Früherkennung und Diagnostik des Prostatakarzinoms
Prof. Dr. med. Franz Recker

Senior Consultant
Kantonsspital Aarau
Stiftung Prostatakrebsforschung

Kantonsspital Aarau

qp

Men at risk of prostate cancer

a) *«The wind has changed» :USPSTF*

b) *Screening: When to start*

c) *Opportunistic is inferior to organized screening*

d) *PSA Fine tuning: Control intervals*

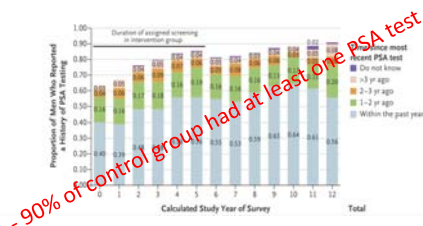g) *Biopsies: How to proceed*

qp

VIEWPOINT
The US Preventive Services Task Force
2017 Draft Recommendation Statement
on Screening for Prostate Cancer
An Invitation to Review and Comment

Recommendation D → C

qp

Reevaluating PSA Testing in the PLCO Trial

- 90% of control group had at least one PSA test

Shoag et al. NEJM *2016*

qp

…………already in 2012

The lack of screening benefit in PLCO was very early underlined by…….

missing an expected pathological stage shift in RP specimen from the control to the screening group

Eur Urol. M. Kwiatkowski/F. Recker 2012

qp

Annals of Internal Medicine — ORIGINAL RESEARCH

Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials

	Mortality reduction 11 years FU	
	Screening	*No Screening*
ERSPC	25-30 % *(first pass effect)* ↓	0
PCLO	27-32 % *(due to prescreening)* ↑	0

No longer the question whether screening makes sence
But: → HOW TO SCREEN

Tsodikov et al.; Annals of Internal Medicine 2017
Vickers A., Annals of Internal Medicine 2017

qp

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Slide 1

Medizin

Prostatakarzinom: Neue Studie sieht Vorteile für das PSA-Screening

Mittwoch, 6. September 2017

PSA Test

/stockadobe.com

Prostatakarzinom

- Prostatakarzinom: Neue Studie sieht Vorteile für das PSA-Screening
- Prostatafrühkarzinom: Operation auch nach fast 20 Jahren ohne Vorteile
- Prostatakarzinom-Studie: PREFERE aus der Retrospektive

Krebsfrüherkennung

Ann Arbor/Michigan – Das umstrittene PSA-Screening, das aufwand widersprüchlicher

Slide 2

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

Fritz H Schröder, Jonas Hugosson, Monique J Roobol, Teuvo L J Tammela, Marco Zappa, Vera Nelen, Maciej Kwiatkowski, Marcos Lujan, Liisa Määttänen, Hans Lilja, Louis J Denis, Franz Recker, Alvaro Paez, Chris H Bangma, Sigrid Carlsson, Donella Puliti, Arnauld Villers, Xavier Rebillard, Matti Hakama, Ulf Hakan Stenman, Paula Kujala, Kimmo Taari, Gunnar Aus, Andreas Huber, Theo H van der Kwast, Ron H N van Schaik, Harry J de Koning, Sue M Moss, Anssi Auvinen, for the ERSPC Investigators*

Follow up years	NN Invite (PSA)	NN Diagnose
9	1410	48
11	979	35
13	781	27

USPSTF: Screening for breast cancer (B recomendation)

Main results

Eight eligible trials were identified. We excluded a biased trial and included 600,000 women in the analyses. Three trials with adequate randomisation did not show a significant reduction in breast cancer mortality at 13 years (relative risk (RR) 0.90, 95% confidence interval (CI) 0.79 to 1.02); four trials with suboptimal randomisation showed a significant reduction in breast cancer mortality with an RR of 0.75 (95% CI 0.67 to 0.83). The RR for all seven trials combined was 0.81 (95% CI 0.74 to 0.87).

Slide 3

Men at risk of prostate cancer

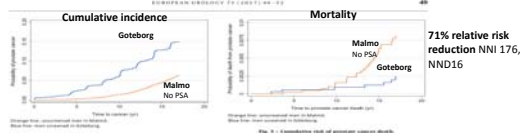a) *«The wind has changed» :USPSTF*

b) *Screening: When to start*

c) *Opportunistic is inferior to organized screening*

d) *PSA Fine tuning: Control intervals*

e)*Biopsies: How to proceed?*

Slide 4

EAU Guidelines

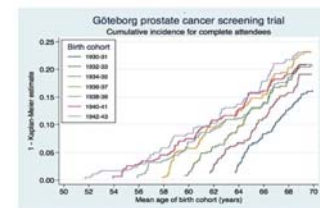| Recommendations for screening and early detection	LE	GR
Do not subject men to prostate-specific antigen (PSA) testing without counselling on the potential risks and benefits.	3	B
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life expectancy of at least ten to fifteen years.	3	B
Offer early PSA testing in well-informed men at elevated risk of having PCa: • men > 50 years of age; • men > 45 years of age and a family history of PCa;	2b	A

Slide 5

Platinum Priority – Prostate Cancer

Screening for Prostate Cancer Starting at Age 50–54 Years. A Population-based Cohort Study

Sigrid Carlsson, Melissa Assel, David Ulmert, Axel Gerdtsson, Jonas Hugosson, Andrew Vickers, Hans Lilja

EUROPEAN UROLOGY 75 (2017) 46–52

Cumulative incidence — Goteborg, Malmo No PSA

Mortality — Malmo No PSA, Goteborg

71% relative risk reduction NNI 176, NND16

Fig. 1 - Cumulative risk of prostate cancer diagnosis.

Fig. 2 - Cumulative risk of prostate cancer death.

Fig. 3 - Cumulative risk of overall mortality.

Slide 6

The Effect of Start and Stop Age at Screening on the Risk of Being Diagnosed with Prostate Cancer

Rebecka Arnsrud Godtman,* Sigrid Carlsson,† Erik Holmberg, Johan Stranne and Jonas Hugosson

Starting 50-60 years!
Early start does not enhance the cumulative incidence
(when 10/12 random biopsies were done, PSA >2.5ng/ml)

Göteborg prostate cancer screening trial
Cumulative incidence for complete attendees

20-23% cum. incidence starting 50 - 60 yrs similar

Cumulative incidence grows more slowly in younger years

= Starting early advances the time of diagnosis
but does not seem to increase the risk of being diagnosed with P-Ca,
indicating that 50-60 yrs does not increase overdiagnosis

Figure 2. Cumulative incidence of PCa among complete attendees (3,488) stratified by age cohorts, Kaplan-Meier estimates.

Slide 1

Men at risk of prostate cancer

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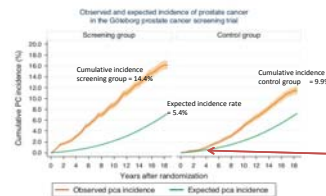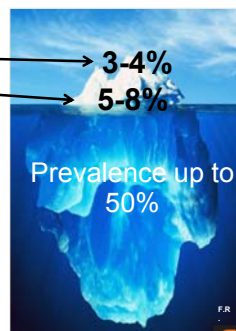
e) *Screening: When to stop*

f) *Biopsies: How to proceed?*

Slide 2

Opportunistic is inferior to organized screening!

Observed and expected incidence of prostate cancer in the Göteborg prostate cancer screening trial

Cumulative incidence screening group = 14.4%

Cumulative incidence control group = 9.9%

Expected incidence rate = 5.4%

Opportunistic screening
→ Delayed onset, irregular
→ "Window of opportunity?"

Fig. 2 – Observed and expected prostate cancer incidence analyzed up to December 31, 2012 (n = 19 899). Expected values are based on incidence in Gothenburg 1990–1994. The shaded area denotes the 95% confidence interval. PC = prostate cancer.

Slide 3

Opportunistic is inferior to organized screening!

Observed and expected mortality of prostate cancer in the Göteborg prostate cancer screening trial

NND 13   NND 23

RR 42%
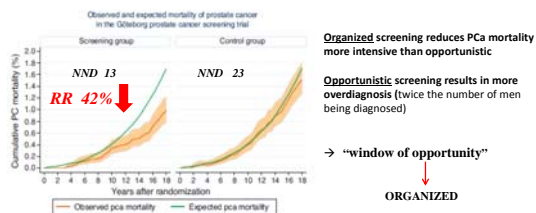
Organized screening reduces PCa mortality more intensive than opportunistic

Opportunistic screening results in more **overdiagnosis** (twice the number of men being diagnosed)

→ "window of opportunity"
↓
ORGANIZED

Slide 4

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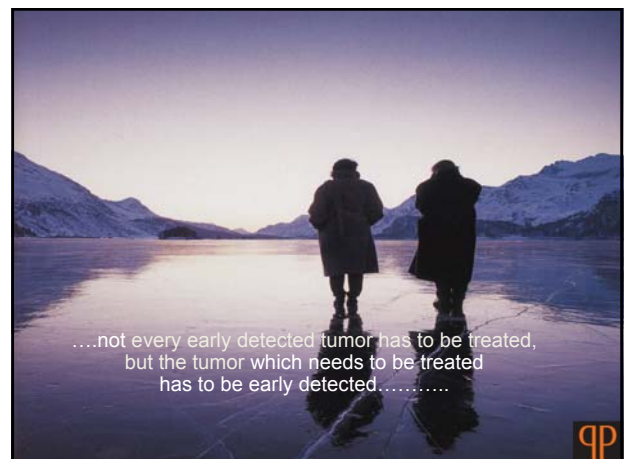d) *PSA Fine tuning: Control intervals*

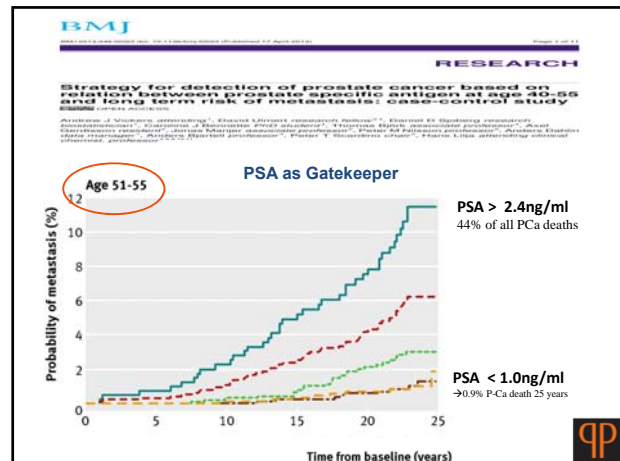f) *Biopsies: How to proceed?*

Slide 5

Epidemiology of P Ca

Life time risk

- **Death from PCa** → 3-4%
- **Risk of suffering from PCA** → 5-8%

Prevalence up to 50%

Franks J. Pathol Bacteriol. 1954
Rich AR J. Urol 1935

Slide 6

….not every early detected tumor has to be treated, but the tumor which needs to be treated has to be early detected………..

Slide 1

PSA: „Gatekeeper" for long term developement of prostate cancer

Slide 2

RESEARCH

Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study

PSA as Gatekeeper

Age 51-55

Probability of metastasis (%)

PSA > 2.4ng/ml
44% of all PCa deaths

PSA < 1.0ng/ml
→0.9% P-Ca death 25 years

Time from baseline (years)

Slide 3

Screening PCa-Incidence within 8 years Baseline PSA < 1ng/ml (n=2416), med. 61 years, Aargau

55.5%

■ 15 (0.62%)
■ 2 (0.08%)
High risk D`Amico

■ NPV 99.9%

Slide 4

ARTICLE IN PRESS

A "PSA Pyramid" for Men with Initial Prostate-specific Antigen ≥3 ng/ml: A Plea for Individualized Prostate Cancer Screening

55-69 years: Screening strategy: Intelligent screening → sparing expence → prolong intervals

PCa free 12 years

PCA free

baseline PSA

Slide 5
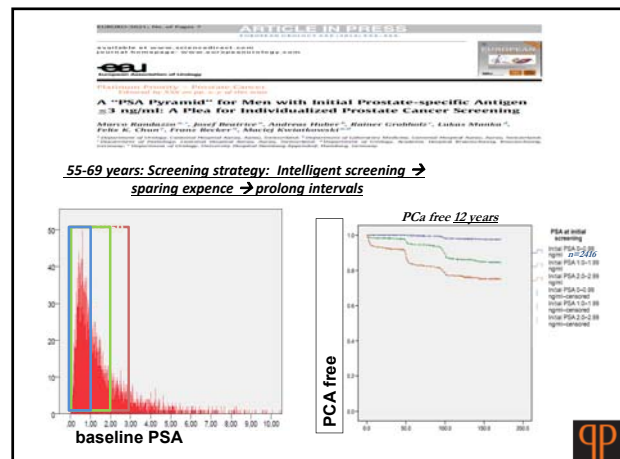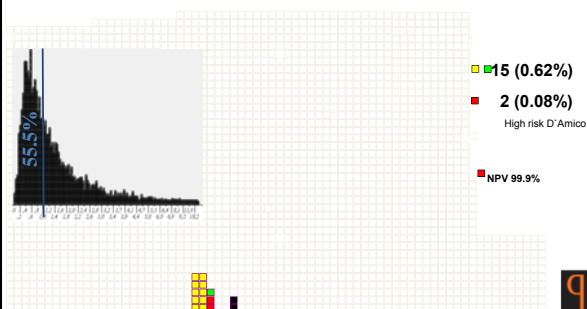
Individualising of control intervals
How often testing at which risk?
Prognostic Calculators

Slide 6

A Calculator for Prostate Cancer Risk 4 Years After an Initially Negative Screen: Findings from ERSPC Rotterdam

ARTICLE IN PRESS

A "PSA Pyramid" for Men with Initial Prostate-specific Antigen ≥3 ng/ml: A Plea for Individualized Prostate Cancer Screening

Risk calculators define precise control intervals

ProstateCheck

SWISS-Medic CE
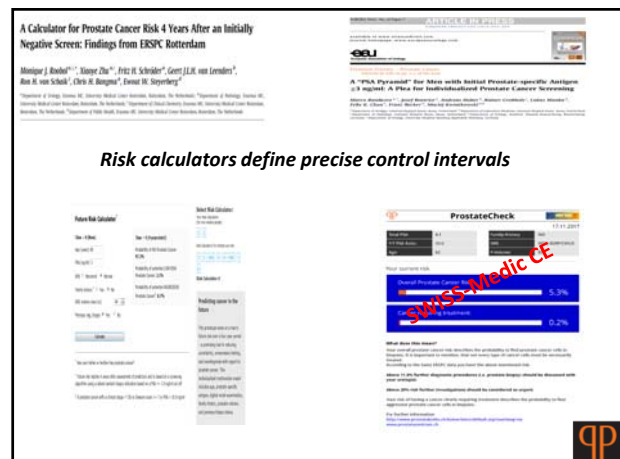
Slide 1: P - Ca Incidence PSA < 1.0

8 years Follow up

static with no clinical FU

Based on the provided risk factors a prostate biopsy performed would have a:

TOTAL PSA: 0.4
ALTER: 59
FAMILIEN-ANAMNESE: NEIN

0.1 % high grade % overall

PCPT

1% chance of high-grade prostate cancer,

9% chance of low-grade cancer,

90% chance that the biopsy is negative for cancer.

10%

control 5/6 years

Slide 2: Individual P-Ca Risk: PSA 1-1.9

4 years   **4 years**

Left:
TOTAL PSA: 1.1ng/ml
F/T PSA VERHÄLTNIS: 35%
ALTER: 60

0.4% high grade
1.1% overall

Control 3 years
No two years
S 3 ,EAU,AUA

Right:
TOTAL PSA: 1.9ng/ml
F/T PSA VERHÄLTNIS: 7%
ALTER: 60

4.1% high grade
9.8% overall

Control latest 1 year
No two years
S 3,EAU,AUA

Slide 3: Individual risk: ProstateCheck App

Left:
TOTAL PSA: 3.1g/
F/T PSA VERHÄLTNIS: 17%
ALTER: 62
DRU: Unsuspicious
P-VOLUMEN: 31

Overall : 22.5%
High risk: 3.6%

Direct examine

Right:
TOTAL PSA: 6.2ng/
F/T PSA VERHÄLTNIS: 29
ALTER: 59
DRU: Unsuspecious
P-VOLUMEN: 72

Overall: 7.3%
High risk: 0.7%

No examine

Slide 4

Impact of Comorbidity on Survival Among Men With Localized Prostate Cancer
Peter C. Albertsen, Dirk F. Moore, Weichung Shih, Yong Lin, Hui Li, and Grace L. Lu-Yao

Screening: When to stop ?

R.S. 66 yrs

Gleason Sc. ≤ 7   Gleason Sc. 8-10

U.E. 77 yrs

(in PIVOT trial 50% died within 10 yrs!)

Slide 5

Biopsies: How to proceed?

→ *mp MRI considerations prebiopy (personal)*

Slide 6

EAU–ESTRO–SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent

Nicolas Mottet, Joaquim Bellmunt, Michel Bolla, Erik Briers, Marcus G. Cumberbatch, Maria De Santis, Nicola Fossati, Tobias Gross, Ann M. Henry, Steven Joniau, Thomas B. Lam, Malcolm D. Mason, Vsevolod B. Matveev, Paul C. Moldovan, Roderick C.N. van den Bergh, Thomas Van den Broeck, Henk G. van der Poel, Theo H. van der Kwast, Olivier Rouvière, Ivo G. Schoots, Thomas Wiegel, Philip Cornford

10-12-core
→bilateral from apex to base, →**as far posterior and lateral as possible** from the peripheral gland.
- Additional cores should be obtained from DRE/TRUS suspect areas.

When the same number of cores are taken, both
transrectal and transperineal approaches have comparable detection rates

Oral or intravenous quinolones are state-of-the-art preventive antibiotics
- The need to **obtain culture results of prebiopsy rectal swabs to identify** the most appropriate antibiotic has been raised by recent studies.

Slide 1:

Rebiopsy → mpMRI

N. Mottet (Chair), J. Bellmunt, E. Briers (Patient Representative), M. Bolla, L. Bourke, P. Cornford (Vice-chair), M. De Santis, A.M. Henry, S. Joniau, T.B. Lam, M.D. Mason, H.G. van der Poel, T.H. van den Kwast, O. Rouvière, T. Wiegel
Guidelines Associates: N. Arfi, R.C.N. van den Bergh, T. van den Broeck, M. Cumberbatch, N. Fossati, T. Gross, M. Lardas, M. Liew, P. Moldovan, I.G. Schoots, P.M. Willemse

Recommendations	LE	GR
Before repeat biopsy, perform multiparametric magnetic resonance imaging (mpMRI) when clinical suspicion of PCa persists in spite of negative biopsies.	1a	A
During repeat biopsy, include systematic biopsies and targeting of any mpMRI lesions seen.	2a	B

Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR.

AUA,SAR

………Thus, when high quality prostate magnetic imaging is available, it should be strongly considered for any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy

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Slide 2:

Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature

EUROPEAN UROLOGY 68 (2015) 1045–1053

Table 6 – Definition of clinically significant disease

Slide 3:

Pathologic and Clinical Findings to Predict Tumor Extent of Nonpalpable (Stage T1 c) Prostate Cancer

Jonathan I. Epstein, MD; Patrick C. Walsh, MD; Marné Carmichael, et al

CAVE: OVERSIAGNOSIS!

Insignificant PCa
- PSA density < 0.15 ng/ml/cc
- Core involvement <50%
- Max. 2 cores involved
- <=GI 3+3=6

Targeted biopsies

significant ?

Epstein JI et al., JAMA 1994,

Slide 4:

Characteristics of Detected and Missed Prostate Cancer Foci on 3-T Multiparametric MRI Using an Endorectal Coil Correlated With Whole-Mount Thin-Section Histopathology
Nelly Tan,[1] Daniel J. Margolis,[1] David Y. Lu,[2] Kevin G. King,[1] Jiaoti Huang,[2] Robert E. Reiter,[3]

mpMRI: CAVE: Underdiagnosis by missing multifocal cancer

Reiter 2017:
The utility of current mpMRI techniques
is limited by the multifocal nature of PCA
with poor detection of non index lesions,
inaccurate estimation of tumor size and geometry,
and the need for **interpretation of radiologists** (interobserver variability)

GI >=7a

Slide 5:

Multifocality and Prostate Cancer Detection by Multiparametric Magnetic Resonance Imaging: Correlation with Whole-mount Histopathology

Jesse D. Le, Nelly Tan, Eugene Shkolyar, David Y. Lu, Lorna Kwan, Leonard S. Marks, Jiaoti Huang, Daniel J.A. Margolis, Steven S. Raman, Robert E. Reiter

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Slide 6:

Multifocality and Prostate Cancer Detection by Multiparametric Magnetic Resonance Imaging: Correlation with Whole-mount Histopathology

Jesse D. Le, Nelly Tan, Eugene Shkolyar, David Y. Lu, Lorna Kwan, Leonard S. Marks, Jiaoti Huang, Daniel J.A. Margolis, Steven S. Raman, Robert E. Reiter

→ Do not not disclaim random biopsies

SUMMARY

- *USPSTF recommendation C*

- *Start screening with 50 yrs, in family risk men: 45yrs*

- *Use individual ORGANIZED control intervals according to age and PSA level (use risk calculators)*

- *Use risk calculator for indication of further diagnostics*

- *Random biopsies 12 cores are still state of the art, also if mpMRI does not show anything*

- *Latest rebiopsy with mpMRI*

- *mpMRI is one part of the future, but cave!*
                A) overdiagnosis
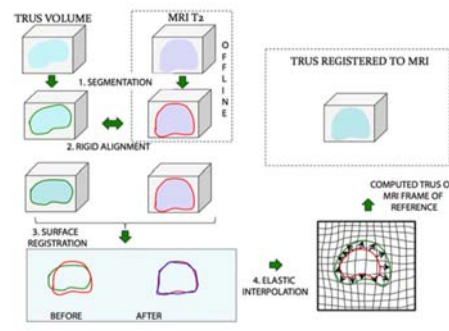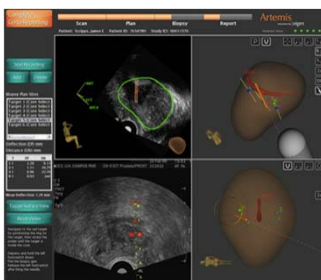   *b) underdiagnosis*

MRT-Ultraschall Fusion

40

MRT-Ultraschall Fusionsbiopsien der Prostata

41

MRT Diagnostik vor Prostatabiopsien

Filson CP, Cancer 2016, 122:884

42

Slide 1
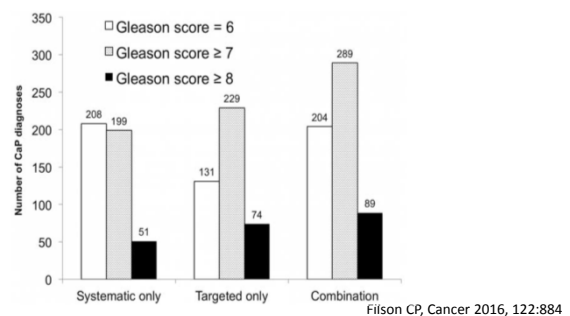
Neue App Risiko-Bestimmung

TOTAL PSA	6.2 ng/ml
F/T PSA RATIO	29%
AGE	60
FAMILY HISTORY	Nein
DRE	Unauff.
P-VOLUME	75

CALCULATE

Slide 2

Prostate Health Index

PHI <24:

- Avoids 24-36%   benign biopsy
- Avoids 17-24%   biopsy in men with low risk Pca
- Miss   4 %   significant/aggressive PCA

De la Calle J Urol,2015

Slide 3

Europe uses diagnostic Risk Calculator PSA >3.0

	Rotterdam	Swiss
Cutoff	12.5%	15%
	11%	
Spared biopsies	33%	33%
	17%	
AUC		
overall	0.79	0.74
high grade	0.86	0.89

Slide 4

Prognostic ProstateCheck-App calculator from Swiss ERSPC Aarau
(PSA <3; incl. free/total PSA)

Screening population
- Started   1998
- FU, 4 screening rounds   12 years
- <3.0 PSA ng/ml   4350
- PSA compliance   96%
- Bx compliance   92%