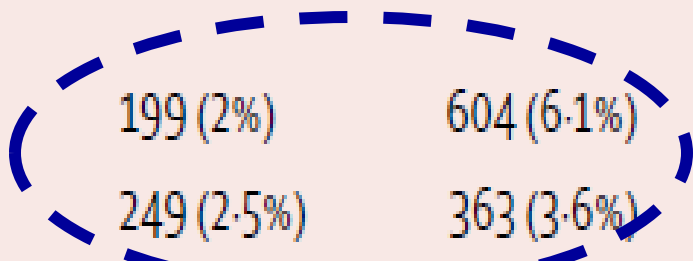
Primary endpoint: Absolute and relative risk reduction in cumulative prostate-cancer mortality



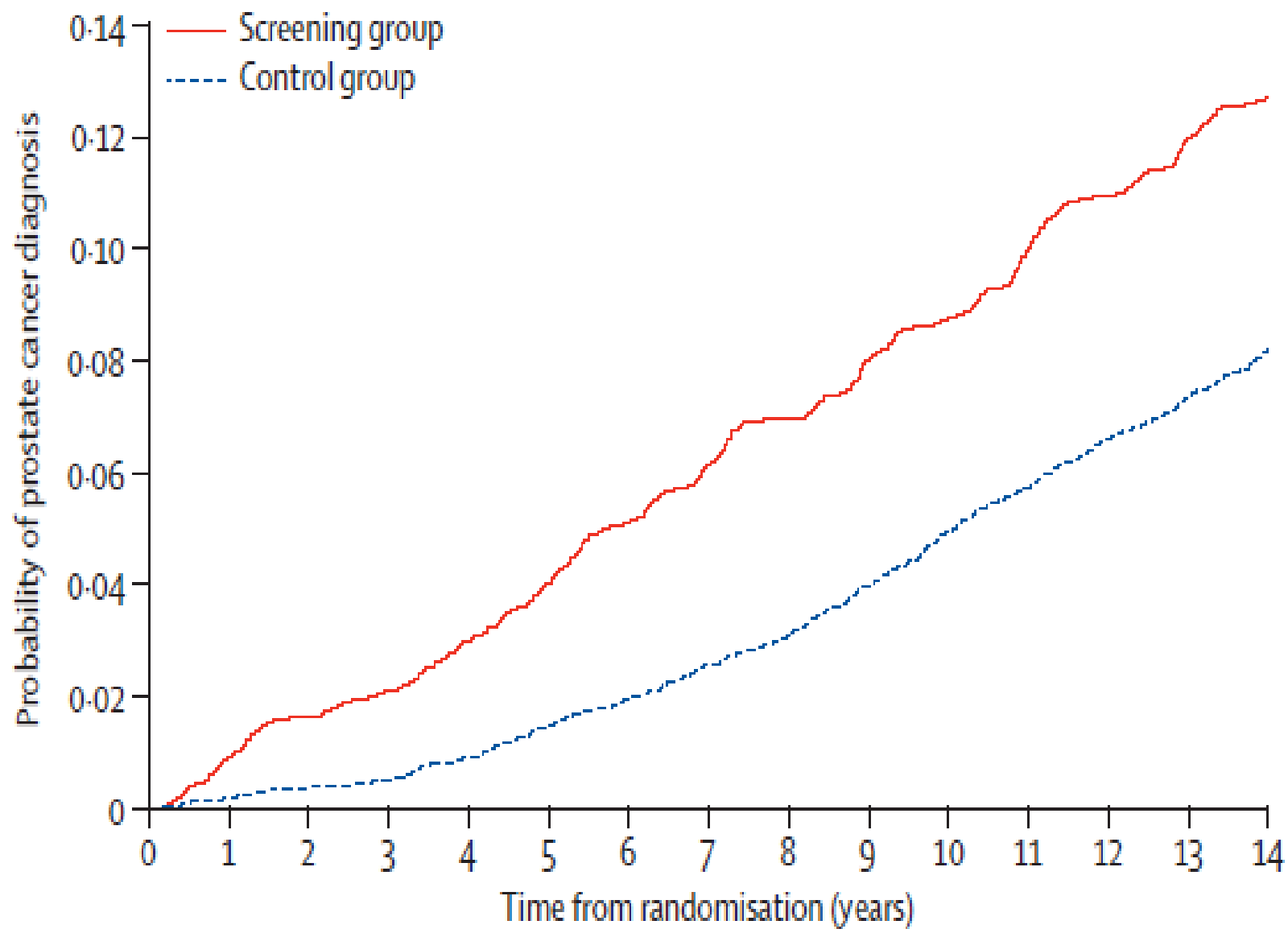
	Screening visit							Total
	1st	2nd	3rd	4th	5th	6th	7th	
<b>1st invitation round (1995–96)</b>								
Number of men invited	..	..	..	..	..	..	..	9890
Number of men participating	5855	..	..	..	..	..	..	5855
Number of men with raised PSA	661	..	..	..	..	..	..	661
Number of men with PC	144	..	..	..	..	..	..	144
<b>2nd invitation round (1997–99)</b>								
Number of men invited	..	..	..	..	..	..	..	9525
Number of men participating	580	4680	..	..	..	..	..	5260
Number of men with raised PSA	66	543	..	..	..	..	..	609
Number of men with PC	15	98	..	..	..	..	..	113
<b>3rd invitation round (1999–2000)*</b>								
Number of men invited	..	..	..	..	..	..	..	6920
Number of men participating	460	632	2283	..	..	..	..	3375
Number of men with raised PSA	79	130	621	..	..	..	..	830
Number of men with PC	29	23	108	..	..	..	..	160
<b>4th invitation round (2001–02)</b>								
Number of men invited	..	..	..	..	..	..	..	7873
Number of men participating	291	549	2251	1531	..	..	..	4622
Number of men with raised PSA	49	63	125	497	..	..	..	734
Number of men with PC	13	13	19	87	..	..	..	132
<b>5th invitation round (2003–04)</b>								
Number of men invited	..	..	..	..	..	..	..	6598
Number of men participating	207	342	547	1880	1138	..	..	4114
Number of men with raised PSA	38	62	54	110	351	..	..	615
Number of men with PC	9	11	6	20	65	..	..	111
<b>6th invitation round (2005–06)</b>								
Number of men invited	..	..	..	..	..	..	..	5733
Number of men participating	117	188	296	468	1556	850	..	3475
Number of men with raised PSA	34	34	51	61	104	418	..	702
Number of men with PC	13	6	14	11	20	81	..	145
<b>7th invitation round (2007–08)</b>								
Number of men invited	..	..	..	..	..	..	..	4148
Number of men participating	68	94	145	241	374	1157	535	2614
Number of men with raised PSA	20	11	24	42	64	87	294	542
Number of men with PC	8	3	3	11	10	11	45	91
<b>Total (1995–2008)</b>								
Total number of invitations in the study	..	..	..	..	..	..	..	50 687
Number of men participating	7578	6334	3794	4393	3325	2452	1439	29 315†
Number of men with raised PSA	947	843	875	710	519	505	294	4693‡
Number of men with PC	231	154	150	129	95	92	45	896

# Prostate Cancers Diagnosed in the Study

	Control group (n=9952)	Screening group (n=9952)		
		All (n=9952)	Attendees (n=7578)	Non-attendees (n=2374)
Number of men with prostate cancers diagnosed (%)	<u>718 (7.2%)</u>	<u>1138 (11.4%)</u>	1046 (13.8%)	92 (3.9%)
Tumour grouping (%)				
Low risk*	199 (2%)	604 (6.1%)	590 (7.8%)	14 (0.6%)
Moderate risk†	249 (2.5%)	363 (3.6%)	339 (4.5%)	24 (1%)
High risk‡	126 (1.3%)	96 (1%)	76 (1%)	20 (0.8%)
Advanced disease§	87 (0.9%)	46 (0.5%)	25 (0.3%)	21 (0.9%)
Unknown¶	57 (0.6%)	29 (0.3%)	16 (0.2%)	13 (0.5%)







**Number at risk**

Screening group	9952	8961	7847	6761
Control group	9952	9214	8185	7168



Scientific reaction to the news of declining sperm-counts was mixed.

# USPTF 2011 Update For PSA Based Screening— October 2011

- Moderate to high certainty that the service has no net benefit or that the harms outweigh the benefits in men < 75 years
- Recommended against PSA screening for prostate cancer - **Grade D** recommendation applies to healthy men of all ages, regardless of age or family history
- **(2008:** Grade D for men > 75 years)

# USPTF Grading

- **"D"**: The USPSTF recommends against routinely providing [the service] to asymptomatic patients;
  - in fact “discourage the use of the service” by the provider
- **"I"**: (2002) The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing (the service)

# AUA 2011 Recommendations

- AUA continues to recommend informing men about risk/benefits and to initiate screening for:
- Men **50** years, with a 10-year life expectancy
- Recommends average risk men consider a baseline PSA at 40 (if LE > 10 years)
- Men **45** years, if African-American, or
- Men with a first-degree relative diagnosed with prostate cancer <65 years; 40, if has several relatives with prostate cancer <65 years
- Finally, no PSA cut off values for biopsy referral

# ACS 2011

- **ACS: Discuss** with patient; if he agrees offer PSA testing **annually beginning at 50**
- **Stresses patient informed decision and discussing decision aids**
- **Recommends cut off of 2.5 ng/ml for undergoing annual PSA testing**
- **Start screening discussions at age 40 – 45 in high risk patients**
- **Biopsy referral threshold of 4.0 ng/ml**

# Against PSA Screening

- Canadian Task Force On Preventive Health Care
- United Kingdom National Screening Committee
- Australian Cancer Council

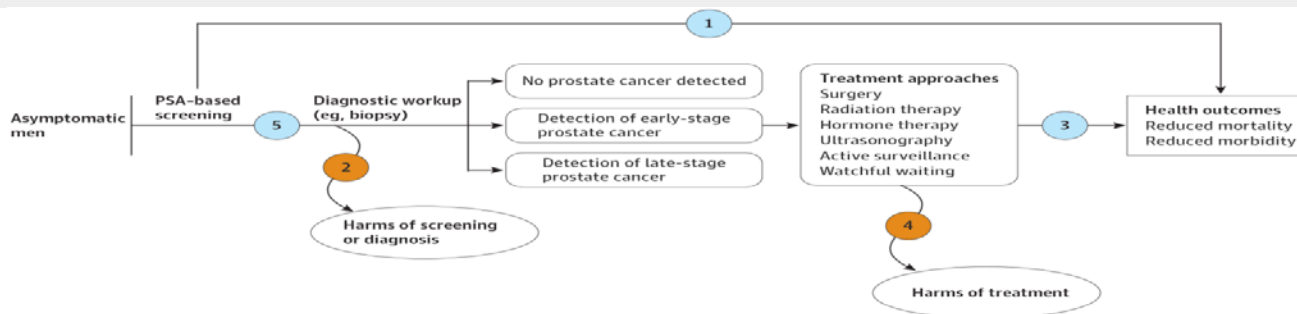
# ACP

- “Rather than screening all men for prostate cancer as a matter of routine, physicians should:
  - Describe the potential benefits and known harms of screening, diagnosis and treatment
  - Listen to patient concerns and
  - Then individualize decision to screen...”



From: Prostate-Specific Antigen–Based Screening for Prostate Cancer Evidence Report and Systematic Review for the US Preventive Services Task Force

JAMA. 2018;319(18):1914-1931. doi:10.1001/jama.2018.3712



Key questions

- 1 Is there direct evidence that prostate cancer–specific antigen (PSA)–based screening for prostate cancer reduces short- or long-term prostate cancer morbidity and mortality and all-cause mortality?
  - a. Does the effectiveness of PSA-based screening vary by subpopulation or risk factor (eg, age, race/ethnicity, family history, or clinical risk assessment)?
- 2 What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up?
  - a. Do the harms of PSA-based screening for prostate cancer and diagnostic follow-up vary by subpopulation or risk factor (eg, age, race/ethnicity, family history, or clinical risk assessment)?
- 3 Is there evidence that various treatment approaches for early-stage or screen-detected prostate cancer reduce morbidity and mortality?
  - a. Does the effectiveness of these treatment approaches vary by subpopulation or risk factor (eg, age, race/ethnicity, baseline PSA value, family history, comorbid conditions, or clinical risk assessment)?
- 4 What are the harms of the various treatment approaches for early-stage or screen-detected prostate cancer?
  - a. Do the harms of these treatment approaches vary by subpopulation or risk factor (eg, age, race/ethnicity, baseline PSA value, family history, comorbid conditions, or clinical risk assessment)?
  - b. Do the harms differ by treatment approach?
- 5 Is there evidence that use of a prebiopsy prostate cancer risk calculator, in combination with PSA–based screening, accurately identifies men with clinically significant prostate cancer (ie, cancer that is more likely to cause symptoms or lead to advanced disease), compared with PSA–based screening alone?

Figure Legend:

Analytic Framework Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Refer to the USPSTF Procedure Manual for further details.

# USPTF- 2018

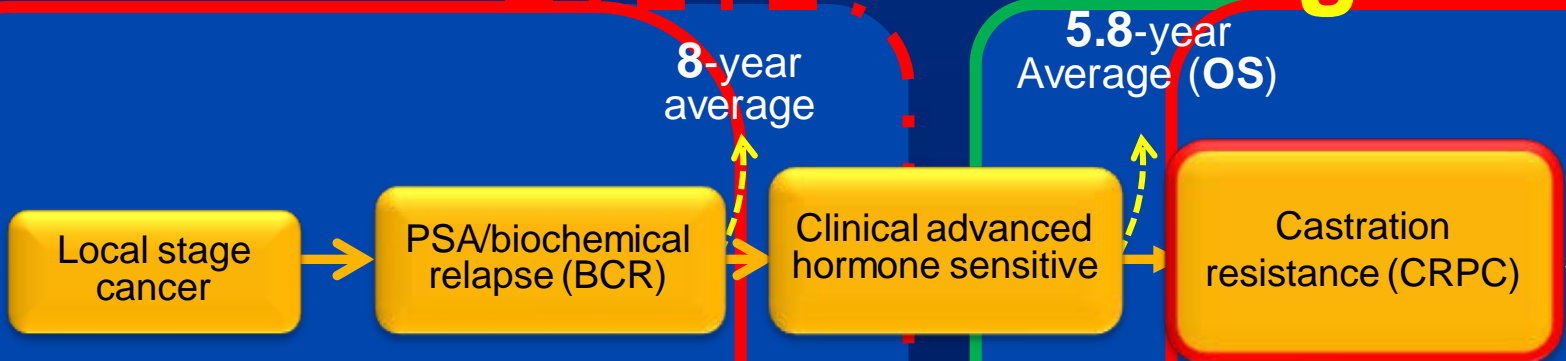
- PSA screening may reduce prostate cancer mortality risk; Is associated with false positives; Biopsy complications and Overdiagnosis
- For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one. **C**
- For men over 70: **D**

# **B: Emerging Therapeutic Developments**

**Based on Novel Therapeutics**

**Based on Novel Combinations of  
older drugs**

# Prostate Cancer Disease Progression



8-year average

5.8-year Average (OS)

Systemic therapies here for “high-risk” patient populations

**2017 additions**  
**STAMPEDE**  
**RTOG-9601**

Apalutamide  
?Enzalutamide  
  
Conditional to  
having started  
ADT

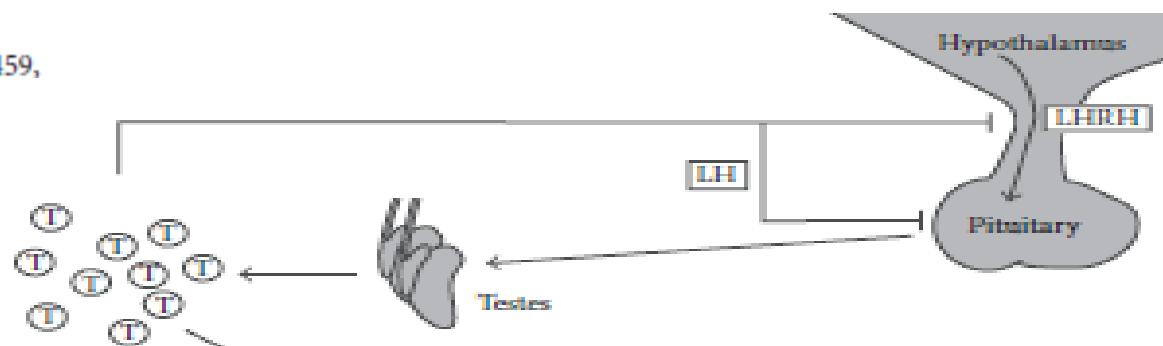
**Seven** new  
targeted and  
Non-targeted systemic  
treatments

**Death**  
**33,000!!**

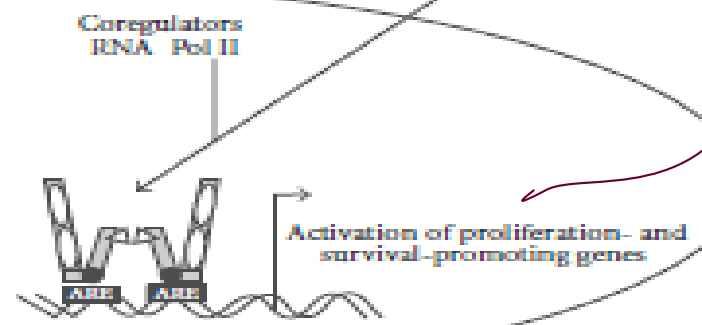
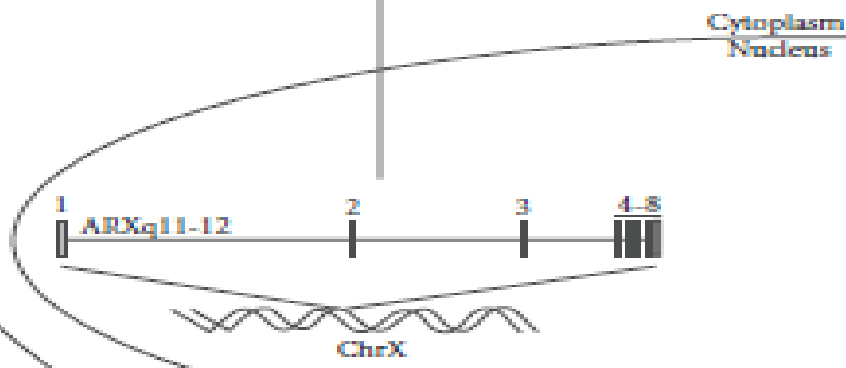
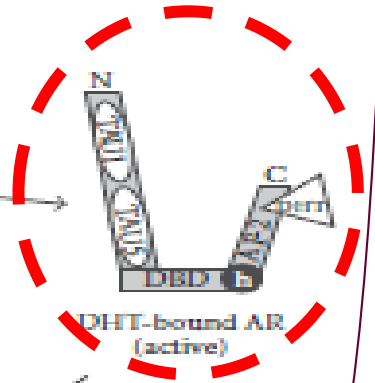
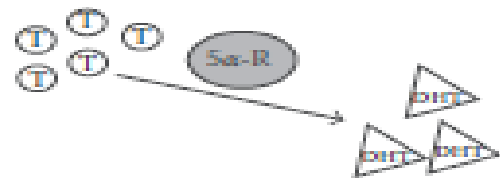
Estimated  
time to death  
**2-3 years**

# 1966: Nobel for Huggins & Hodges for ADT

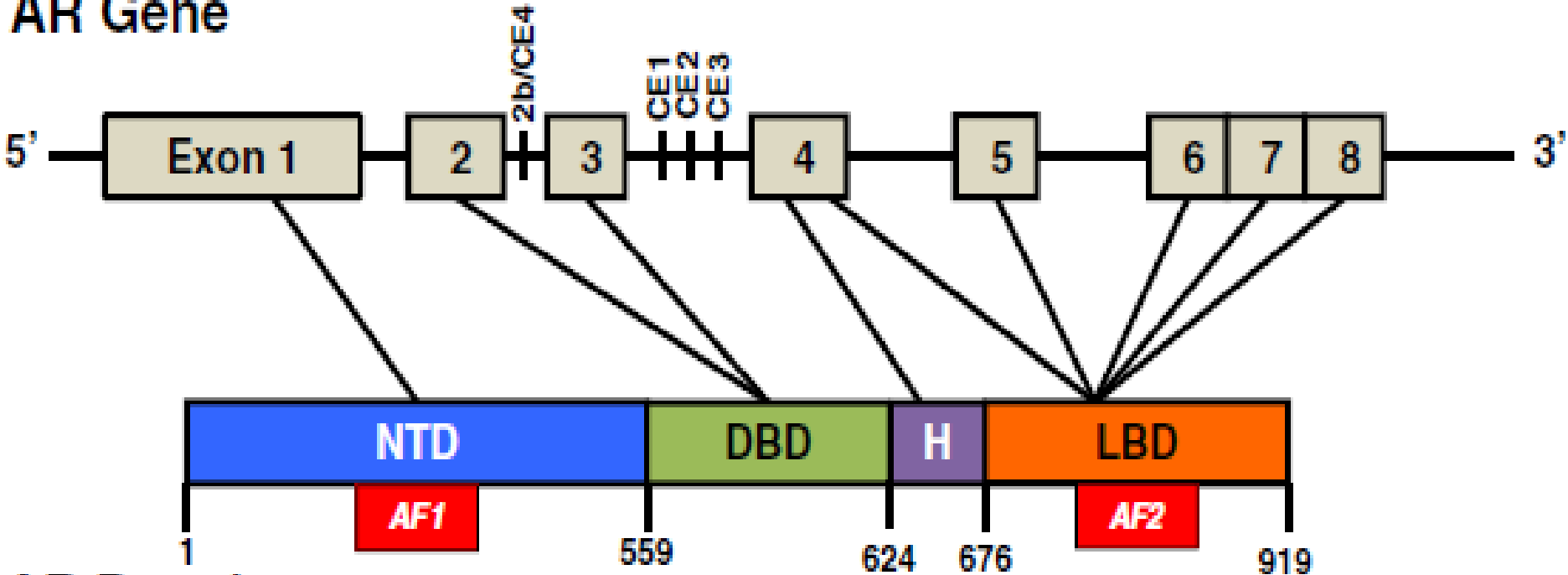




**PSA**  
Another 40 years...



# AR Gene



# AR Protein

B

## AR-V7



## AR-V<sup>e567s</sup>

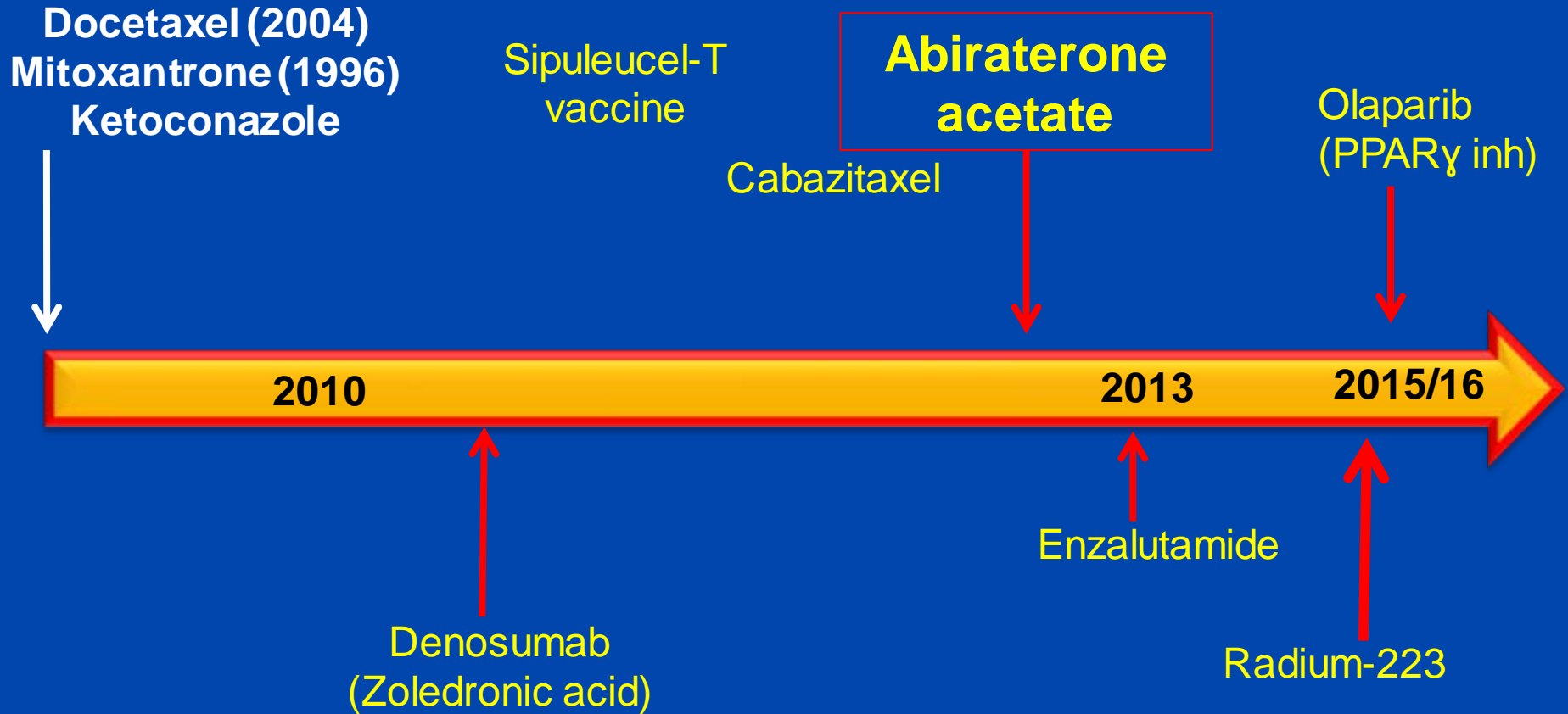


*AA. Shafi et al. / Pharmacology & Therapeutics 140 (2013) 223-238*





# Seven New Drugs for CRPC 2010-2015



# E3805 / CHARTED Treatment

## STRATIFICATION

### Extent of Mets

-High vs Low

### Age

≥70 vs < 70yo

### ECOG PS

- 0-1 vs 2

### CAB > 30 days

-Yes vs No

### SRE Prevention

-Yes vs No

### Prior Adjuvant ADT

≤12 vs > 12 months

R  
A  
N  
D  
O  
M  
I  
Z  
E

### ARM A:

ADT + docetaxel  
75mg/m<sup>2</sup> every 21  
days for maximum  
6 cycles

Evaluate  
every 3 weeks  
while  
receiving  
docetaxel and  
at week 24  
then every 12  
weeks

### ARM B:

ADT (androgen  
deprivation therapy  
alone)

Evaluate  
every 12  
weeks

Follow for time  
to progression  
and overall  
survival

Chemotherapy  
at investigator's  
discretion at  
progression

- ADT allowed up to 120 days prior to randomization
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

# E3805: Study Endpoints

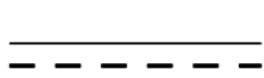
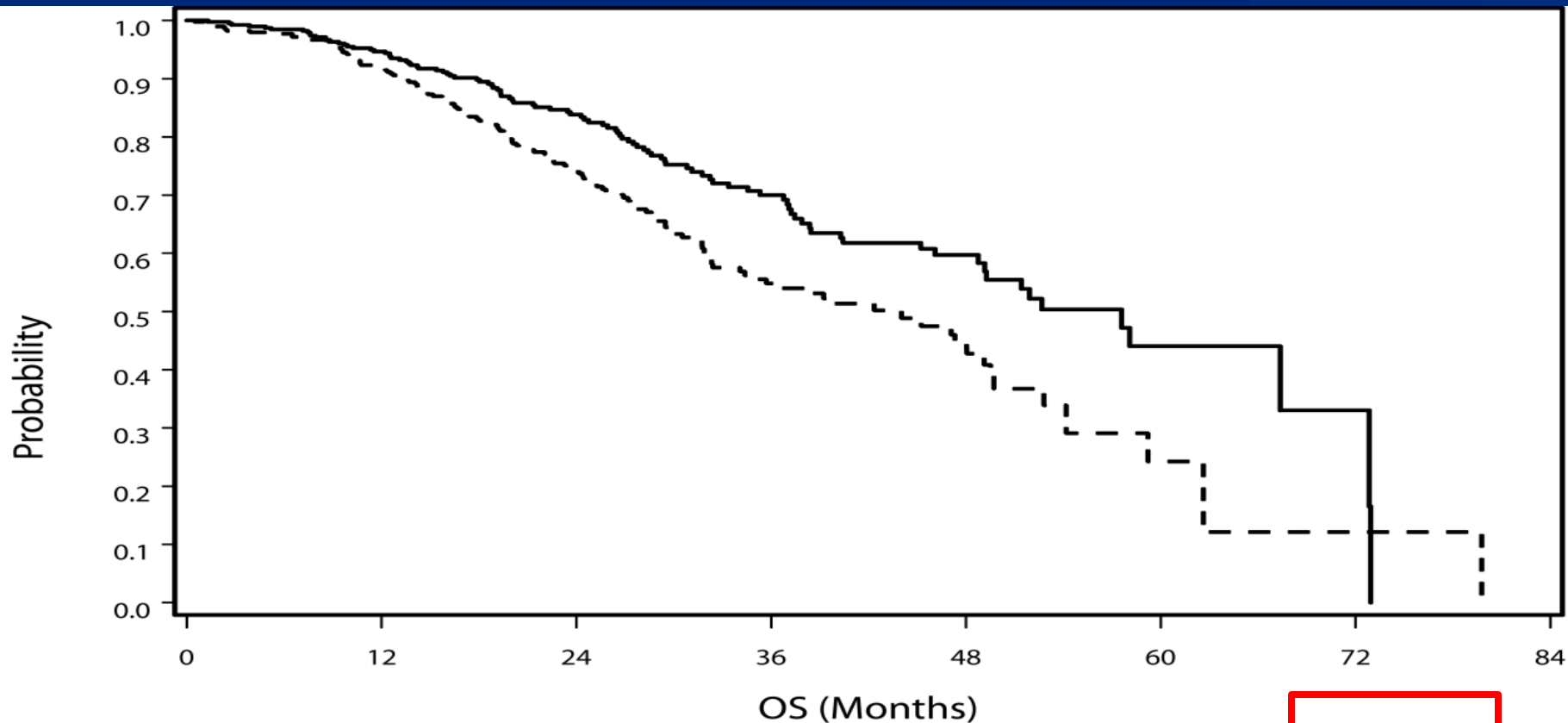
- **Primary Endpoint**

- Overall survival

- **Secondary Endpoints**

- Rate of PSA < 0.2 ng/mL at 6 months and 12 months
- Time to biochemical, radiographic or symptomatic PD
- Time to radiographic or symptomatic progressive disease (PD)

# E3805: Overall Survival (Entire Intent to Treat Population)



Arm  
A  
B

TOTAL

397

393

DEAD

101

136

ALIVE

296

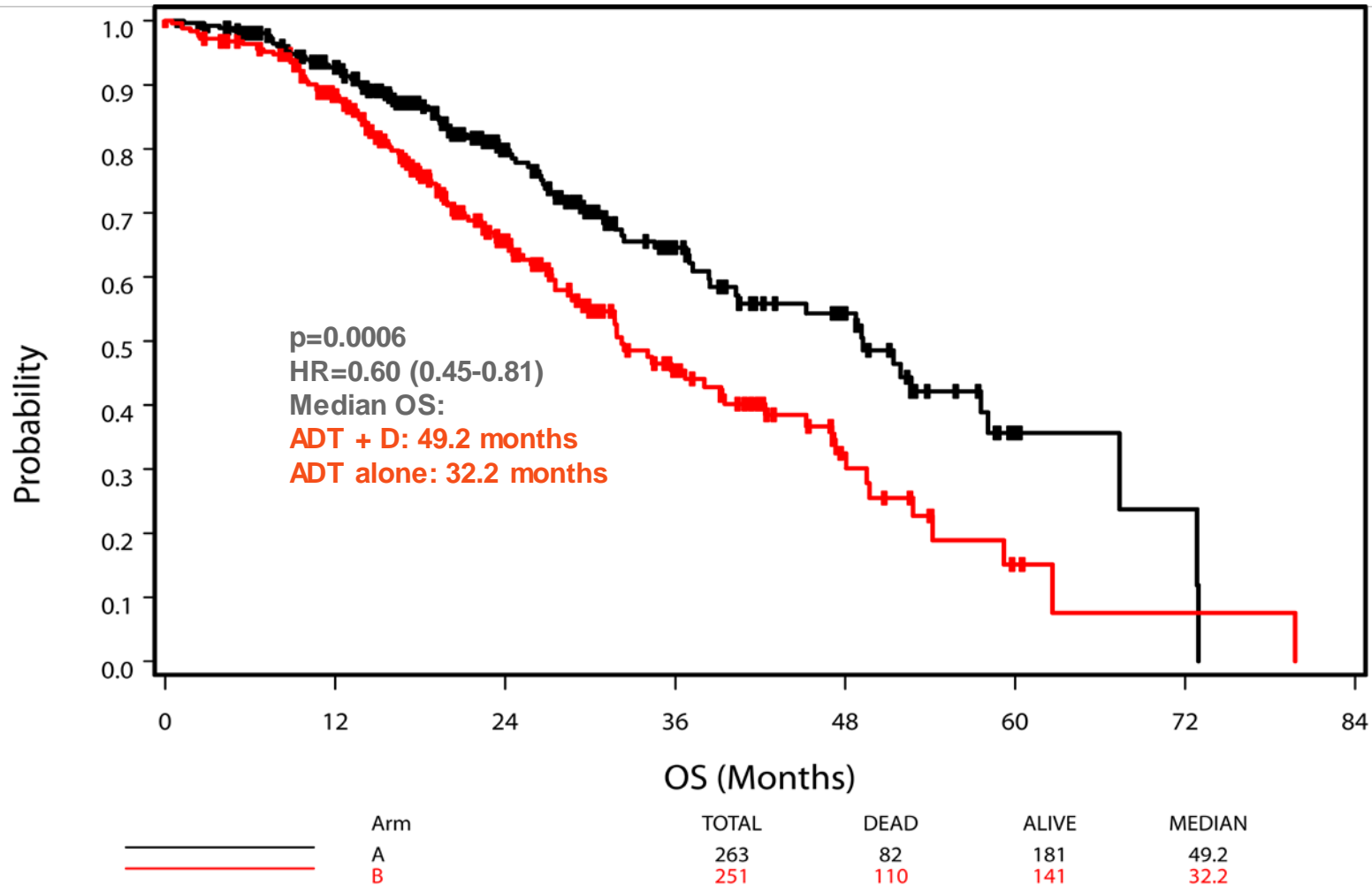
257

MEDIAN

57.6

44.0

# OS for Patients with High Volume Metastatic Disease at Start of ADT



In patients with high volume metastatic disease, there is a **17 month improvement in median** overall survival from 32.2 months to 49.2 months. (Projected 33 months in ADT alone arm)

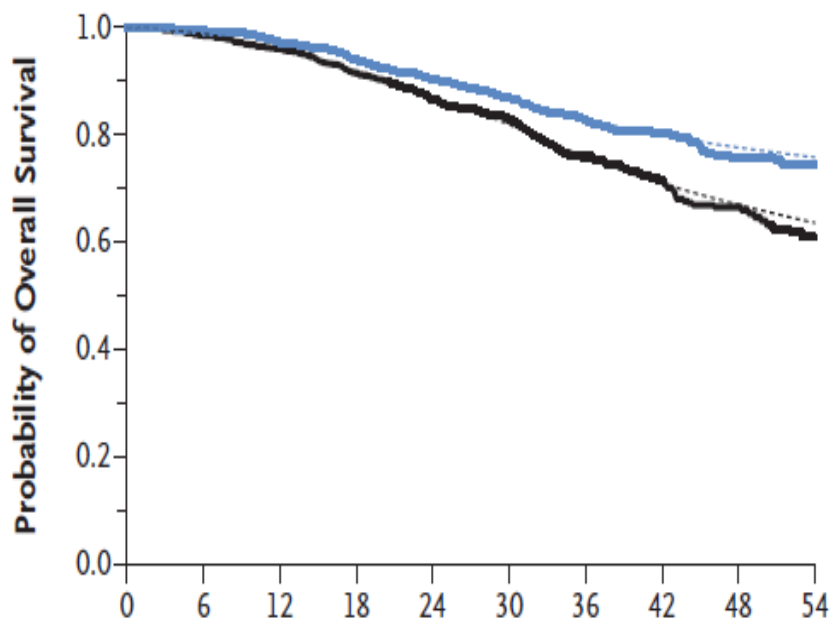
	Standard of care (n=1184)	Standard of care plus zoledronic acid (n=593)	Standard of care plus docetaxel (n=592)	Standard of care plus zoledronic acid and docetaxel (n=593)
<b>T category at randomisation</b>				
T0	7 (1%)	3 (1%)	2 (0%)	2 (0%)
T1	21 (2%)	7 (1%)	0 (0%)	5 (1%)
T2	113 (10%)	53 (9%)	60 (10%)	67 (11%)
T3	756 (64%)	395 (67%)	390 (66%)	371 (63%)
T4	211 (18%)	92 (16%)	105 (18%)	100 (17%)
TX	76 (6%)	43 (7%)	35 (6%)	48 (8%)
<b>N category at randomisation</b>				
N0	522 (44%)	258 (44%)	260 (44%)	265 (45%)
N+	594 (50%)	303 (51%)	298 (50%)	293 (49%)
NX	68 (6%)	32 (5%)	34 (6%)	35 (6%)
<b>Metastases</b>				
None	460 (39%)	227 (38%)	230 (39%)	228 (38%)
Any metastases	724 (61%)	366 (62%)	362 (61%)	365 (62%)
Bone metastases	634 (54%)	302 (51%)	307 (52%)	310 (52%)
Liver metastases	15 (1%)	12 (2%)	6 (1%)	9 (2%)
Lung metastases	33 (3%)	17 (3%)	13 (2%)	14 (2%)
Nodal metastases	220 (19%)	120 (20%)	102 (17%)	116 (20%)
Other metastases	46 (4%)	33 (6%)	25 (4%)	21 (4%)
<b>Broad disease grouping</b>				
Newly diagnosed NOM0	256 (22%)	120 (20%)	131 (22%)	131 (22%)
Newly diagnosed N+M0	171 (14%)	88 (15%)	86 (15%)	76 (13%)
Newly diagnosed M1	690 (58%)	351 (59%)	347 (59%)	350 (59%)
Previously treated M0	33 (3%)	19 (3%)	13 (2%)	21 (4%)
Previously treated M1	34 (3%)	15 (3%)	15 (3%)	15 (3%)
<b>Gleason sum score</b>				
≤7	282 (24%)	122 (21%)	110 (19%)	117 (20%)
8–10	810 (68%)	421 (71%)	436 (74%)	425 (72%)
Unknown	92 (8%)	50 (8%)	46 (8%)	51 (9%)

# STAMPEDE- Abiraterone Acetate/Prednisone

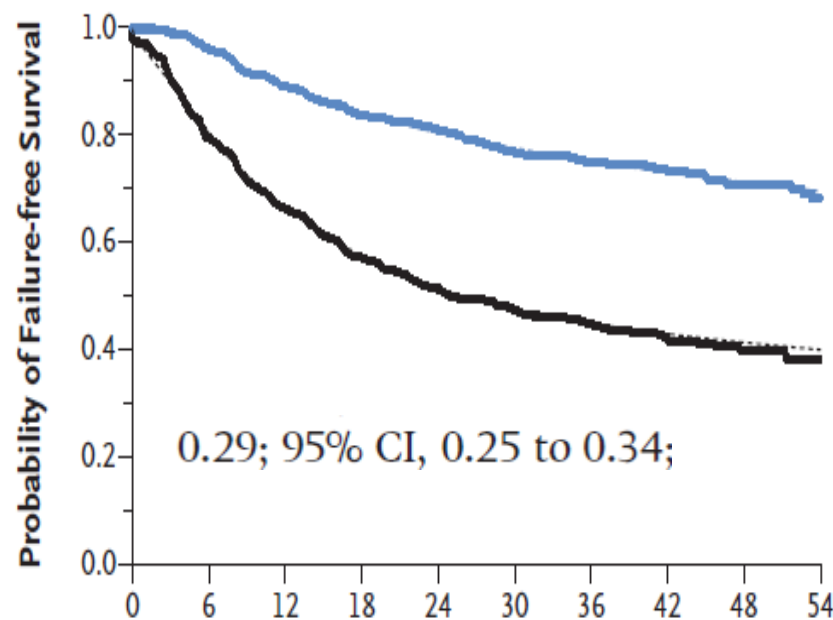
Characteristic	ADT Alone (N=957)	Combination Therapy (N=960)
Newly diagnosed node-negative, nonmetastatic disease	256 (27)	253 (26)
Newly diagnosed node-positive, nonmetastatic disease	187 (20)	182 (19)
Newly diagnosed metastatic disease	476 (50)	465 (48)
Previously treated nonmetastatic disease	12 (1)	25 (3)
Previously treated metastatic disease	26 (3)	35 (4)

N ENGL J MED 377:4 NEJM.ORG JULY 27, 2017

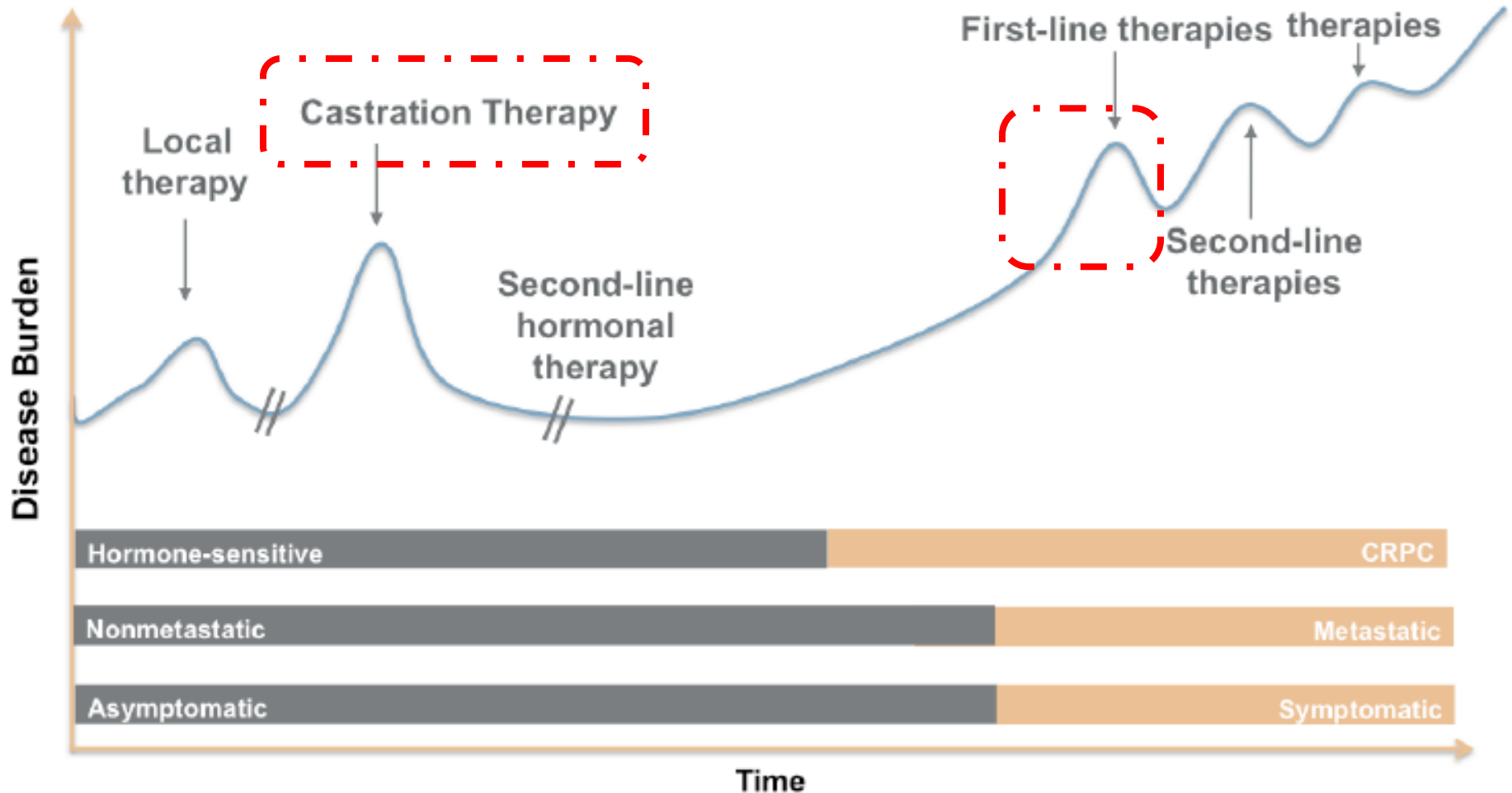
**A Overall Survival in All Patients**



**B Failure-free Survival in All Patients**



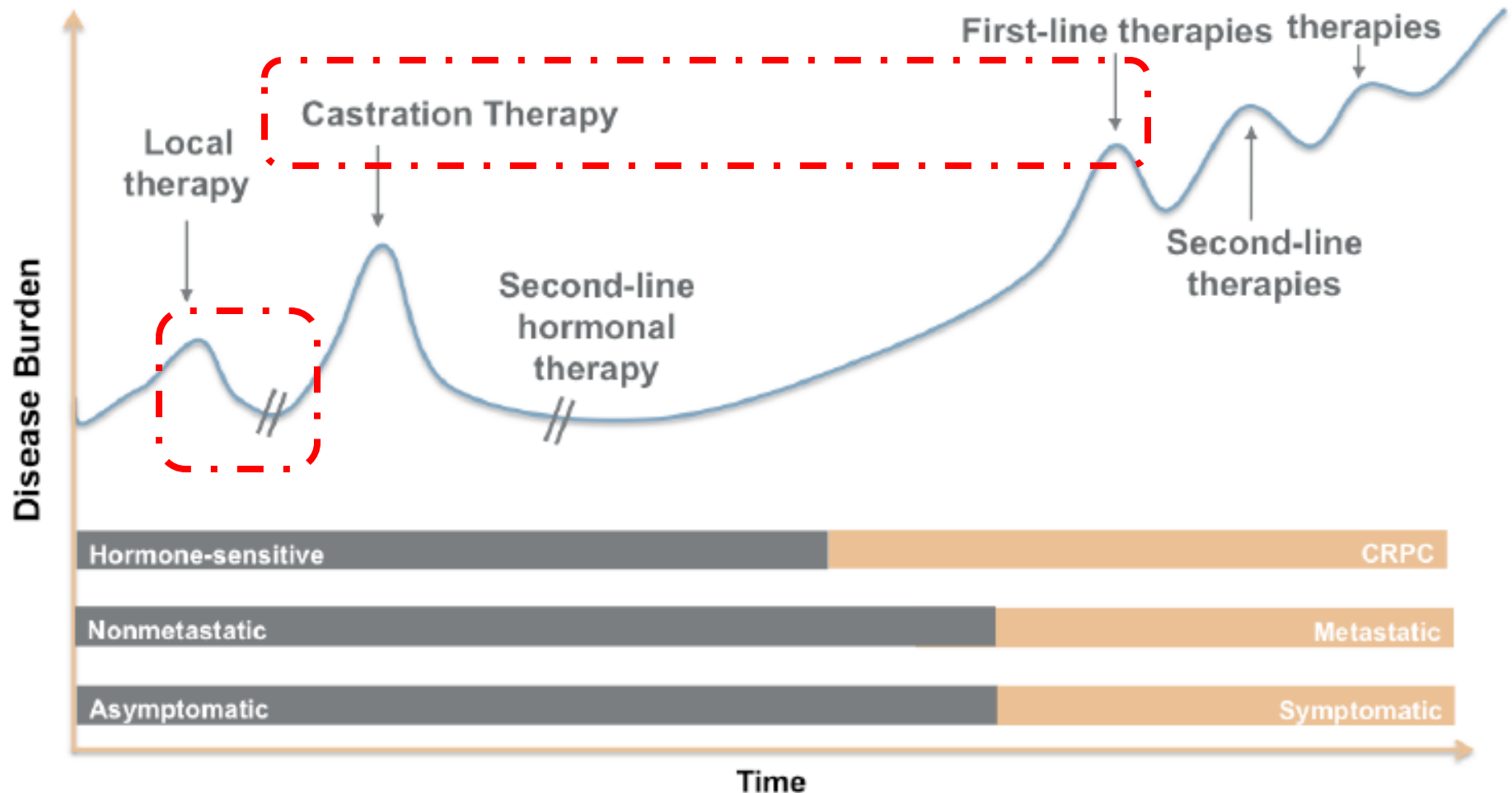
## Disease Continuum in Prostate Cancer



CRPC = castration-resistant prostate cancer  
 Heidenreich A, et al. *Eur Urol.* 2013;64(2):260.

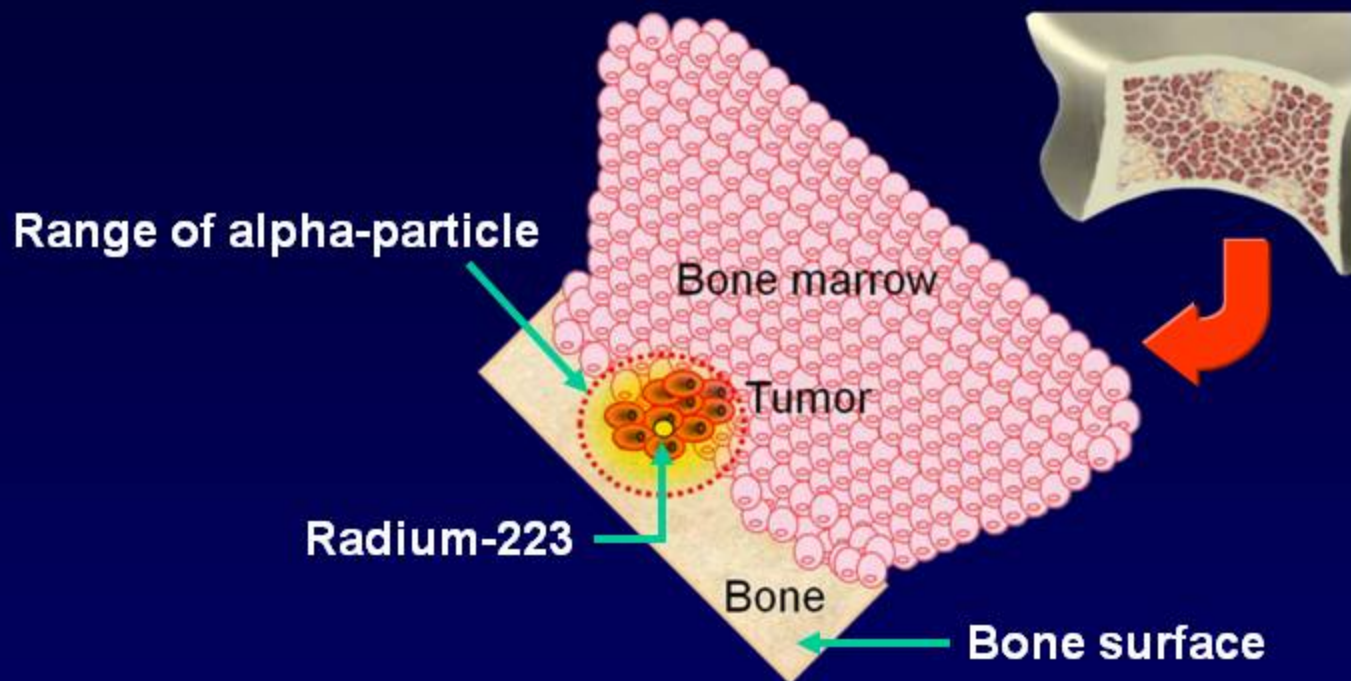


## Disease Continuum in Prostate Cancer



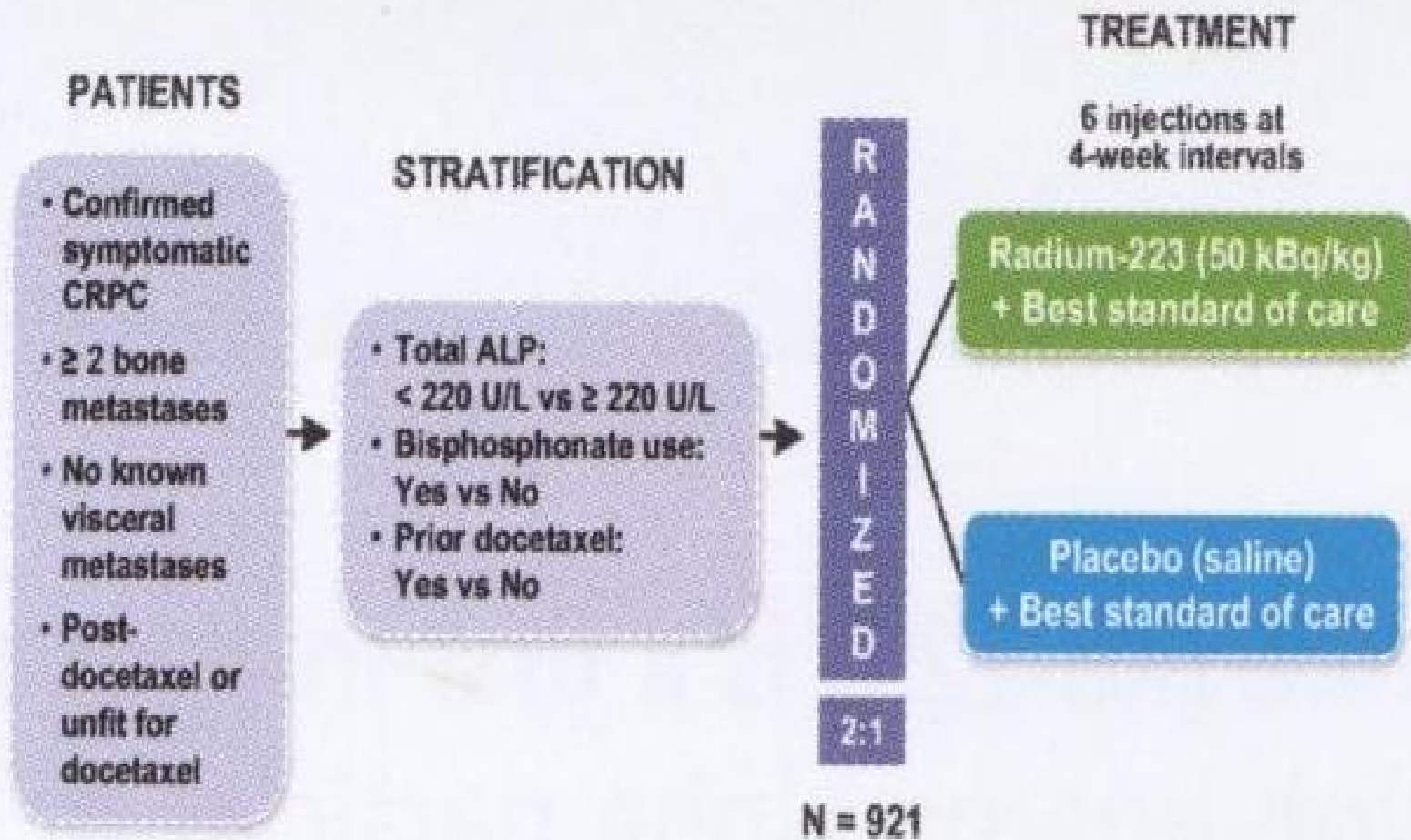
CRPC = castration-resistant prostate cancer  
Heidenreich A, et al. *Eur Urol.* 2013;64(2):260.

# Radium-223 Targets Bone Metastases



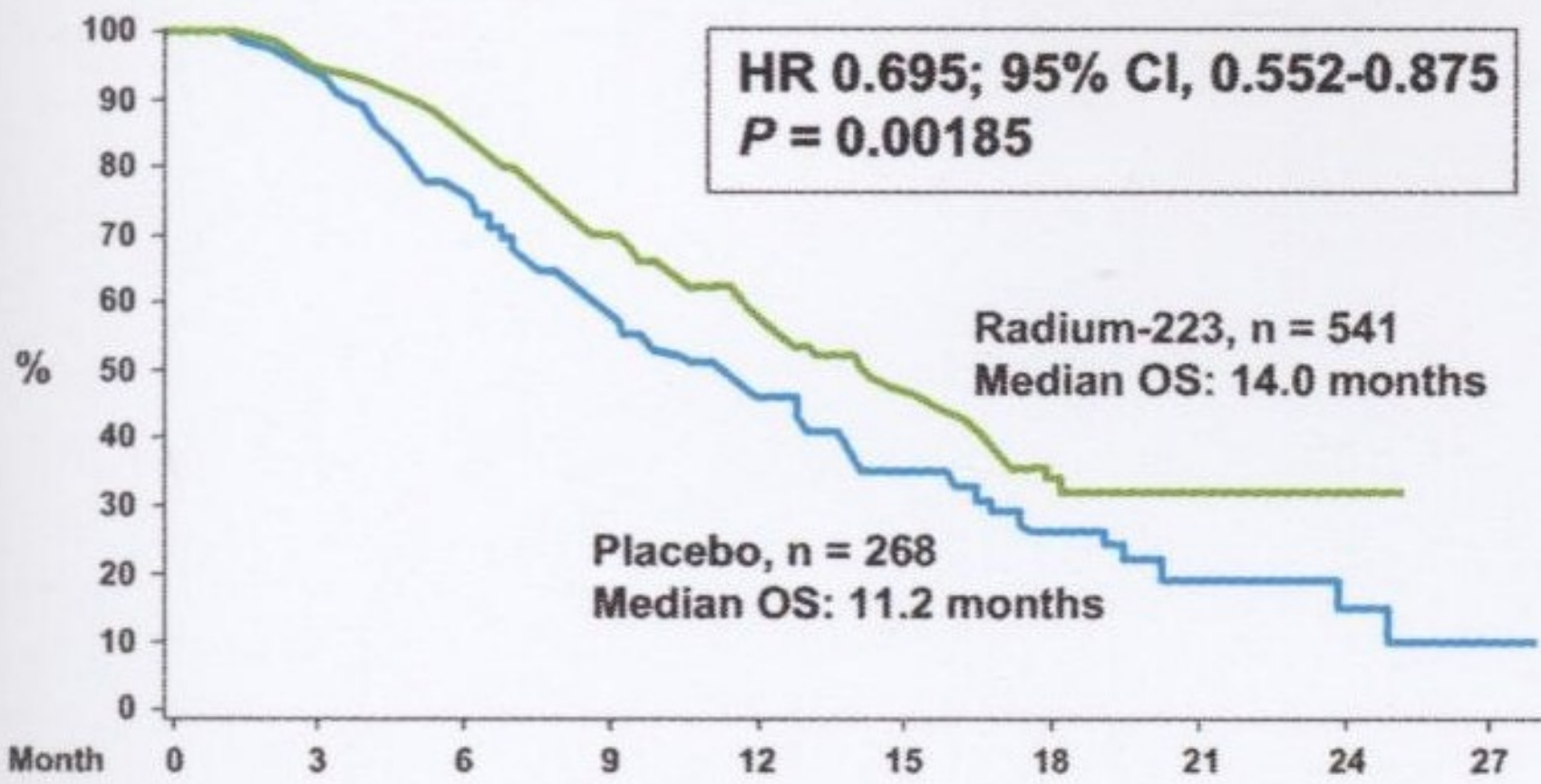
- **Alpha-particles induce double-strand DNA breaks in adjacent tumour cells<sup>1</sup>**
- **Short penetration of alpha emitters (2-10 cell diameters) = highly localised tumour cell killing and minimal damage to surrounding normal tissue**

# Figure 1. ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) Phase III Study Design



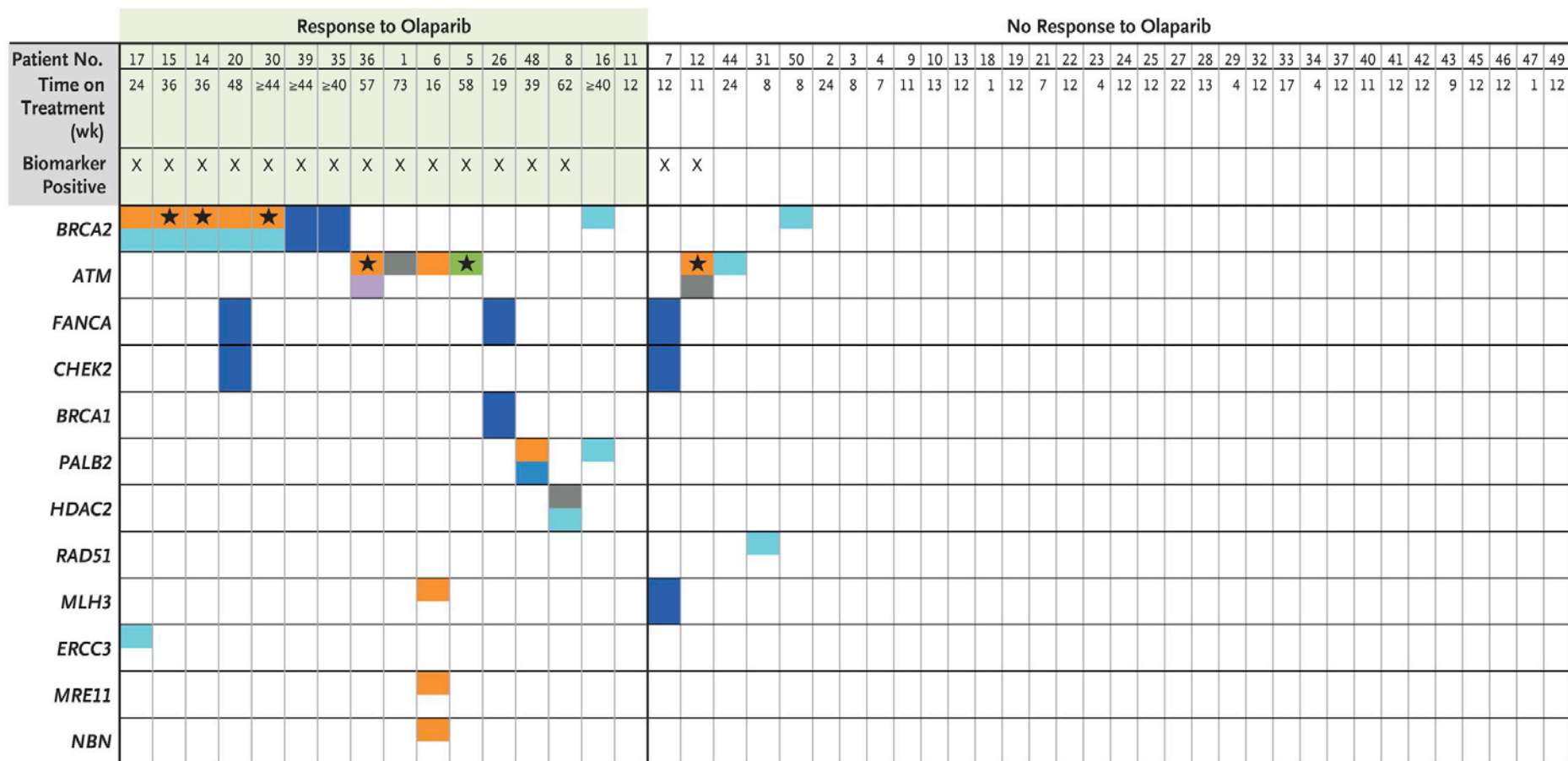
Planned follow-up is 3 years

# Figure 3. Overall Survival in Patients With CRPC and Bone Metastases



Radium- 223	541	450	330	213	120	72	30	15	3	0
Placebo	268	218	147	89	49	28	15	7	3	0

# Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer



■ Frameshift mutation    ■ Single copy deletion    ■ Missense mutation    ★ Germline event  
■ Stop gain    ■ Homozygous deletion    ■ Copy-neutral loss of heterozygosity

# PSA Response Rates For Therapeutic Drugs In mCRPC Stage

Pre-Chemotherapy Abiraterone Acetate--PSA Response **62%**

Post Chemotherapy Abiraterone Acetate- PSA response **40%**

PSA IS

Pre Chemotherapy Enzalutamide: PSA response **78%**

NOT A

Post Docetaxel Cabazitaxel: - PSA response **40%**

PREDICTIVE

Docetaxel Chemotherapy: PSA Response **45-50%**

MARKER

# **C: Guidelines on Genomic Biomarker applications in the Prostate Cancer Management**

# Oncology Biomarker Applications

**Predictive**

*Who is going to benefit from a therapy? Does the patient require immune stimulation prior to therapy?*

**Monitor Disease Progression**

*Is the treatment working?*

**Monitor Recurrence**

*Is the disease returning?*

**Predict Progression**

*How will the disease progress?  
What is the likelihood of recovery?*

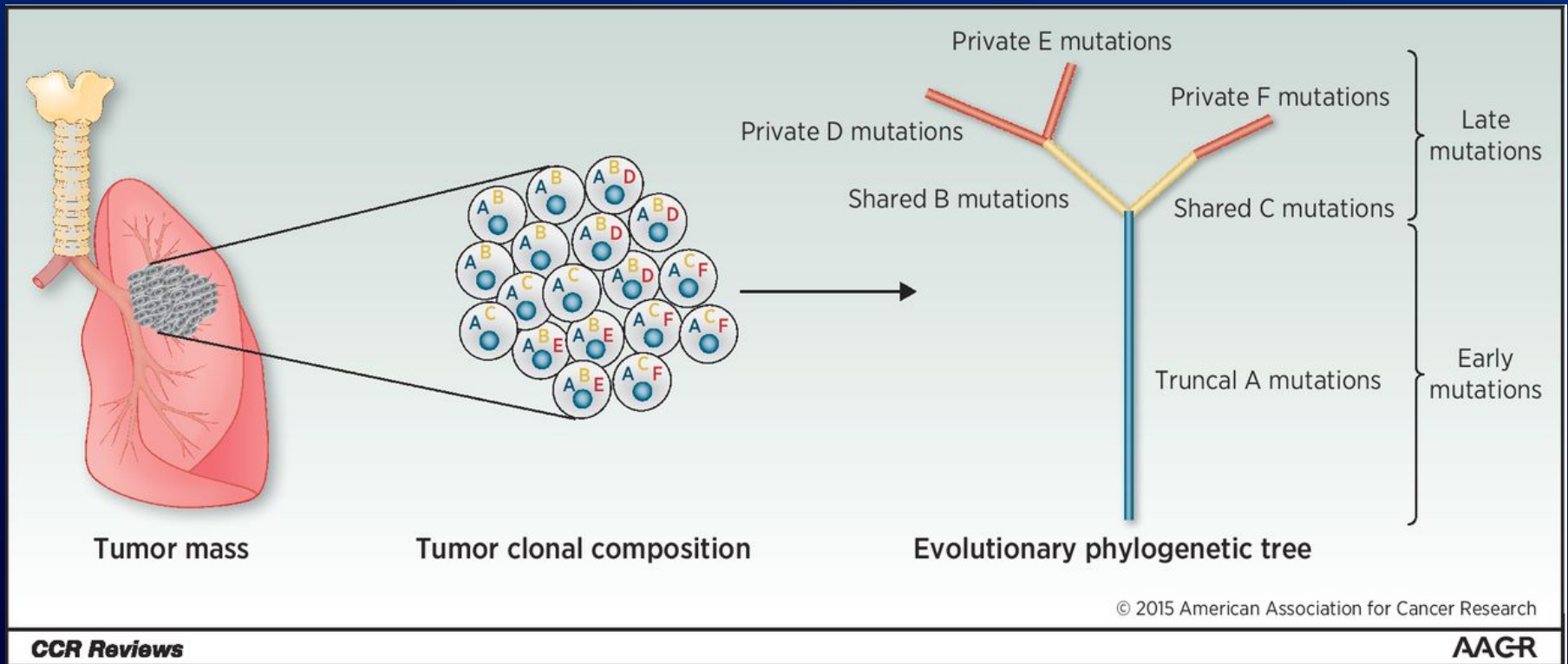
**Mechanism of Action**

*What rational combinations make sense based on how each therapy functions?*



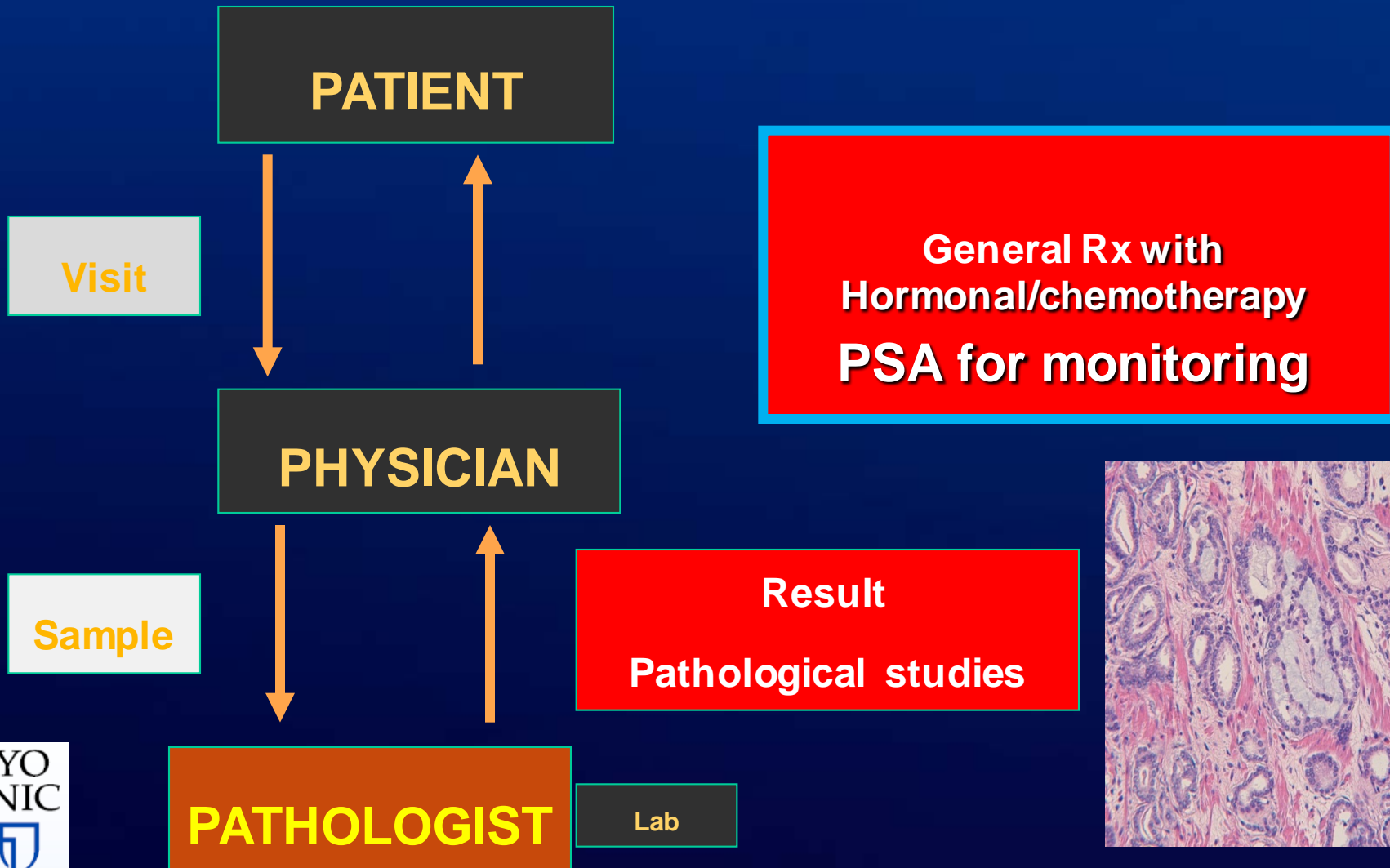
# Clonal Evolution and Phylogenetic Analyses

The clonality of somatic mutations can be estimated by bioinformatic analysis using tumor purity, allelic copy number and mutation variant allele frequency.

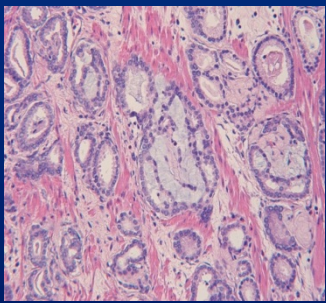


Jamal-Hanjani M, Clin Cancer Res 2015

# Current Paradigm



# Future Paradigm: Based on Structural & Functional Genomics



Visit

PATIENT

Personalised Treatment

Matched PHARMA

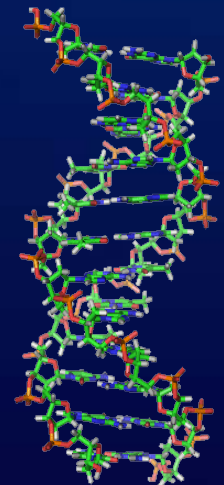
PHYSICIAN

Result  
Molecular Profile  
Bx testing

Sample

Pathologist

LAB



Biomarker	Type	Specimen type	Clinical Setting	Use	US FDA* approved/cleared indication for clinical use
Prostate Specific Antigen	Protein	Blood	Screening, diagnosis, monitoring	Diagnostic/prognostic	Approved for monitoring post therapy to evaluate recurrence of disease
(-2)proPSA	Protein	Blood	Diagnosis, early stage prostate cancer	Diagnostic, Prognostic	Approved for diagnosis of prostate cancer in men with PSA between 4 and 10.
Serum Chromogranin-A	Protein	Blood	Advanced prostate cancer	Prognostic	Not approved
Decipher™	RNA	Prostate tissue	Organ confined prostate cancer	Prognostic	Not approved
Prolaris™	RNA	Prostate tissue	Organ confined prostate cancer	Prognostic	Not approved
hsa-MiR-96	miRNA	Prostate tissue	Organ confined prostate cancer	Prognostic	Not approved
miR-1290, miR-375	miRNA	Plasma	Advanced prostate cancer	Prognostic	Not approved
AR-V7	RNA	Blood	Advanced prostate cancer	Predictive, Prognostic	Not approved

Biomarker	Type	Specimen type	Clinical Setting	Use	US FDA* approved/cleared indication for clinical use
ConfirmMDX	Epigenetic	Prostate tissue	Diagnosis	Diagnostic	Not approved
Alpha-methylacyl coenzyme A racemase (AMACR)	DNA	Prostate tissue	Diagnosis	Diagnostic	Not approved
OncotypeDX™	DNA	Prostate tissue	Organ confined prostate cancer	Prognostic	Not approved
DNA repair defects	DNA	Blood	Advanced prostate cancer	Predictive	Not approved
SLBO2B1 genotyping	SNP	Non-neoplastic tissue	Advanced prostate cancer	Prognostic	Not approved
TRMT11 genotyping	SNP	Non-neoplastic tissue	Advanced prostate cancer	Prognostic	Not approved
HSD3B1 genotyping	SNP	Non-neoplastic tissue	Advanced prostate cancer	Prognostic	Not approved
CTC counts	--	Blood	Advanced prostate cancer	Prognostic	FDA clearance for prognostication in patients with CRPC

# Conclusions