Are we going to recommend prostate cancer screening in 10 years? - urologist's point of view

Fritz H. Schröder, MD
Professor of Urology
Erasmus University Medical center
Rotterdam, The Netherlands

To be covered

- Why population screening for prostate cancer?
- The European Randomized Study of Screening for Prostate Cancer (ERSPC) – current status
- Harms of screening
- How to improve over diagnosis?
- Conclusions

“Screening” and “early detection”

- “Screening” is the application of diagnostic tests to the general population
- “early detection” or “opportunistic screening” entails the use of diagnostic tests upon request of an individual
- A test not suited for “screening” may still be applicable for “early detection”

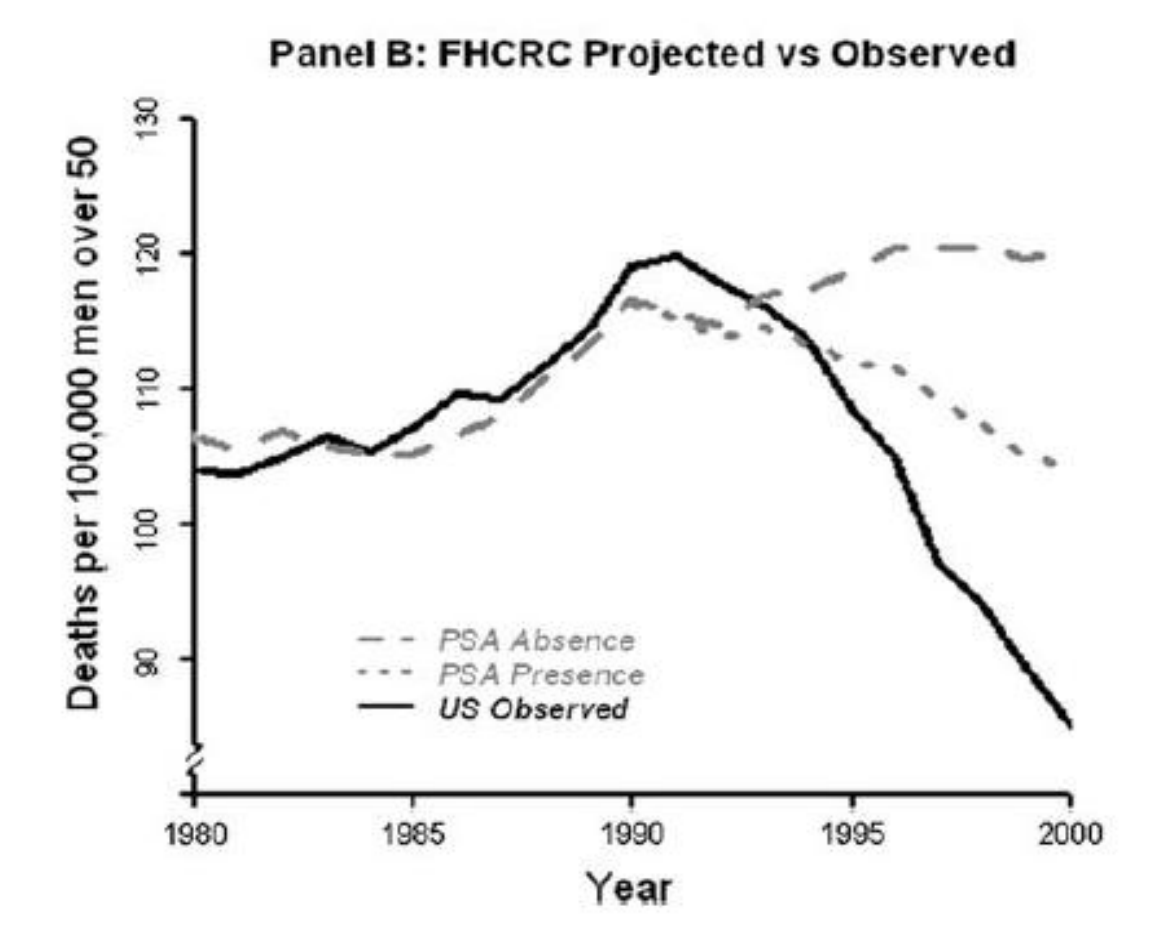
Why try to decrease prostate cancer mortality?

- Worldwide in 2008 903.000 men were diagnosed, 258.000 died of prostate cancer (Globocan 2008)
- Health systems target cancer mortality
- 35% mortality reduction world wide (90.300 men) achievable goal – if the price is acceptable

Evidence for mortality reduction

- USA 35% (or more), NL 22% since 1993
- Level 3-5 evidence: contradictory case-control registry and cohort studies
- Randomized screening trials
- Modelling US mortality: screening contributes 45 to 70% to reduction of 30% (Etzioni et al 2007)

PC mortality – projected and observed (Etzioni et al 2007)



Most likely explanations for mortality reduction in many countries

- Prevalent screening
- Improved treatment in T2 and T3 disease
- Use of statins?
- Change of lifestyle?
- Others

To be covered

- Why population screening for prostate cancer?
- The European Randomized Study of Screening for Prostate Cancer (ERSPC) – current status
- Harms of screening
- How to improve over diagnosis?
- Conclusions

Methods
European Randomized study of Screening for Prostate Cancer (ERSPC)

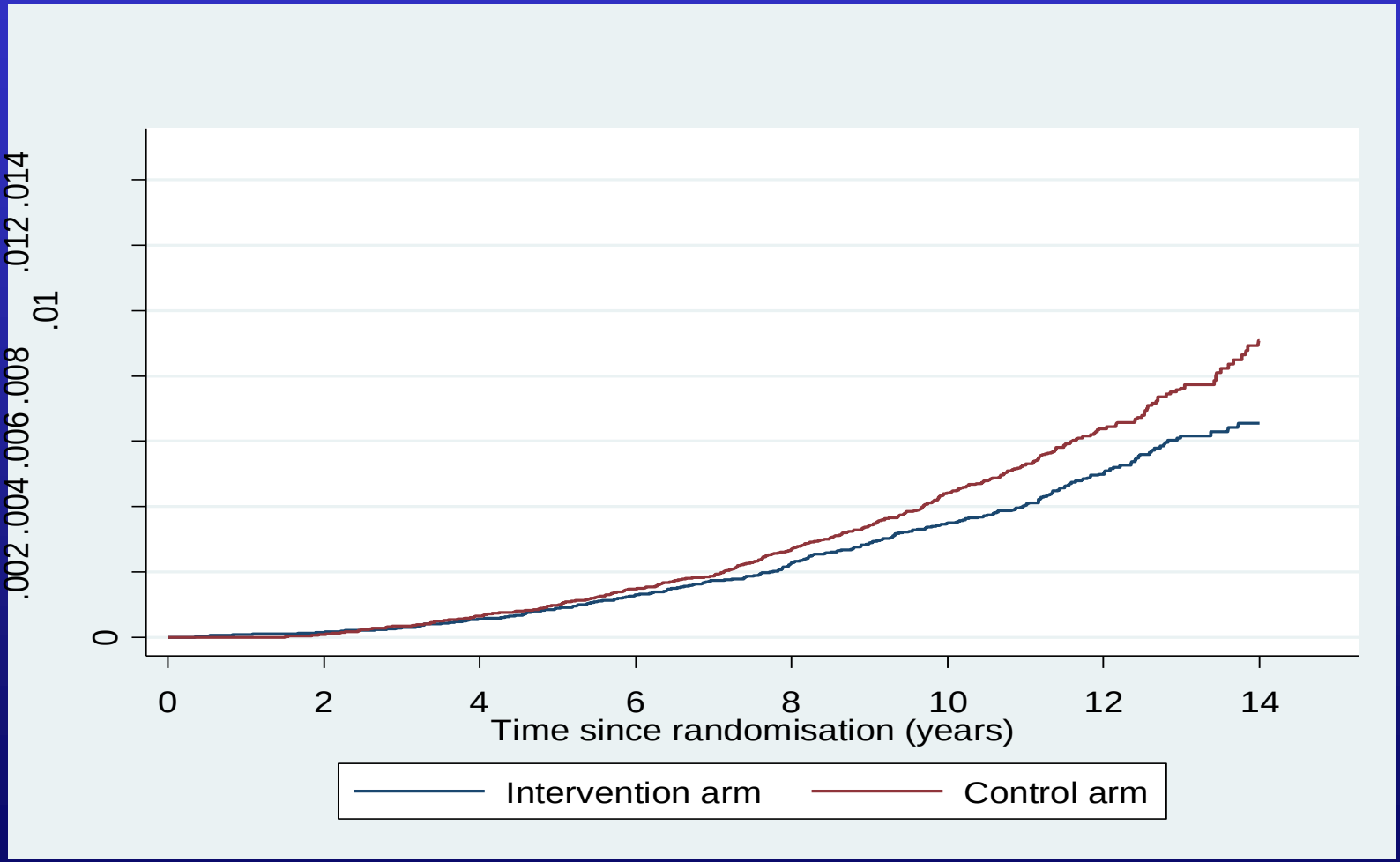
(Schröder et al NEJM 2012)

- Main end point: Prostate Cancer (PC) mortality, not all cause mortality
- Ages: 50-74, core age group for ITS analysis 55-69 (N= 162.160)
- Screen interval 4 years (87%) or 2 years (13%)
- Sextant (lateral) biopsy recommended for PSA >= 3.0 ng/ml
- Has 80% power to show a 25% difference in PC mortality in screened men after 10 years of FU

Prostate cancer mortality I Intention to screen analysis, FU 11 and ≥12 years

- Relative risk of PC death 0.79 (95%CI 0.68-0.91) p=0.001, a 21% reduction
- NNI (NNS): 936 NND (NNT): 33 (in excess of the control group)
- The absolute rate difference increased from 0.71 to 1.07 per 1.000 men, an increase of 34%

Cumulative risk of death from prostate cancer after 11years of follow-up (Relative risk reduction 21%, p=0.001)



Schröder et al. NEJM 2012

Prostate cancer mortality II
Adjustment for non compliance

- Results adjusted for non compliance relate to men who are actually screened
- RR of PC death is 0.71 (95% CI 0.58-0.86), a 29% relative mortality reduction (whole study period)
- And for the years 10-11: RR 0.53 (95% CI 0.36-0.80, a relative reduction of 47%
- NNI and NND overall are 673 and 33

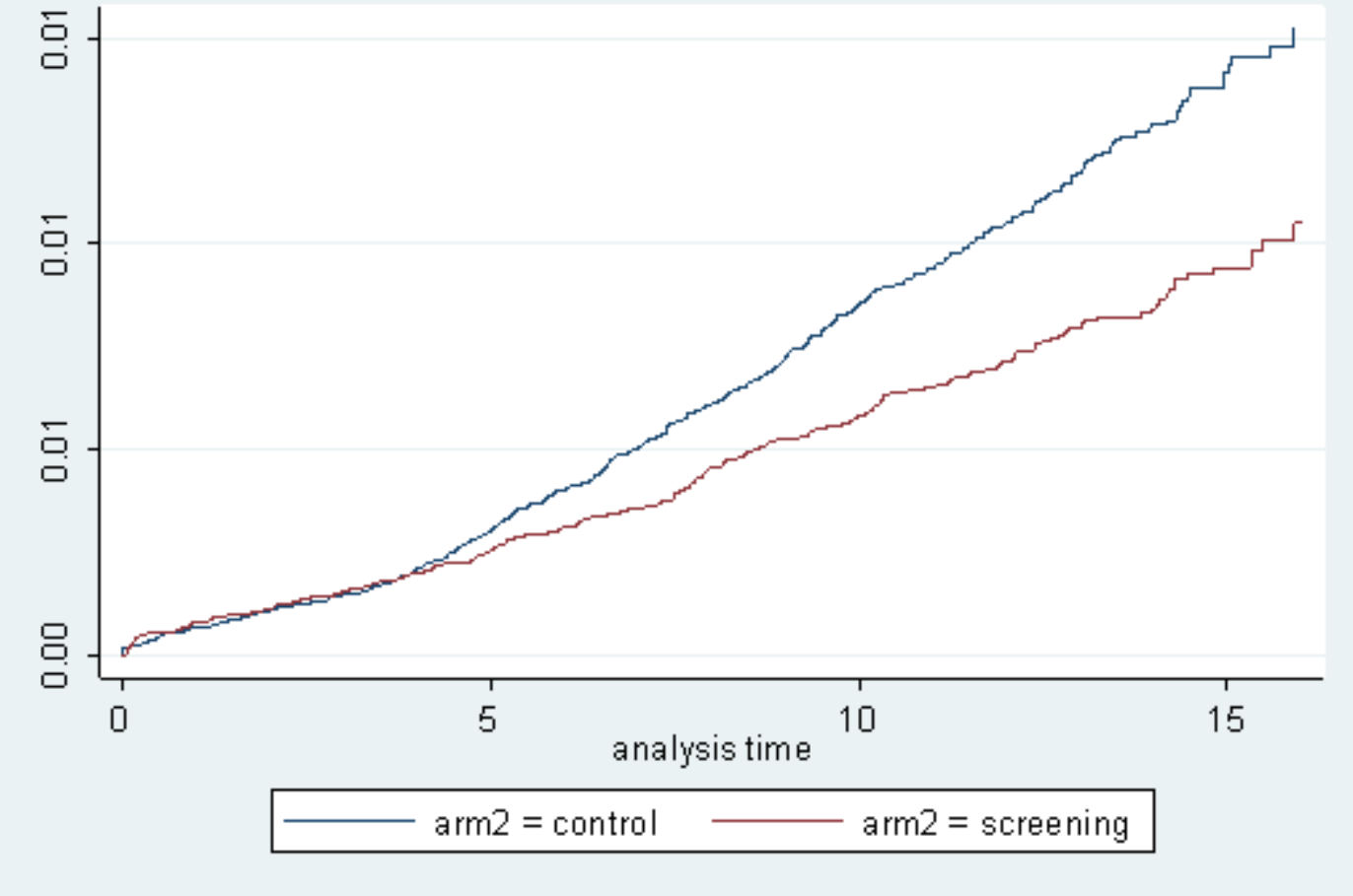
All cause and PC mortality by age at randomization

	Intervention arm		Control arm		Rate ratio's (95% CI)
	Deaths	Rate per 1000 p.y.	Deaths	Rate per 1000 p.y.	
All causes					
55-69	13917	18.2	17256	18.5	0.99 (0.97-1.01) P=0.50
Prostate cancer					
≤ 54	6	0.09	9	0.14	0.65 (0.23-1.83)
55-59	94	0.25	144	0.30	0.81 (0.62-1.05)
60-64	106	0.47	136	0.52	0.92 (0.71-1.18)
65-69	99	0.62	182	0.95	0.67 (0.53-0.86)
70+	59	1.33	51	1.13	1.18 (0.81-1.72)

Other benefit: reduction of M+ PC
(Schröder et al 2012)

- A subgroup analysis by 4 ERSPC centers shows an absoute reduction of M+ disease of 3/1.000 men randomized
- The relative reduction amounts to 31% and to 42% in screened men
- The NNI and NND to prevent 1 case of M+ disease within 12 years were 328 and 12
- Prevention of morbidity was a predefined end point withon ERSPC and is of great clinical relevance

Nelson-Aalen M+ curves overall



Nelson-Aalen cumulative hazard estimates of M+ PCa.

Risk ratio 0.688, relative reduction in S arm 31.2%, P < 0.001

Conclusions

- With a median follow-up of 11 years ERSPC shows a modest but significant increase in PC mortality reduction of 21%
- Adjustment for non compliance: a relative risk reduction of 29% results
- A significant reduction of metastatic disease of 31% is shown in 4 ERSPC centers
- The ERSPC study continues, >70% of all men are still alive

ERSPC, Toledo 2007

To be covered

- Why population screening for prostate cancer?
- The European Randomized Study of Screening for Prostate Cancer (ERSPC) – current status
- Harms of screening
- How to improve over diagnosis?
- Conclusions

“Harms are known, benefits are to be shown”

- Side effects of the screening procedures, stress
- Side effects of biopsy, low specificity
- Over diagnosis
- Side effects of treatment
- Over treatment

Quality of life (QoL) effects of PSA screening
(Heijnsdijk et al NEJM 2012)

- Qol effects of screening can be estimated by modeling approaches
- Predict QoL adjusted life years using weight estimates of health effects of screening (utilities)
- Estimate the effect of screening on simulated life histories (MISCAN model)
- Uses 11 year ERSPC data as basis

Example I: Effect of yearly screening and 4-year interval

- For 1000 men age 55-69 followed for life PC mortality reduction is 28%, 73 life years would be gained
- Estimated adjustment for loss QoL: 23%
- Application reduces 73 life years gained to 56 Quality of Life adjusted Life years or QALY's (73 - 23%)
- 4 year screening interval: 52 life years gained, reduction 20%, 41 QALY's

Example 2: Effect of over diagnosis on QALY's

- The model predicted 56 QALY's after a 23% reduction from 73 life years gained
- Model estimate over diagnosis is 41%
- Assuming NO over diagnosis increases QALY'S from 56 to 79
- Over diagnosis and post treatment complications are major determinants of loss of QoL

To be covered

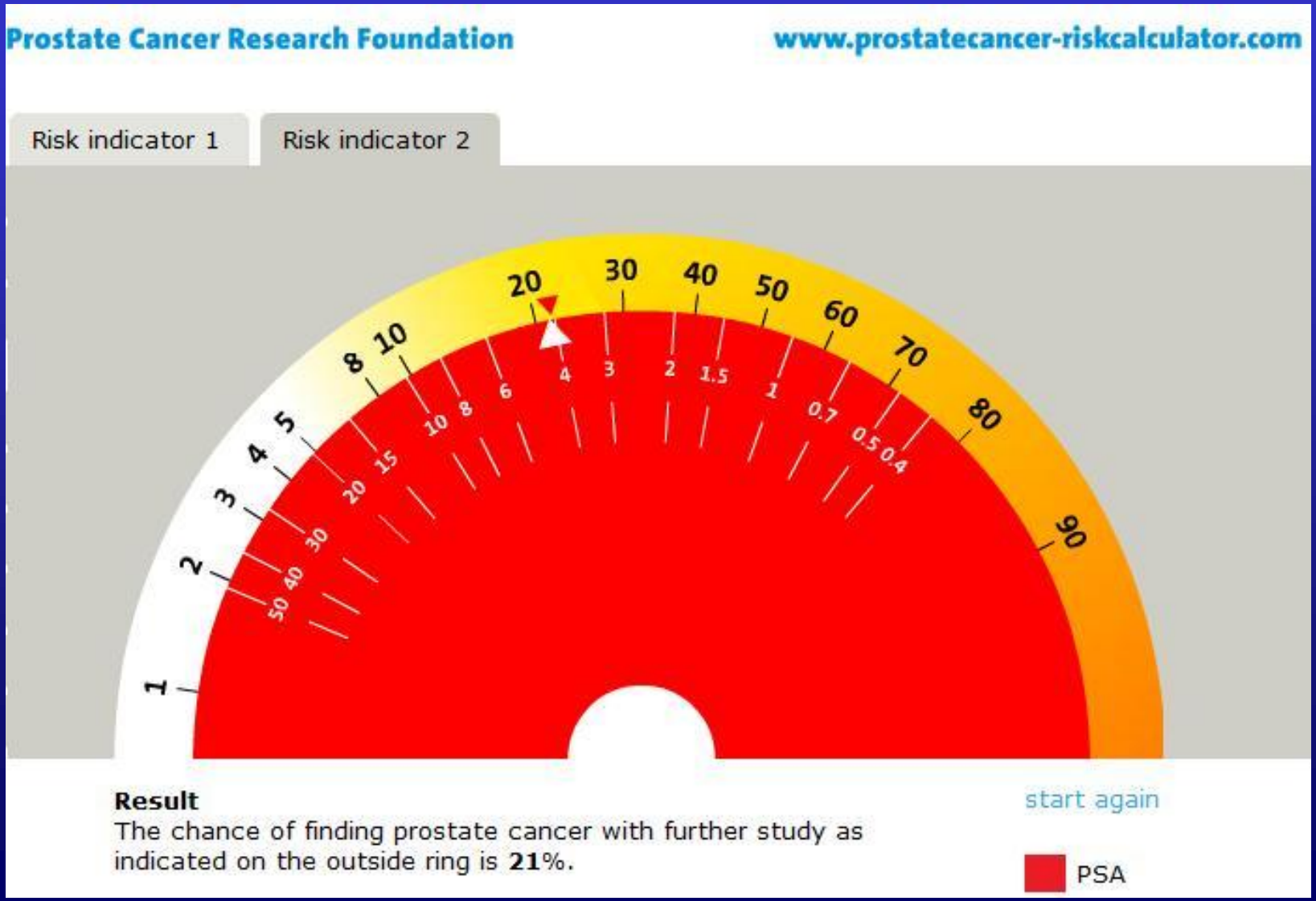
- Why population screening for prostate cancer?
- The European Randomized Study of Screening for Prostate Cancer (ERSPC) – current status
- Harms of screening
- How to improve over diagnosis?
- Conclusions

Main task: Reduce over diagnosis

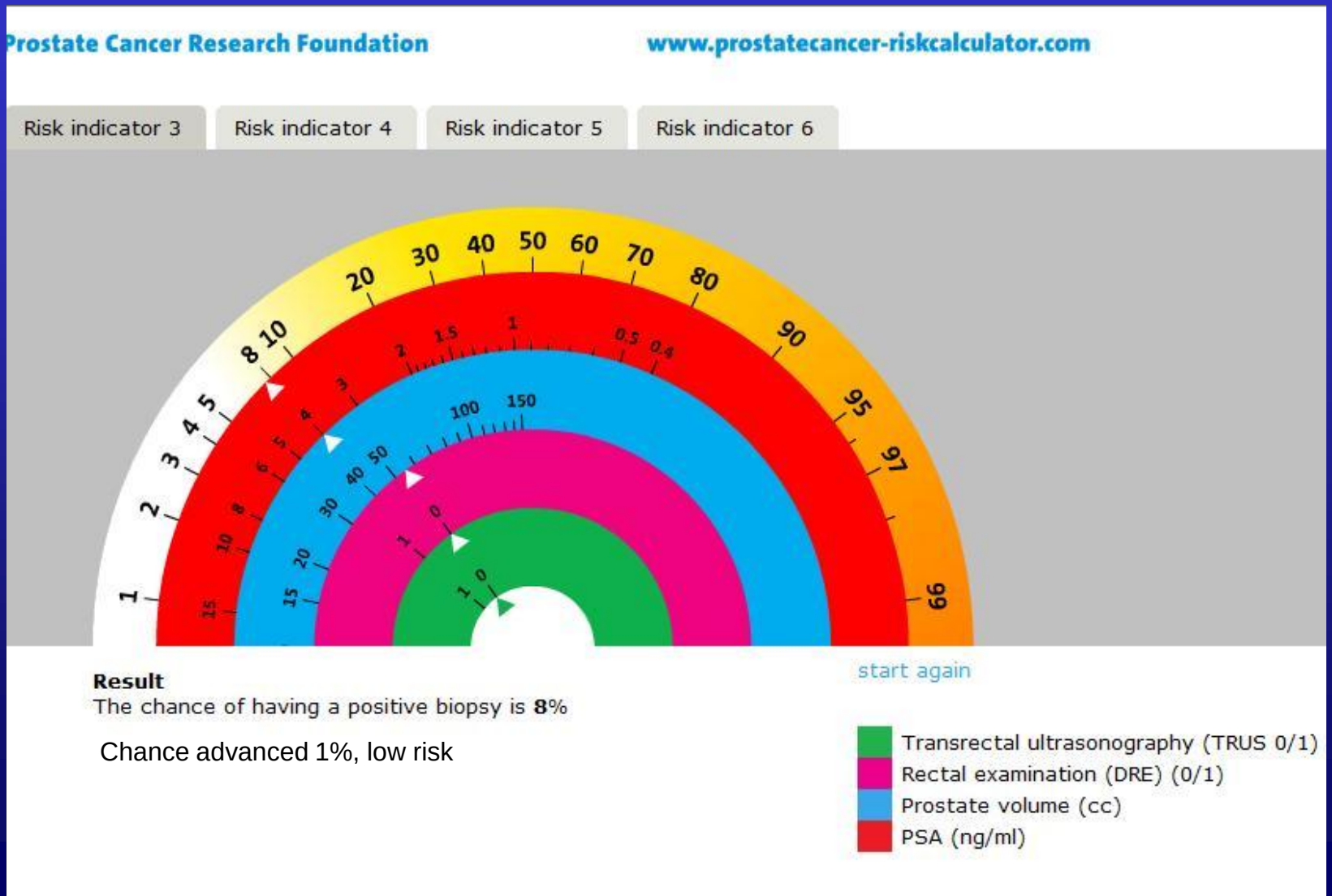
- We as urologists can contribute by applying the risk calculator
- Best option: avoid “unnecessary” biopsies
- Future: mpMRI fusion guided biopsy

- Example for use of your risk calculator number 3 and a PSA of 4 ng/ml

Example 1: PSA = 4 ng/ml

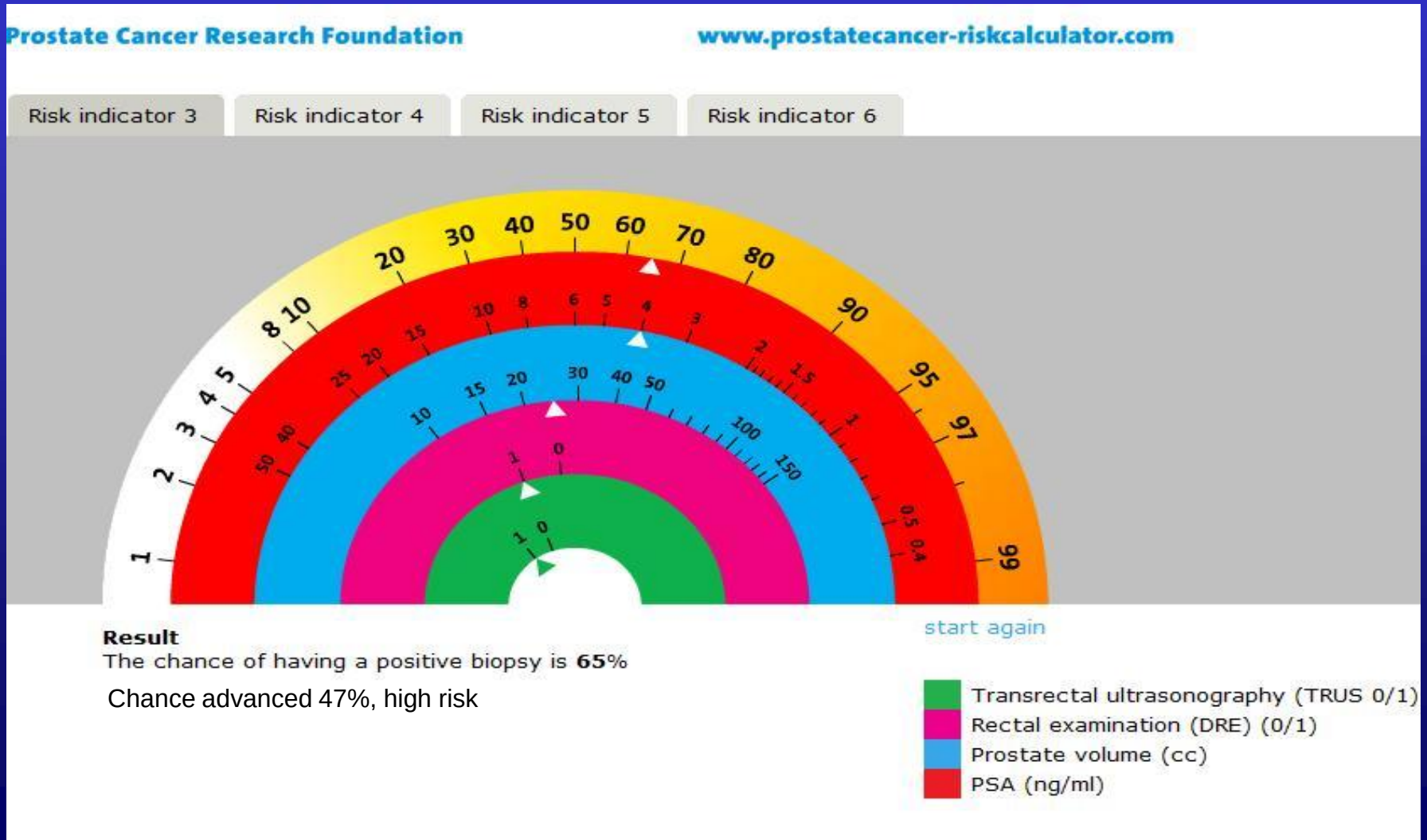


Example 2: PSA = 4 ng/ml – low risk



Chance advanced 1%, low risk

Example 3: PSA = 4 ng/mL – High risk

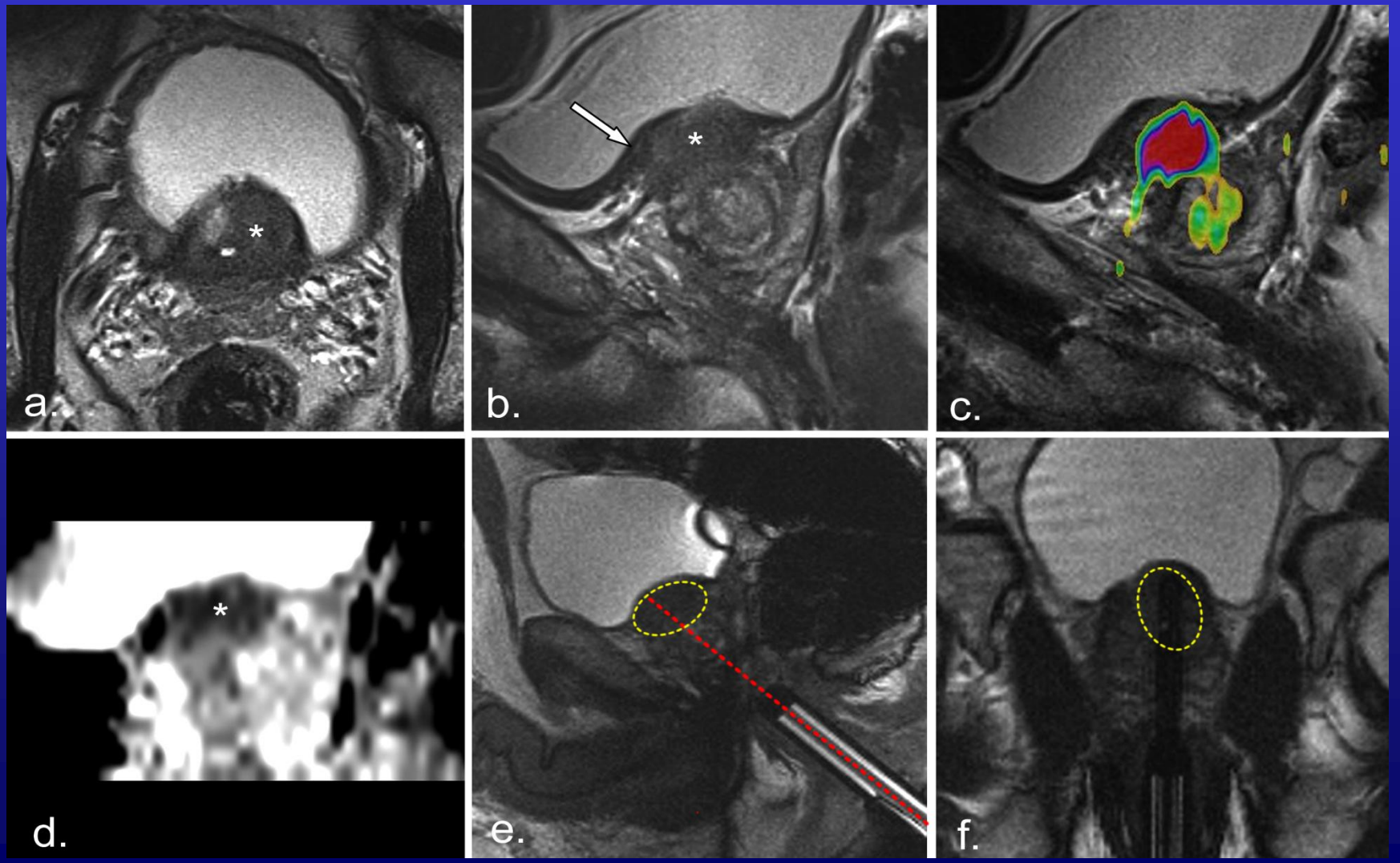


Chance advanced 47%, high risk

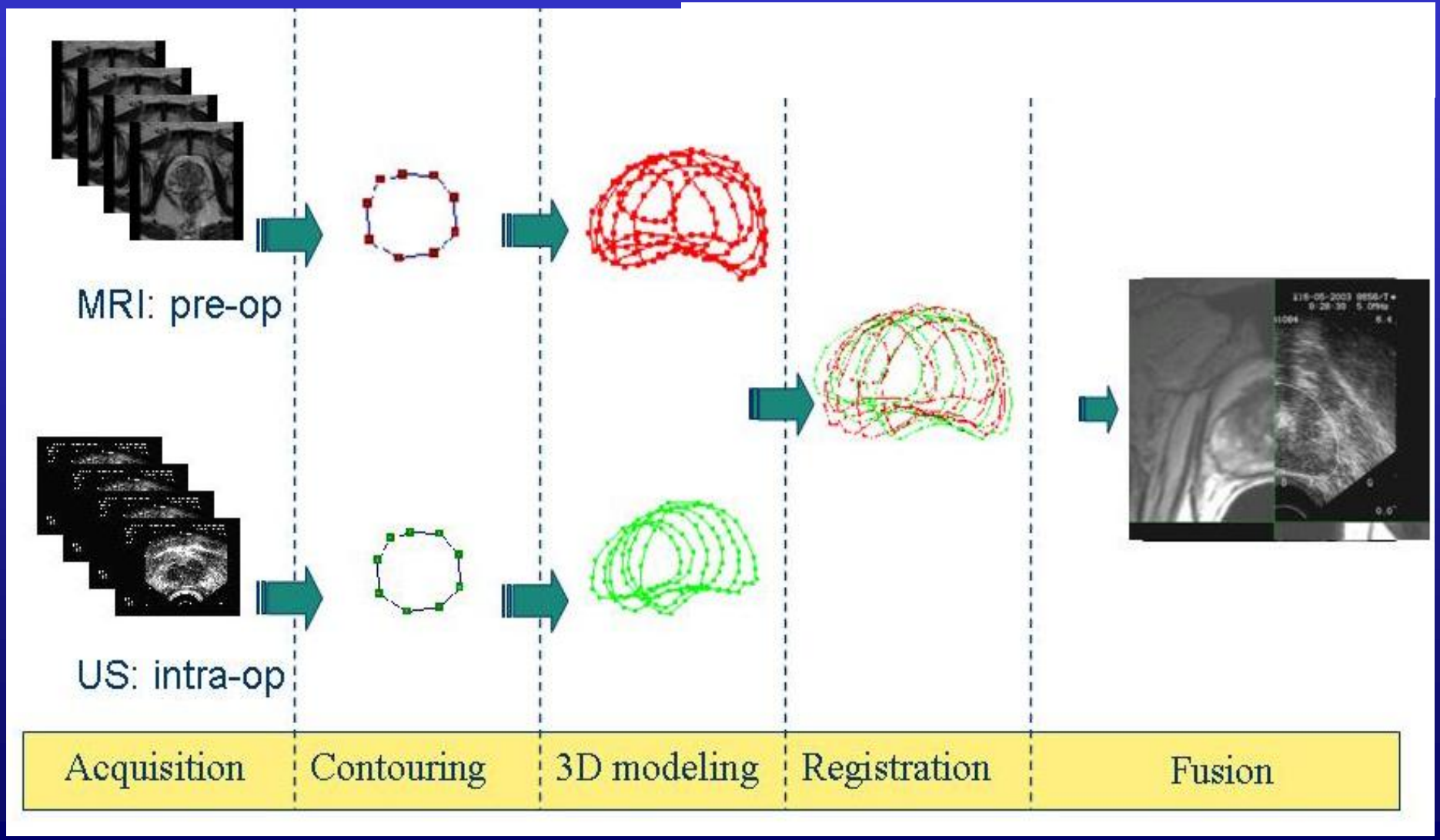
Promises of MRI

- MRI studies promise >80% sensitivity in detecting aggressive PC
- Claim: Biopsies in15-45% insignificant PC can be avoided
- BUT:
  - valid multicenter studies are missing
  - present information is often contra-dictory
- A controlled trial TRUS versus MRI biopsy is needed

MRI guided biopsy – anterior PC



3 dimensional, dynamic MR/TRUS fusion (Slide by courtesy of Inderbir Gill)



Conclusions I – how to deal with present uncertainty?

- Introduction of population based screening will depend on decreasing over diagnosis and over treatment
- Testing cannot be denied after “informed decision”
- Little chance for selective detection PC by present of new markers
- mpMRI is the best option

PSA TESTING:
TO TEST OR NOT TO TEST

Prostate health is a serious concern for men as they get older. PSA is a blood test to check the health of your prostate, a gland that helps reproduction.

A PSA test shows the levels of prostate-specific antigen (PSA) in your blood. High levels of PSA may suggest a possible abnormal growth of the prostate that may be or may not be cancer.

No test is perfect. There are advantages and disadvantages to PSA testing. Discuss your situation with your doctor to decide if PSA testing is right for you.

The following information may help you decide what questions you want to ask your family doctor or urologist. Together you will choose the best course of action for you.

INFORMATION TO CONSIDER ABOUT PSA TESTING

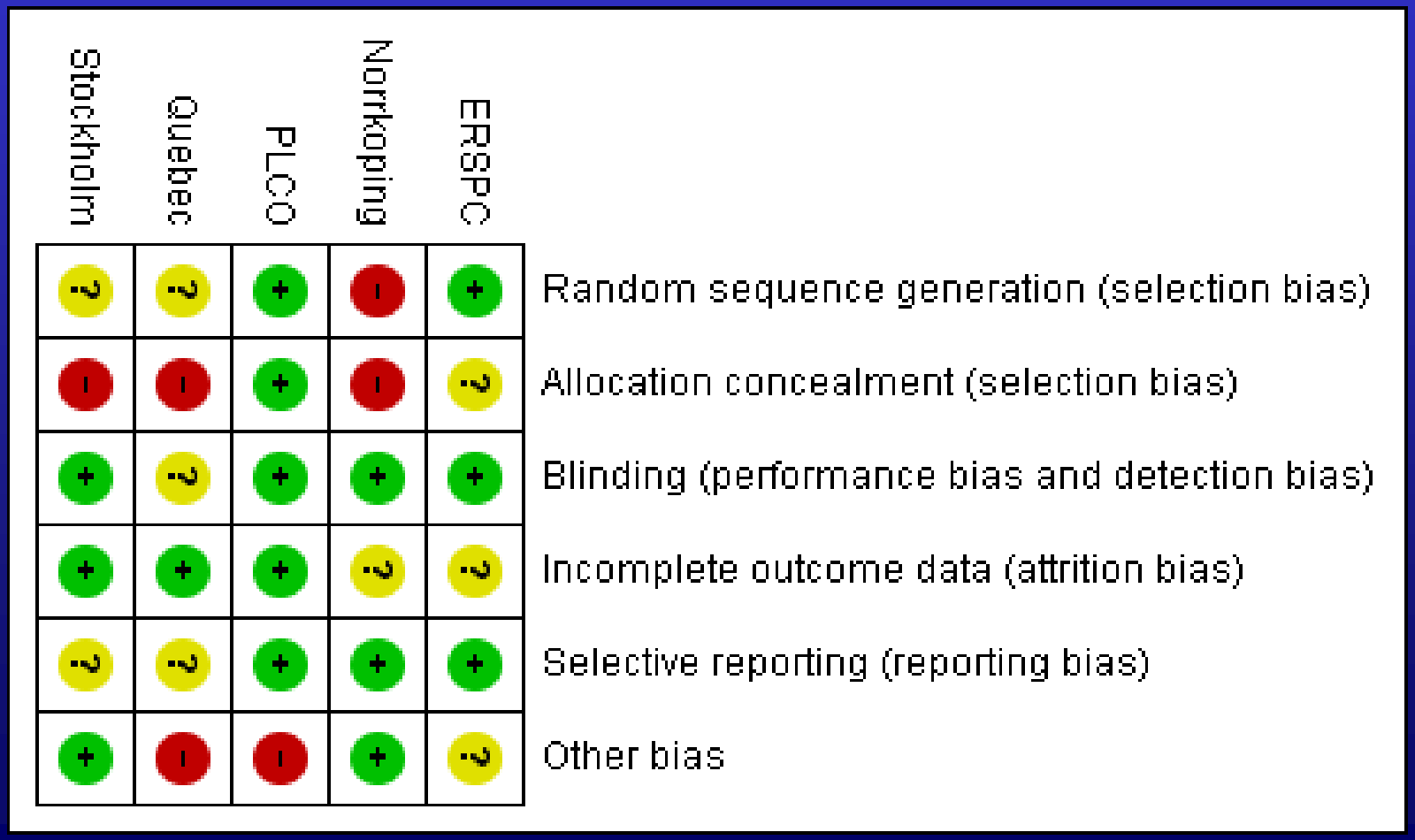
ADVANTAGES	DISADVANTAGES
If you get a normal result with no sign of cancer	
The result may put your mind at ease.	No test is perfect. Sometimes results are incorrect. The test may suggest a normal prostate when in fact there is abnormal growth (*false negative*). This can give you a false sense of reassurance, but you may in fact have a condition that needs treatment.
If you get a result that shows a possible abnormal growth	
The test may show early signs of disease before your health is affected. Early treatment can delay the spread of the disease, and improve your chances of cure and a longer life. If you did not take a PSA test, you may not find the cancer until it is too late.	A test may detect a slow-growing tumor which would never give you any problem. Δ This could lead to unnecessary treatment and side effects. Testing may give a *false positive* result, which suggests an abnormal growth when there actually is none. This could lead to: Δ unnecessary further testing Δ medical complications and side effects Δ high levels of stress and anxiety

Dr. Fritz Schröder and Dr. Monique Roobol are responsible for the scientific content of this decision aid.

Cochrane Library, RCT's of PC screening (Ilic, D et al 2013)

- 5 trials qualified: PLCO, Quebec, Norrköping, Stockholm and ERSPC
- PLCO and ERSPC were classified as "low risk for bias" and given the same weight
- Meta analysis of PLCO and ERSPC was done
- No significant difference in PC mortality was seen

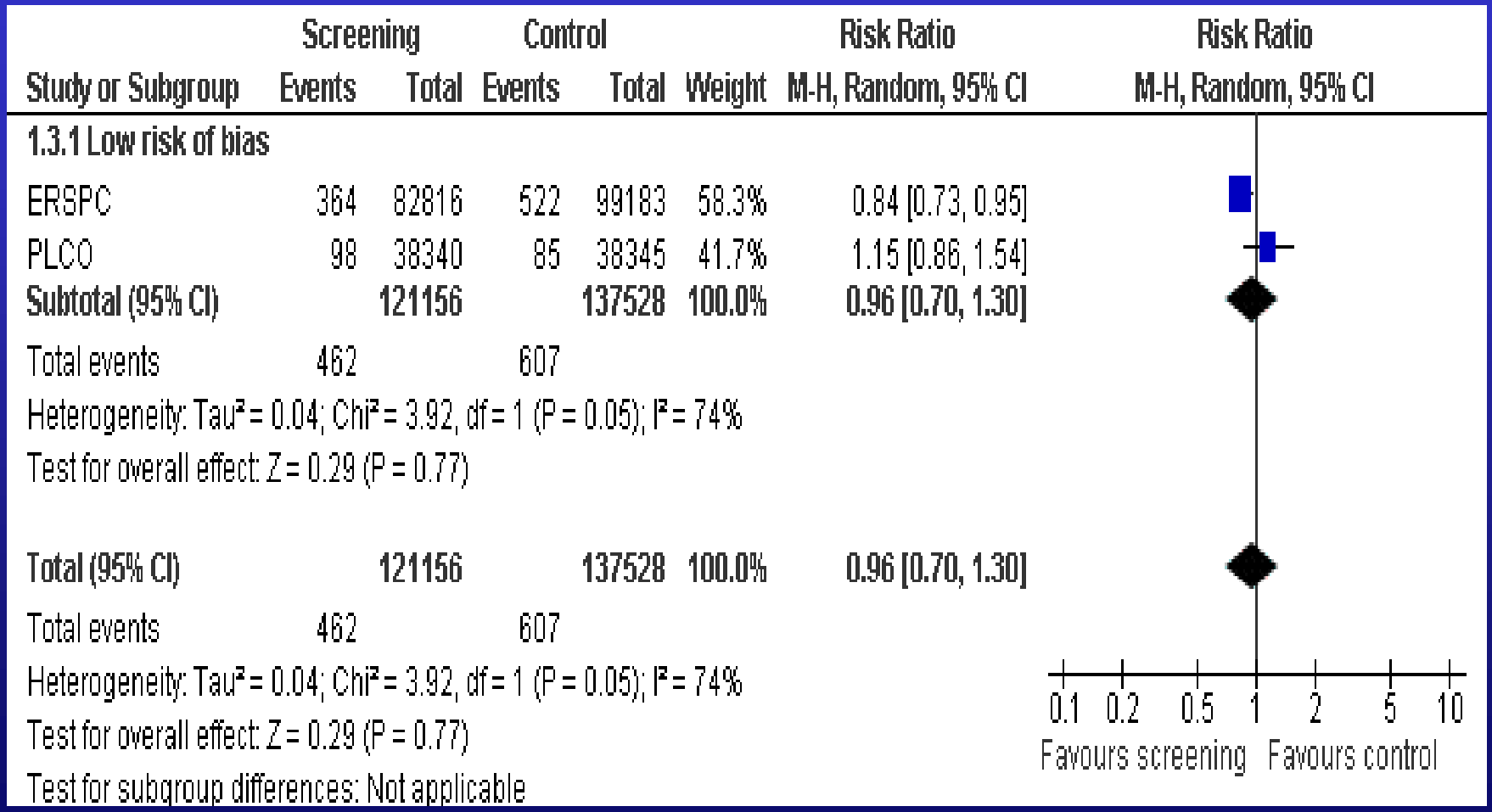
What is bias?
(Ilic et al Cochrane Library 2013)



We need to quantify bias in relation to quality criteria

- Example: Category “other bias” includes control group and upfront contamination
- No attempt is made to quantify the effect on outcomes in either study
- No quantitative relation is established in relation to other biasses
- The effect of individual biasses with different weights on outcomes remains unexplored
- Is the identical classification of ERSPC and PLCO as “low risk bias studies” justified?

Forest plot comparing screening versus control in ERSPC and PLCO, PC specific mortality, adjusted for risk of bias



Ilic D, Neuberger MM, Djulbegovic M, Dahm, P, Cochrane Library 2013

PLCO Cancer Screening Trial and ERSPC results differ – why?[1]

- Only 40% compliance with biopsy indications[2]
- Testing in 44% of men prior to randomization decreased numbers of events
- >70% contamination by PSA use in the C arm (3)
- Low rates of PCa deaths in both arms and no difference in PCa mortality
- The rate of effective screening is very low
- PLCO does not provide an answer to the value of screening but compares screening to current US practice

1. Andriole et al. N Engl J Med 2009
2. Grubb et al. BJU Int 2008, 3. Pinsky 2010

ERSPC versus PLCO – comparable weight of evidence?

- The Cochrane review gives ERSPC and PLCO the same weight of evidence
- Different biases have different effects on outcomes
- These outcome effects are not quantified in the Cochrane system
- The comparison of quantified biases would confirm that both trials should not be classified at the same level of evidence