

# PSA testiranje: Afirmacijski stav

**dr.sc. Igor Tomašković, FEBU**  
Klinika za urologiju KBC "Sestre milosrdnice"



# Koliko ljudi umire od raka prostate?

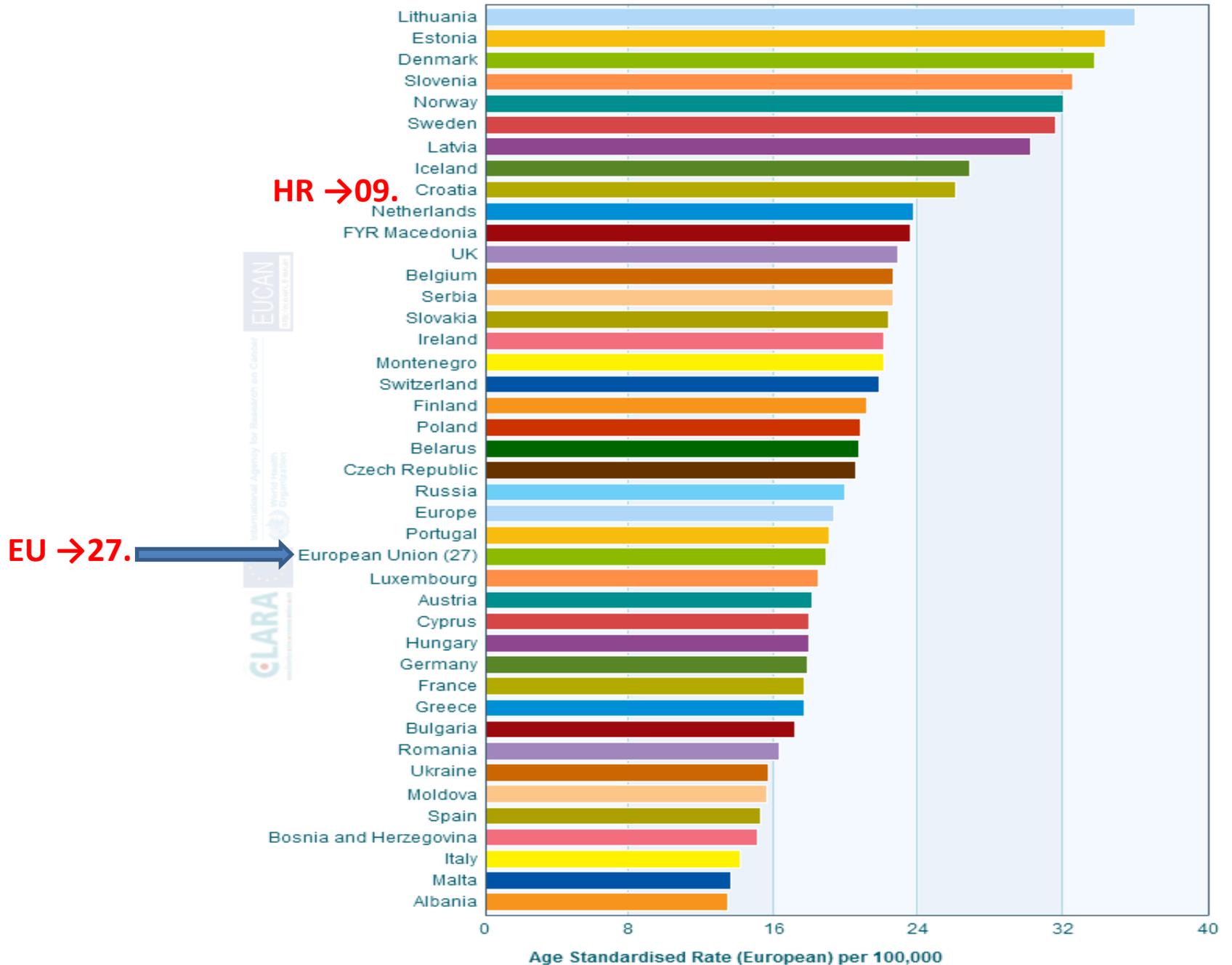
## SMRTI U HRVATSKOJ U 2014. GODINI - MUŠKI

	mkb	DG	N
1	C33-34	Ca pluća i dušnika	2 074
2	C18-21	Ca colona i rectuma	1 237
3	C61	Ca prostate	750

## SMRTI U EU U 2014. GODINI - MUŠKI

	mkb	DG	N
1	C33-34	Ca pluća i dušnika	254 532
2	C18-21	Ca colona i rectuma	113 168
3	C61	Ca prostate	92 247

### Estimated mortality of prostate cancer, 2012



# Pitanja

- Smanjuje li se uporabom PSA smrtnost od raka prostate?
- Koje su dobrobiti?
- Koje su štete?

# EBM o probiru?

Table 1. Overview of randomized controlled trials on screening for prostate cancer

	Göteborg (Hugosson) <sup>12</sup>	ERSPC (Schroder) <sup>11</sup>	PLCO (Andriole) <sup>17</sup>	Norrköping (Sandblom) <sup>20</sup>	Stockholm (Kjellman) <sup>18</sup>	Quebec (Labrie) <sup>19</sup>
PCM RR	0.56 (0.39-0.82)	0.79 (0.68-0.91) 0.84* (0.71 - 0.98)	1.09 (0.87-1.36)	1.16 (0.88-1.73)	1.04 (0.76-1.45)	1.04 (0.82-1.43)
NNS	290 (209 to 709)	1209 (667 to 9670)	N/A		N/A	
Age	50-64 years	50-74 years 55-69 years in core group	55-74 years	55-74 years	55-70 years	55-74 years
Test	PSA every 2 years (3.0; 2.9; 2.5 ng/mL)†	PSA every 4 years (3.0 ng/mL)†				
Follow-up	14 years					
RoB	Low					

“Compliance” u skupini probira: 23%  
u kontrolnoj skupini: 93%

Neprikladna analiza probir vs. kontrole

- Ner...
- Ner...

PCM RR = Relative risk of prostate cancer-specific mortality; NNS = number needed to screen; DRE = digital rectal exam; RoB = risk of bias  
\*RR excluding Göteborg study results; †PSA threshold was lowered throughout the study period, beginning at 3.0ng/mL in the first year and ending with a threshold of 2.5 ng/mL; ‡most sites included in ERSPC used a threshold of 3.0 ng/mL

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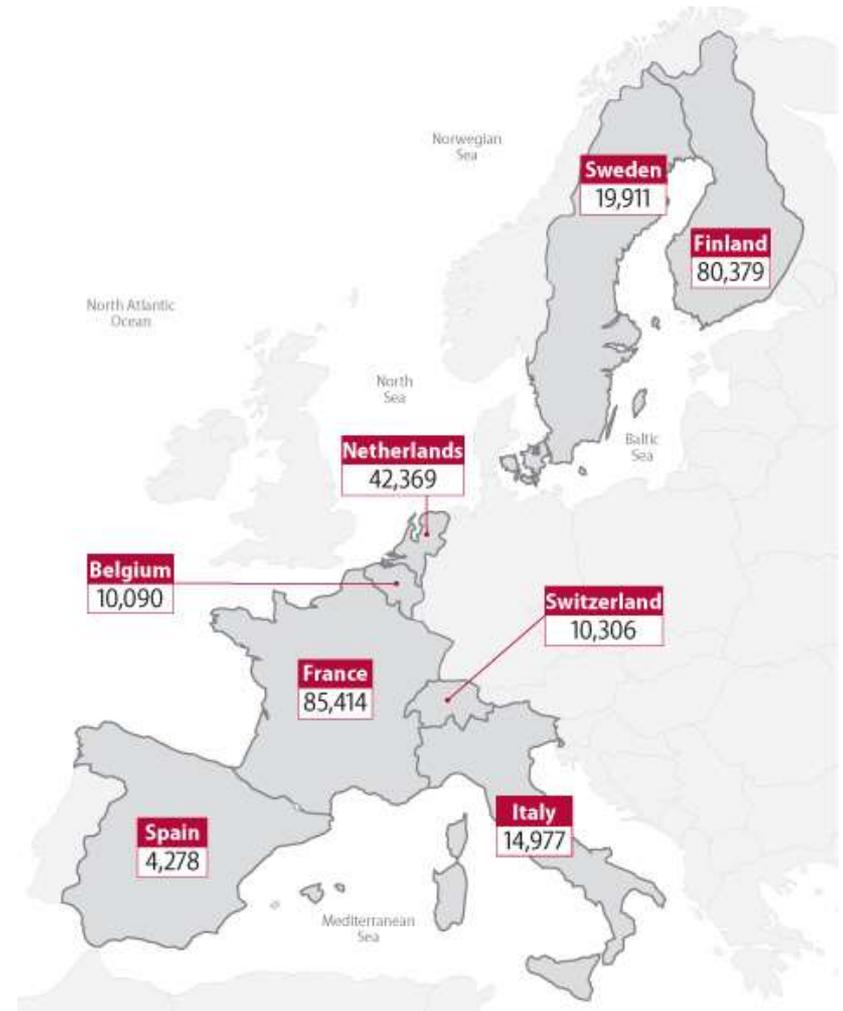
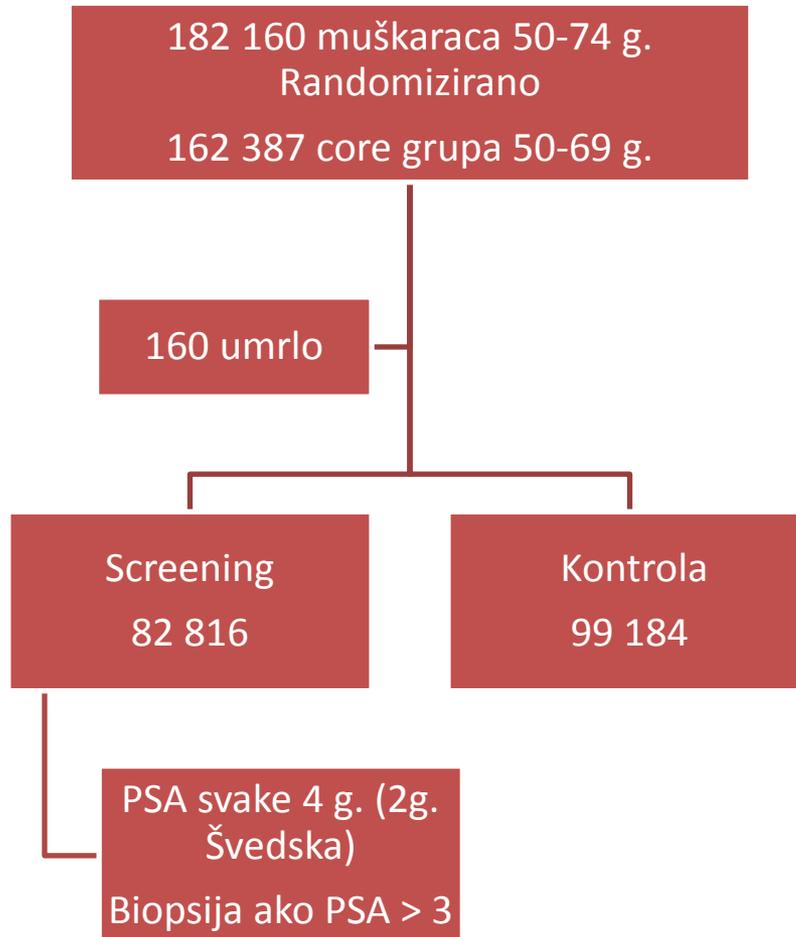
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<b>Test</b>	PSA every 2 years (3.0; 2.9; 2.5 ng/mL)†	PSA every 4 years (3.0 ng/mL‡)	Annual PSA (4.0 ng/mL) & DRE every 4 years	DRE; then DRE & PSA every 3 years (4.0 ng/mL; last rounds)		Annual PSA (3.0 ng/mL) and DRE
<b>Follow-up</b>	14 years	11 years	13 years	20 years	10 years	10 years
<b>RoB</b>	Low	Low	Low	High	High	High

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# ERSPC : 1993.-sada

The European Randomized study of Screening for Prostate Cancer



# ERSPC ukupni rezultati:

## - karcinom specifični mortalitet nakon 13 godina

- **27 %** (CI 0.68-0.91, p=0.001) manja smrtnost u S-skupini
- NNS- broj screeniranih = **781** (prije 1410)
- NNT- broj koje je potrebno liječiti = **27** (prije 48)
- Incidencija karcinoma S/C skupine = 1.57

### Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

Prof [Fritz H Schröder](#) MD <sup>a</sup>, Prof [Jonas Hugosson](#) PhD <sup>b</sup>, Prof [Monique J Roobol](#) PhD <sup>a</sup>, Prof [Teuvo L J Tammela](#) MD <sup>c</sup>, Prof [Marco Zappa](#) MD <sup>d</sup>, Prof [Vera Nelen](#) MD <sup>e</sup>, Prof [Maciej Kwiatkowski](#) MD <sup>f</sup>, Prof [Marcos Lujan](#) MD <sup>g</sup>, Prof [Liisa Maattänen](#) PhD <sup>h</sup>, Prof [Hans Lilja](#) PhD MD <sup>i</sup>, Prof [Louis J Denis](#) MD <sup>j</sup>, Prof [Franz Recker](#) MD <sup>k</sup>, Prof [Alvaro Paez](#) MD <sup>l</sup>, Prof [Chris H Bangma](#) MD <sup>m</sup>, Prof [Sigrid Carlsson](#) MD <sup>n</sup>, Prof [Donella Puliti](#) MSc <sup>o</sup>, Prof [Arnaud Villiers](#) MD <sup>p</sup>, Prof [Xavier Rebillard](#) MD <sup>q</sup>, Prof [Matti Hakama](#) PhD <sup>r</sup>, Prof [Ulf-Hakan Stenman](#) PhD <sup>s</sup>, Prof [Paula Kujala](#) MD <sup>t</sup>, Prof [Kimmo Taari](#) MD <sup>u</sup>, Prof [Gunnar Aus](#) MD <sup>v</sup>, Prof [Andreas Huber](#) MD <sup>w</sup>, Prof [Theo H van der Kwast](#) PhD MD <sup>x</sup>, Prof [Ron H N van Schaik](#) PhD <sup>y</sup>, Prof [Harry J de Koning](#) MD <sup>z</sup>, Prof [Sue M Moss](#) PhD <sup>aa</sup>, Prof [Anssi Auvinen](#) MD <sup>ab</sup>, for the ERSPC Investigators<sup>†</sup>

# PLCO (SAD studija)

Prostate, lung, colorectal, ovarian Cancer screening trial

- 76,693 randomiziranih u dobi 55-74 g. (screen vs. not screen)
- Nakon 13 g. rizik umiranja od raka prostate je isti

Andriole GL et al. Mortality results from a randomized prostate cancer screening trial. *N Engl J Med*, 360 (13): 1310, 2009.

Andriole GL et al. *J Natl Cancer Inst*. 2012. Jan 18;104(2):125-32.

# PLCO - prigovori

- kontaminacija PSA u kontrolnoj skupini 52%
- poštovanje protokola u *screening* skupini 86%
- <50% muškaraca s indikacijom bioptirano u *screen* skupini

Dakle, PLCO vjerojatno nikada neće odgovoriti može li screening utjecati na smrtnost raka prostate.

# PLCO versus ERSPC

- PLCO :
  - “PSA *screening* u zajednici” versus “organizirani *screening*” program
- ERSPC :
  - “*no screening*” versus “*PSA screening*”
- PLCO studija pokazuje da malo versus više *screeninga* ne pravi razliku u mortalitetu
- ERSPC pokazuje da *screening versus not screening* smanjuje mortalitet od raka prostate, ali uz rizik pretjerane dijagnoze

# Smanjuje li PSA screening mortalitet od raka prostate ?

**PLCO:** Ne

**ERSPC:** Da, ali uz cijenu

ORIGINAL ARTICLE

## Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D.,  
Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,

Nakon 13 godina smrtnost od raka prostate nije se razlikovala među skupinama.

Andriole GL et al. J Natl Cancer Inst. 2012. Jan 18;104(2):125-32

ORIGINAL ARTICLE

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

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,  
Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D.,

Nakon 13 god. PSA screening smanjuje mortalitet od CAP **27%**, ali uz visok rizik “pretjerane dijagnoze”:

**781** muškarac treba biti podvrgnut screeningu i

**27** treba biti liječen da bi se izbjegla **1** smrt.

Schroder F i sur. The Lancet, Early Online Publication, 7 August 2014

# Što duže čekamo, rezultat je vidljiviji...

	ERSPC 2009	ERSPC 2014	Göteborg 2010
Number needed to screen-NNS	1410	781	293
Number needed to treat-NNT	48	27	12
Redukcija smrtnosti	21%	27%	44%

Schröder F et al. *New England Journal of Medicine*, 2009

Schröder F et al. *EAU abstract Milan*, March 2013

Hugosson J, Carlsson S, Aus G, et al. *Lancet Oncol* 2010;11:725–32

# Migracija stadija

stadij T3–4	per 100,000
1988–1989	55.5
1996–1997	44.6
2004–2005	8.4

# Migracija gradusa

Incidencija **Gleason zbroja 8–10** na biopsiji

GS 8-10	per 100,000
1988–1989	47.5
2004–2005	38.3

# Redukcija metastatske bolesti (ERSPC)

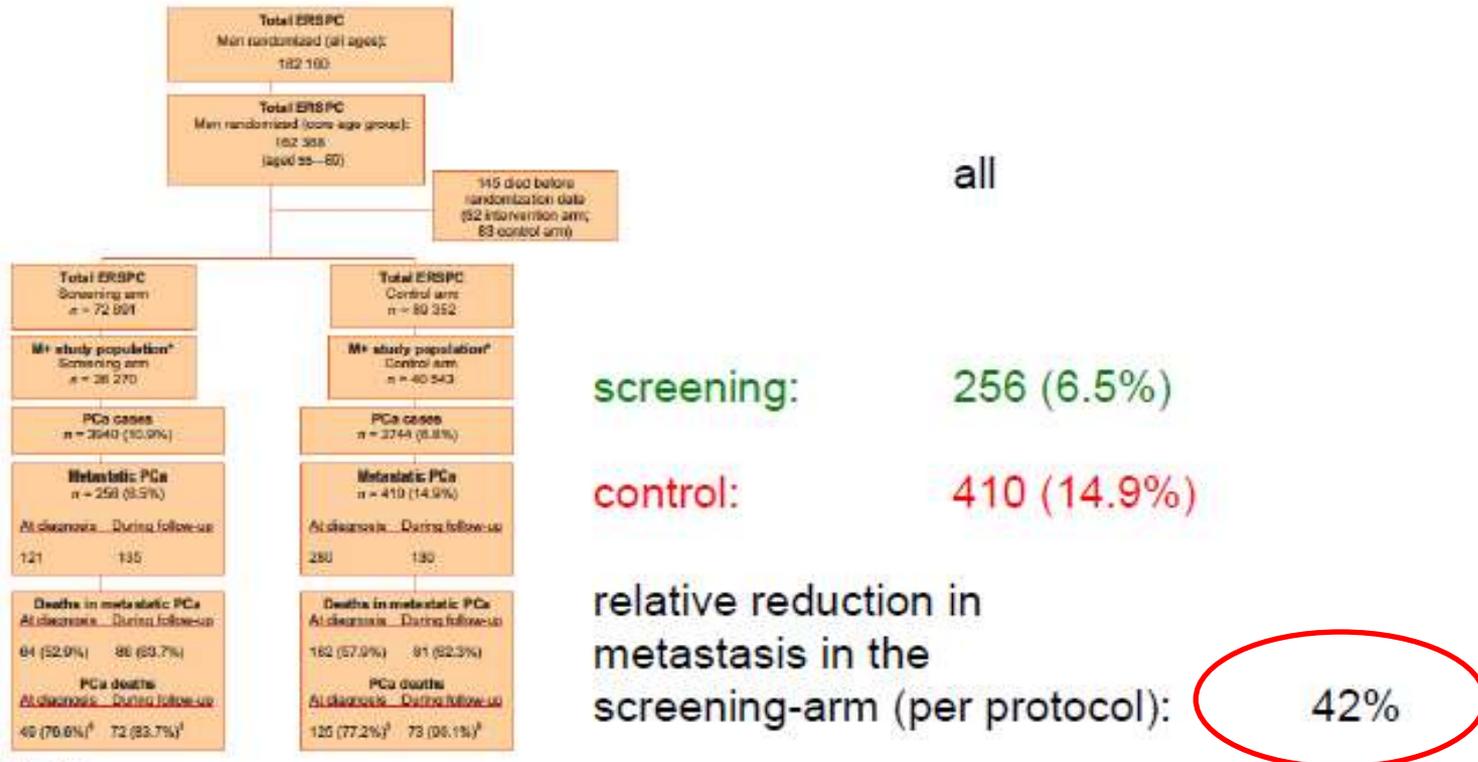
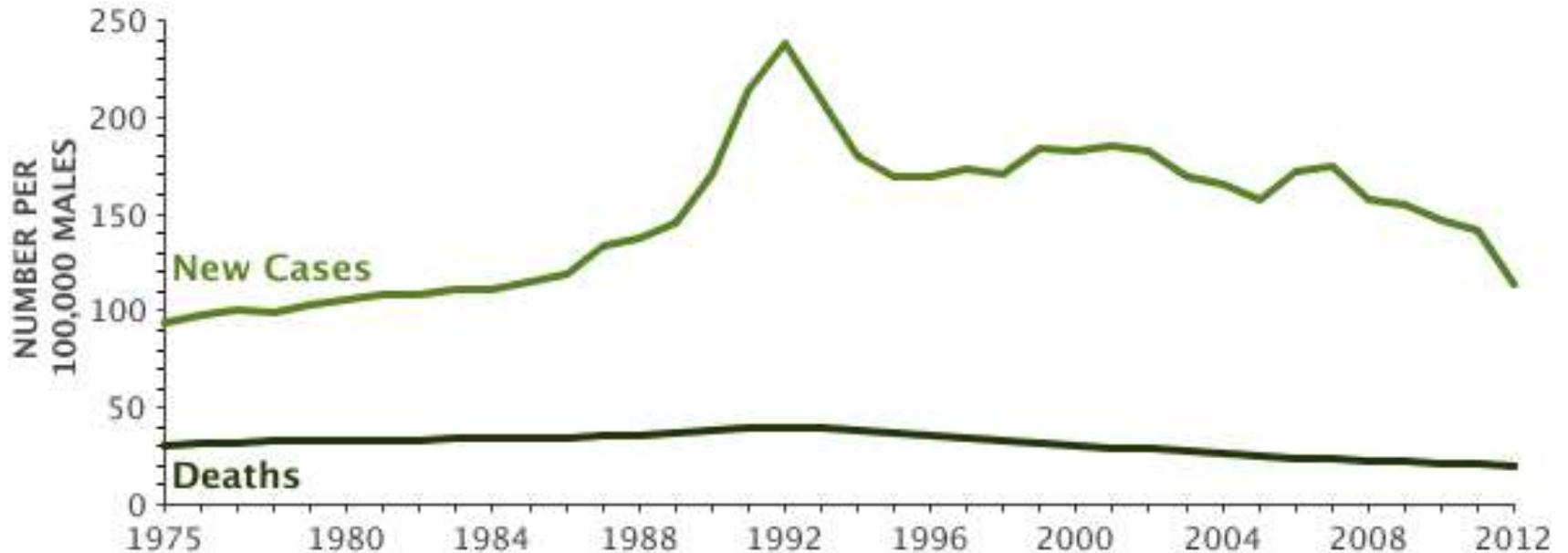


Fig. 1 – Flow diagram of the study.  
 ERSPC = European Randomized Study of Screening for Prostate Cancer; PCa = prostate cancer.  
 \*Comparing data of four of the eight ERSPC centers: The Netherlands, Sweden, Finland (Tampere) and Switzerland.  
 † Percentage of cases with M = PCa that died.

# Smrtnost i trendovi-USA

The Surveillance, Epidemiology, and End Results (SEER) program, initiated by the NCI in 1973, collects cancer incidence and survival data from 17 population-based tumor registries across the United States.



Year	1975	1980	1985	1990	1995	1999	2003	2007
5-year survival	66.0%	70.2%	74.9%	88.4%	95.7%	99.2%	99.1%	99.7%

SEER 9 Incidence & U.S. Mortality 1975-2012, All Races, Males. Rates are Age-Adjusted.

# 5-godišnje preživljenje

Site	1975-1977	1984-1986	1996-2002
•All sites	50	53	66
•Breast (female)	75	79	89
•Colon	51	59	65
•Leukemia	35	42	49
•Lung and bronchus	13	13	16
•Melanoma	82	86	92
•Non-Hodgkin lymphoma	48	53	63
•Ovary	37	40	45
•Pancreas	2	3	5
<b>•Prostate</b>	<b>69</b>	<b>76</b>	<b>100</b>
•Rectum	49	57	66
•Urinary bladder	73	78	82

Pre PSA

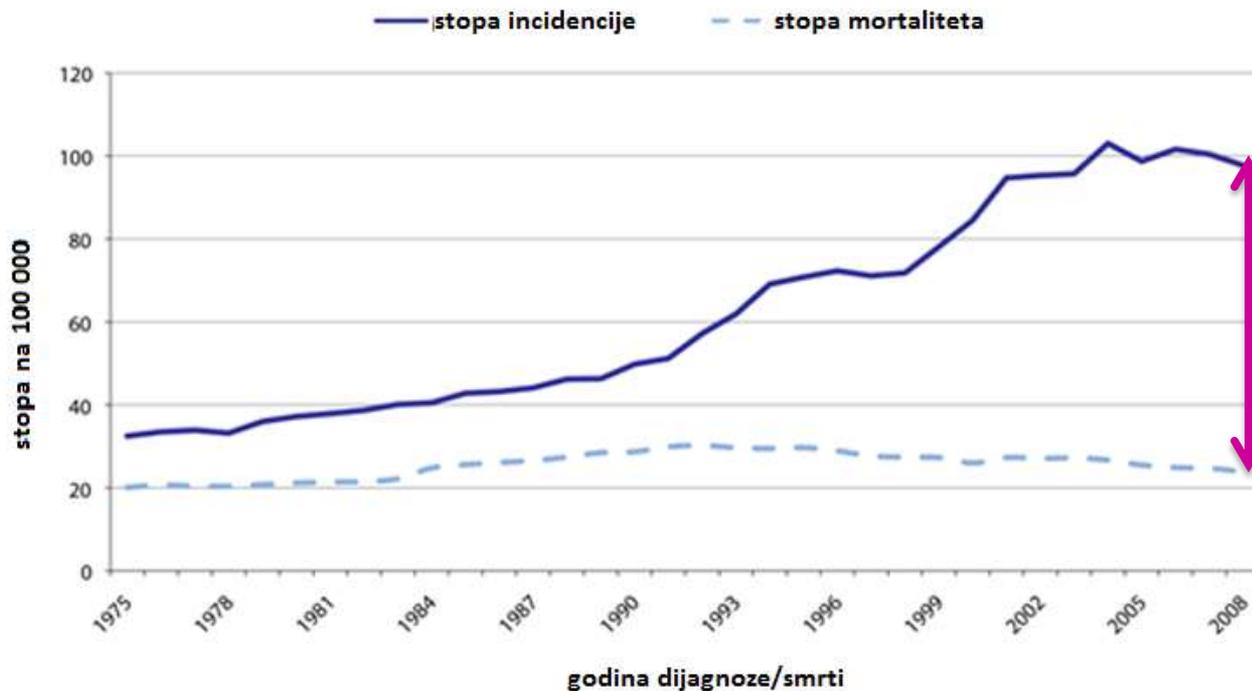
PSA era

\*5-year relative survival rates based on follow up of patients through 2003.

†Recent changes in classification of ovarian cancer have affected 1996-2002 survival rates.

Source: Surveillance, Epidemiology, and End Results Program, 1975-2003, Division of Cancer Control and Population Sciences, National Cancer Institute, 2006.

Koristi probira	Šteta od probira
Migracija stadija: više lokalizirane bolesti, a manje uznapredovale / metastatske	Visoka incidencija indolentnih tumora (i do 50%)
Ranija dijagnoza	Rizik od biopsije (75% negativnih u „sivoj zoni“, komplikacije, osobito infekcije)
Niži PSA kod dijagnoze (prognostički parametar)	Problemi pretjerane dijagnoze (50% niskorizičnih do indolentnih karcinoma u eri PSA)
Bolje preživljenje u eri PSA	Problem pretjeranog liječenja (jednom dijagnosticirani s rakom prostate > 80% bolesnika podvrgava se agresivnom liječenju)



**Populacijski ili masovni probir (*screening*)** je definiran kao sustavni pregled asimptomatskih osoba (pod rizikom) i obično je potaknut od zdravstvenih službi.

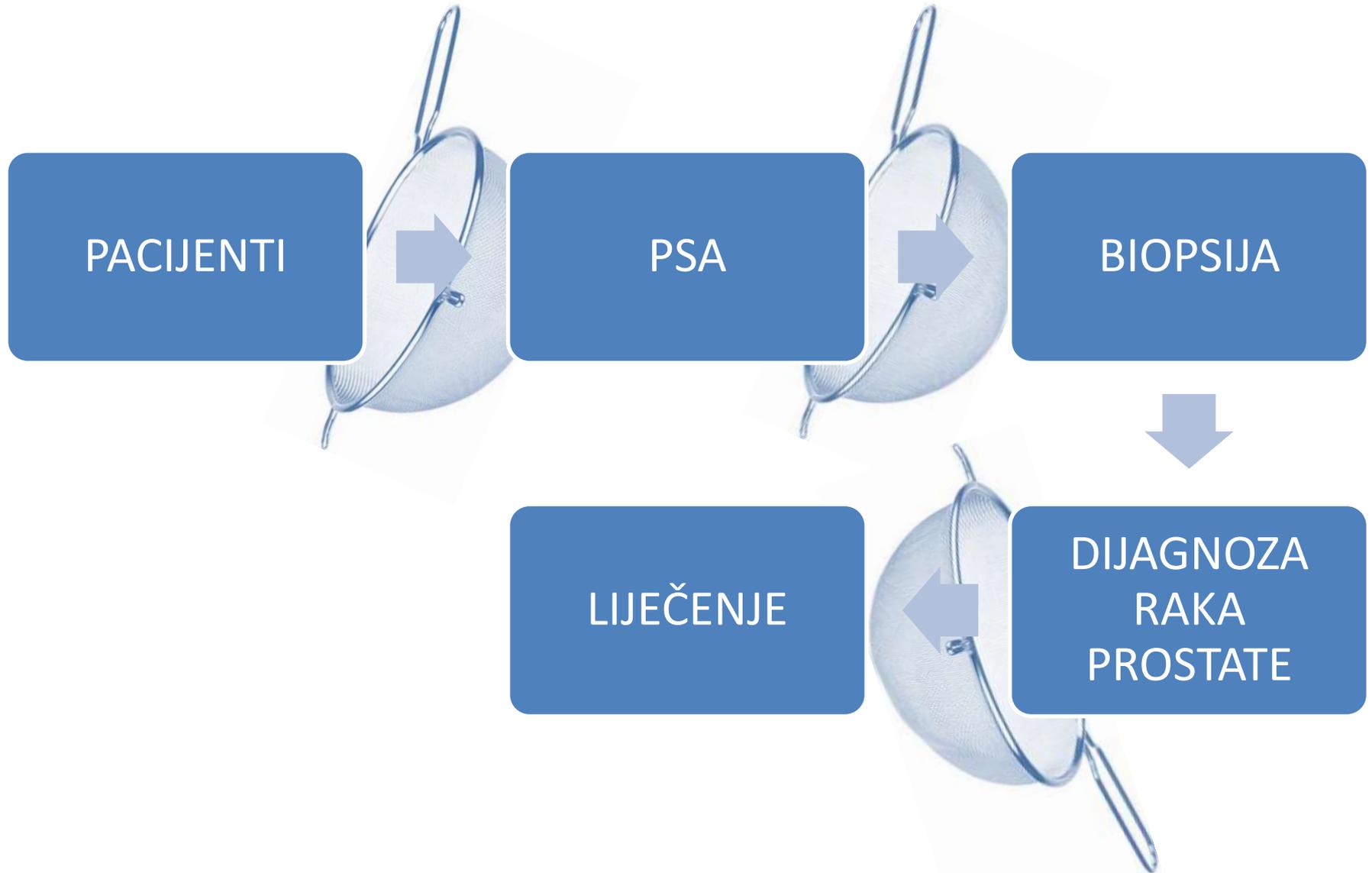
**Rano otkrivanje (*early detection*) ili oportunistički *screening*** sastoji se od pronalaženja individualnih slučajeva na inicijativu pacijenta i/ili njegova liječnika.

Krajnji cilj oba pristupa je

- smanjenje mortaliteta od raka prostate;
- očuvanje kvalitete života

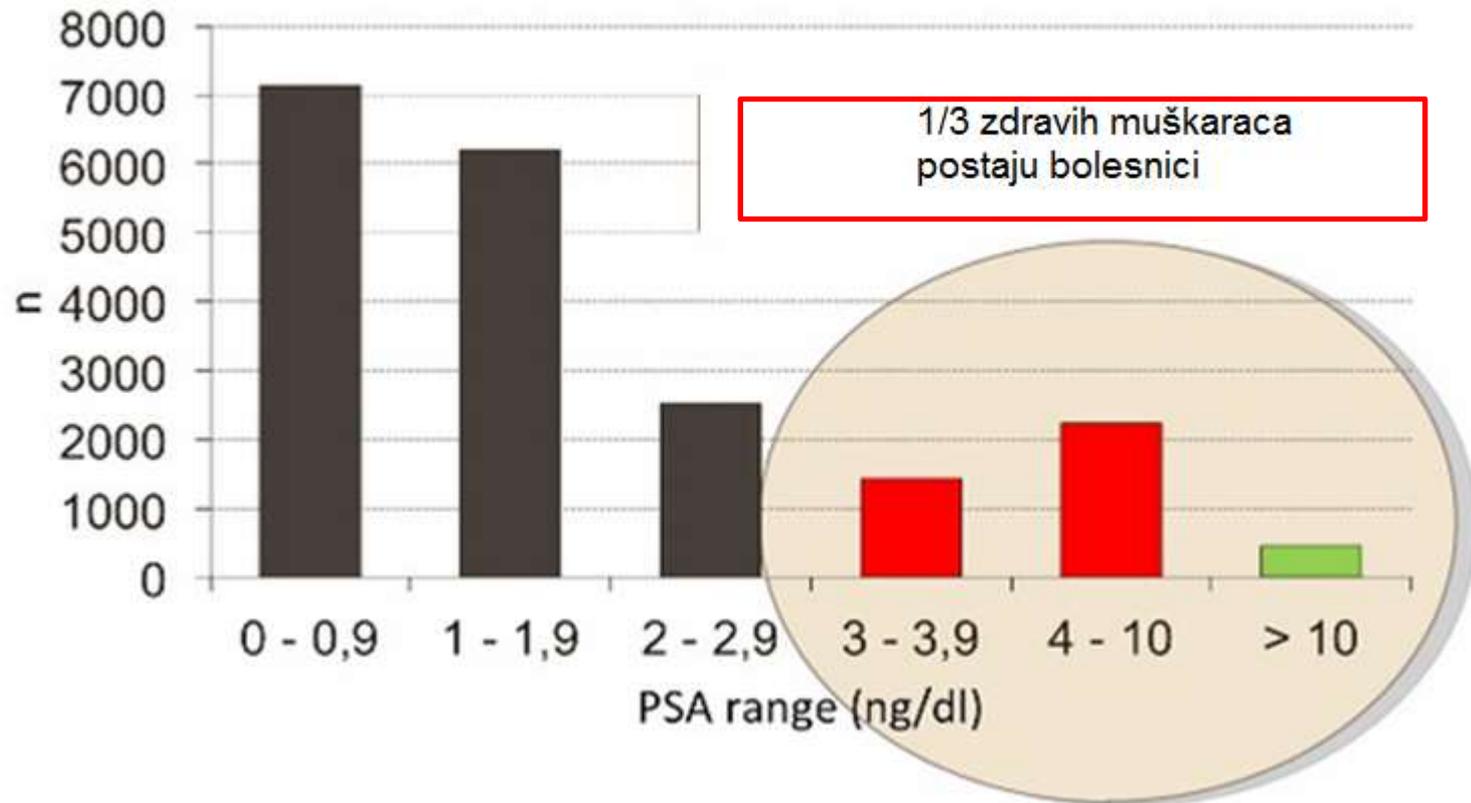
EAU guidelines 2015.

# *“Risk adapted” strategija*



# ERSPC i distribucija PSA u populaciji 50-75 god.

From the 1<sup>st</sup> Screening Round of the ERSPC (n=19970)



# Sažetak smjernica o uporabi PSA

**Table 1** | Summary of guidelines on PSA screening

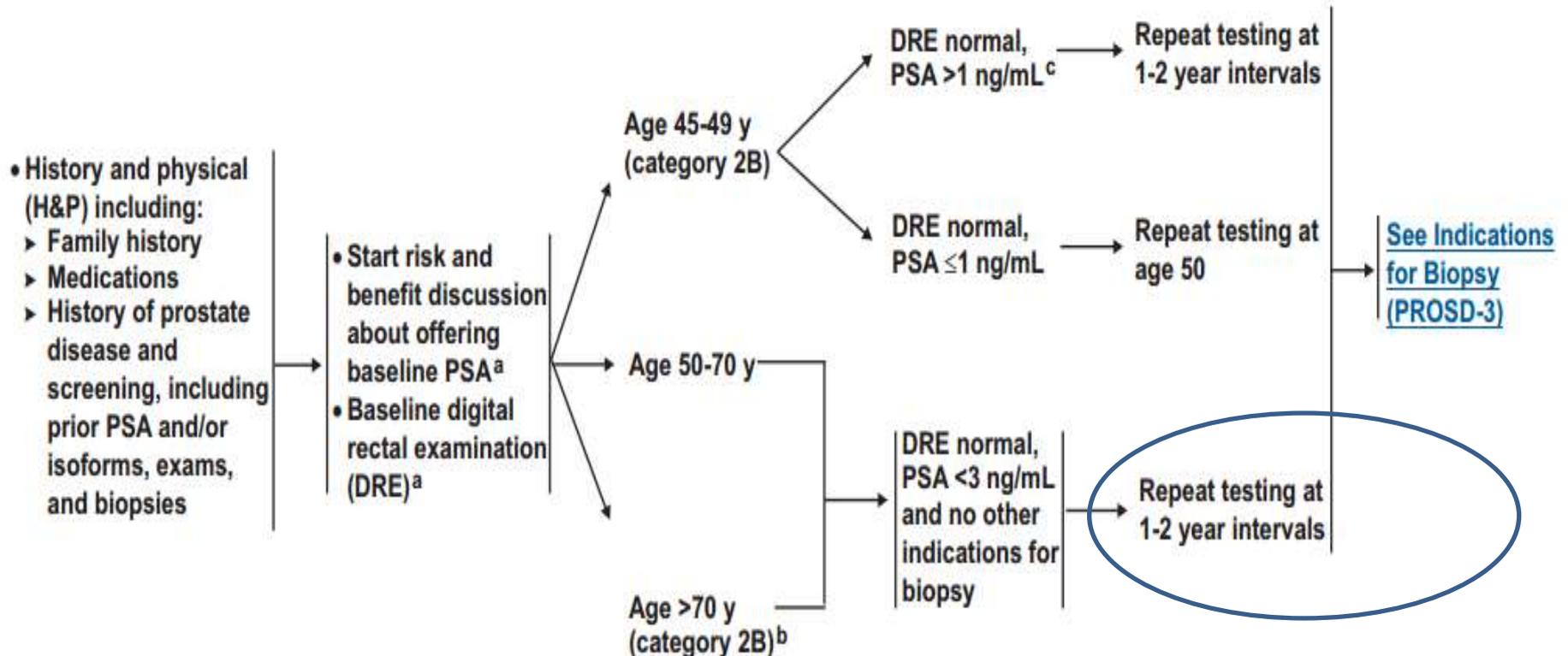
Guideline group	Recommendation	Age to start screening	Screening algorithm
ACPM <sup>122</sup>	Insufficient evidence to recommend widespread routine screening	Discussion about screening should occur annually, during the routine periodic examination or in response to a request by the patient	NA
ACS <sup>123</sup>	Informed decision making	40 years for men at highest risk (several first-degree relatives diagnosed with prostate cancer under age 65 years); 45 years for men at high risk (African American or first-degree relative with prostate cancer); 50 years for men at moderate risk with a life-expectancy of more than 10 years	Men who choose to be tested who have a PSA <2.5 ng/ml only need to be retested every 2 years, annual screening for men with PSA ≥2.5 ng/ml
AUA <sup>29</sup>	Informed decision making	40 years for baseline DRE and PSA	Screening intervals based on baseline PSA
EAU <sup>40,124</sup>	Insufficient evidence to recommend widespread routine screening; opportunistic screening should be offered to all well informed men	40 years for baseline PSA	Screening interval based on baseline PSA 8 years generally sufficient for men with initial PSA <1 ng/ml; further PSA testing unnecessary in men >75 years old with baseline PSA <3 ng/ml
NCCN <sup>125</sup>	Informed decision making	40 years for baseline DRE and PSA; 50 years for annual screening	Screening algorithm based on initial PSA and DRE: repeat screening at age 45 years if PSA <1.0 ng/ml
USPSTF <sup>13</sup>	Against screening (grade D)	NA	NA

Abbreviations: ACPM, American College of Preventive Medicine; ACS, American Cancer Society; AUA, American Urological Association; DRE, digital rectal examination; EAU, European Association of Urology; NA, not applicable; NCCN, National Comprehensive Cancer Network; USPSTF, US Preventive Services Task Force.

## BASELINE EVALUATION

## RISK ASSESSMENT

## EARLY DETECTION EVALUATION



<sup>b</sup>Testing above the age of 70 years of age should be done with caution and only in very healthy men with little or no comorbidity as a large proportion may harbor cancer that would be unlikely to affect their life expectancy, and screening in this population would substantially increase rates of over-detection. However, a clinically significant number of men in this age group may present with high-risk cancers that pose a significant risk if left undetected until signs or symptoms develop. One could consider increasing the PSA threshold for biopsy in this group (i.e., >4 ng/mL). Very few men above the age of 75 years benefit from PSA testing. Finally, men at age 60 years with a serum PSA <1.0 ng/mL have a very low risk of metastases or death due to prostate cancer. Similarly, a cut point of 3.0 ng/mL at age 75 years has a similarly low risk of such outcomes.

# Kome PSA? Koliko često?

## 5.1 Recommendations for screening and early detection

	LE	GR
An individualized risk-adapted strategy for early detection might be offered to a <u>well-informed man with a good performance status and at least 10-15 years of life expectancy.</u>	3	B
Early PSA testing in men at <u>elevated risk</u> of having PCa: <ul style="list-style-type: none"> <li>• men over <u>50 years of age</u></li> <li>• men over <u>45 years of age and a family history of PCa</u></li> <li>• African-Americans</li> <li>• men with a <u>PSA level of &gt; 1 ng/mL at 40 years of age</u></li> <li>• men with a <u>PSA level of &gt; 2 ng/mL at 60 years of age</u></li> </ul>	2b	A
A risk-adapted strategy might be considered (based on initial PSA level), which may be every <u>2 years for those initially at risk, or postponed up to 8 years in those not at risk.</u>	3	C
The age at which early diagnosis of PCa should <u>be stopped</u> is influenced by life expectancy and performance status; men who have <u>&lt; 15-year life expectancy</u> are unlikely to benefit based on the PIVOT and the ERSPC trials.	3	A

# Pola stoljeća PSA....2015!

The optimal intervals for PSA testing and DRE follow up are unknown, and it has varied between several prospective trials. A risk-adapted strategy might be considered based on the initial PSA level. This could be every 2 years for those initially at risk, or postponed up to 8 years in those not at risk (LE: 3; GR: C).

The age at which attempts to make an early diagnosis of PCa should be stopped remains controversial but is influenced by an individual's life expectancy. Men who have less than a 15-year life

# PSA Screening: Are We 'Falling Backwards'?

Gerald Chodak, MD

- ...significant **decrease in the detection** of prostate cancer during the year following the initial recommendation,
  - **28% drop** in the detection of prostate cancer in the following year. The decrease occurred for diagnoses of low-, **moderate-, and high-risk** prostate cancers.

Barocas DA, Mallin K, Graves AJ, et al. The effect of the United States Preventive Services Task Force grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the US. J Urol. 2015 Jun 15.

# Zaključci

- pretjerano dijagnosticiramo (indolentne tumore)
- pretjerano liječimo (niskorizične tumore)
- promiču agresivni tumori u ranoj fazi (smrtnost raka prostate još uvijek visoka)
- Stratifikacija rizika!!!
  - kritičan pristup uporabi PSA u dijagnostici
  - Aktivno liječenje bolesnika koji će imati koristi



**HVALA**

# Slučaj 1

- I.K. 61 god.
- 1. pregled
- Prijatelju u uredu dijagnosticiran uznapredovali rak prostate.
- Nema tegoba.
- Nije teže bolovao, ne uzima lijekove



- DRP: prostata veličine kestena, glatka, ograničena, elastična, bezbolna
- Urin: alb. opal. Sed. 2-3E, 1 L
- PSA 5.5 ng/ml
- UZV/ rezidualni urin 0ml
- Uroflow 13 ml/s

# Slučaj 1

- Ponovljeni PSA 6.0 ng/nl nakon 4 mj
- Upućen na biopsiju
- Bx- 10 cilindara
- PHD: Adenocarcinoma prostatae,
- u 4/10 cilindara
- Gleason score 7 (4+3) do 50%



# TERAPIJA

- TH/

Nerve sparing radikalna prostatektomija

- Follow up: 5 godina nakon op.- PSA 0,0ng/ml
  - KONTINENTAN
  - EREKTILNA FUNKCIJA UZ 5PDEI

# SLUČAJ 2.



- P.P. 56 godina star
- Otežano mokri unazad 1 godinu
- Koristio biljne preparate samoinicijativno; bez poboljšanja
- Mlaz slab, nocturija 2x
- Stric imao ca prostate

- DRP: prostata veličine mandarine, glatka, u desnom lobusu **nodus**, ograničena, elastična, bezbolna
- Urin: alb. opal. Sed. 2E, 5L
- UK: sterilna
- **PSA 11.5 ng/ml, f/T PSA 18%**
- UZV/ rezidualni urin 100ml
- Uroflow 10 ml/s

# SLUČAJ 2.

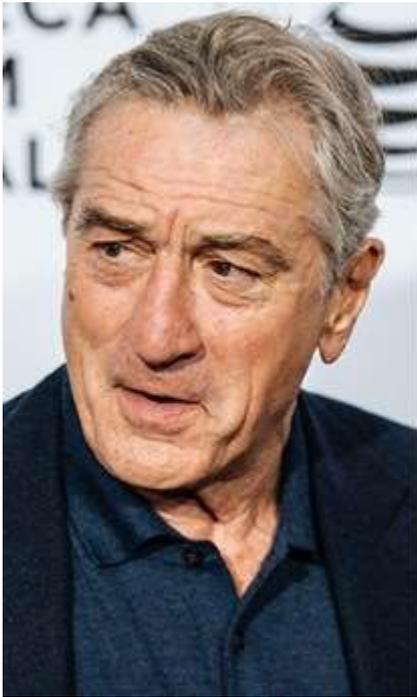


- Biopsija prostate
- PHD/ Adenoca prostate, **Gleason score 8 (4+4)**, u 8/10 cilindara
- TH/ Radikalna prostatektomija
- PHD/ **T3aN0Mx, GS 8**
- Adjuvantno zračenje+ konkomitantna i adjuvantna androgen deprivacijska th.

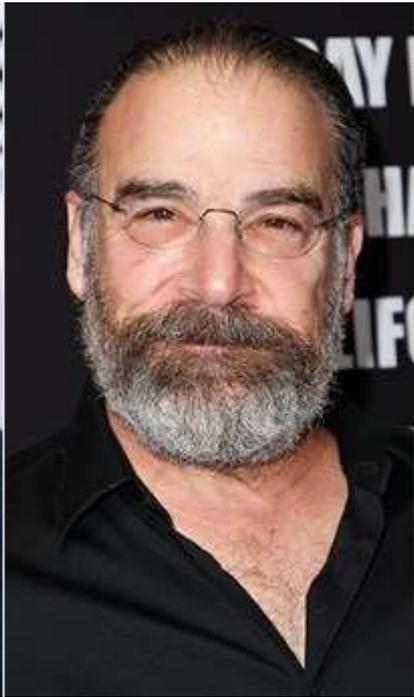
# Follow up

- Nakon 4 godine porast PSA
- Scintigrafija skeleta pozitivna
- Učinjena orhidektomija

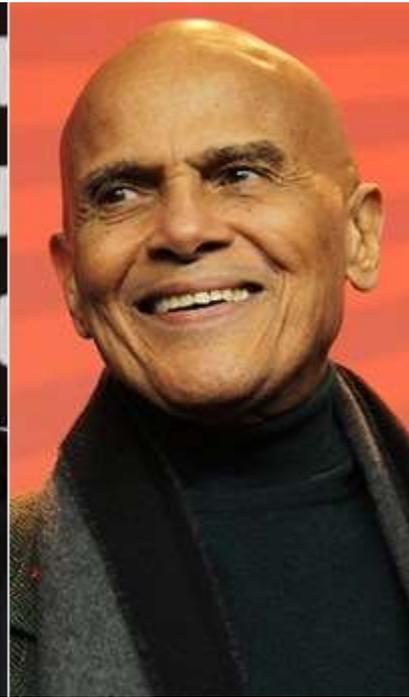
# *Prostate cancer survivors*



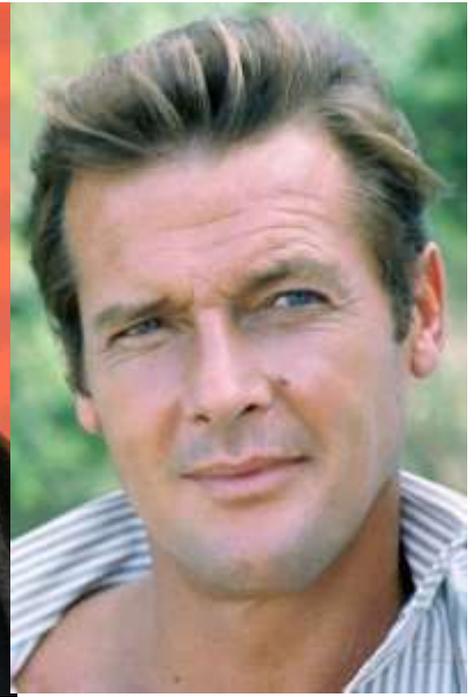
Robert De Niro



Mandy Patinkin



Harry Belafonte



Sir Roger Moore