# Update on the PROBASE Trial: Baseline PSA in Young Men (Aged 45 and 50)

Peter Albers, MD on behalf of PROBASE investigators

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Comprehensive Cancer Center of Integrated Oncology Aachen-Bonn-Cologne-Düsseldorf (CIO-ABCD)

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dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION
Research for a Life without Cancer

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no conflict of interest regarding this talk

# Opportunistic Screening leads to Overdiagnosis and Overtreatment

thebmj

## Current policies on early detection of prostate cancer create overdiagnosis and inequity with minimal benefit

Informed choice approaches lead to high rates of unsystematic PSA testing, especially among those least likely to benefit and most likely to be harmed, argue **Andrew Vickers and colleagues**

Andrew Vickers, [1] Frank O'Brien, [2] Francesco Montorsi, [3] David Galvin, [4] Ola Bratt, [5] Sigrid Carlsson, [1,5,6] James WF Catto, [7] Agne Krilaviciute, [8] Michael Philbin, [9] Peter Albers[8,10]

Vickers A et al. British Medical Journal 2023

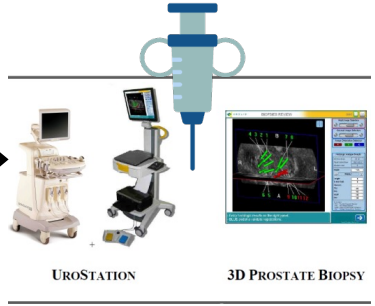
# „smart screening“

age

family history

PSA
+
Biomarker X
(STHLM3,
4k,…)

MRI




MRI-guided biopsy

# „smart screening“

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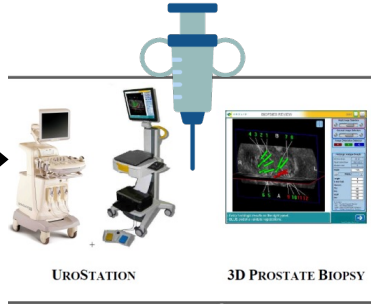
MRI




MRI-guided biopsy

The PROBASE trial

# PROBASE hypothesis: PSA in young men is most predictive

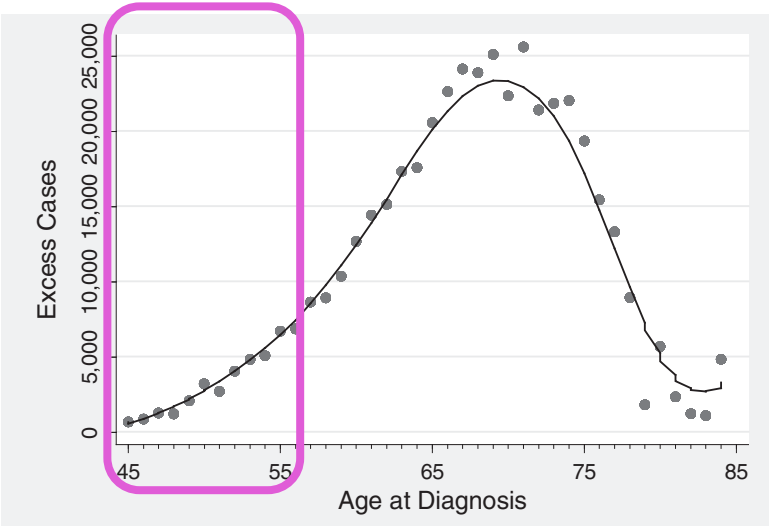



**Figure 1 Number of excess prostate cancer cases by age at diagnosis 1987 to 1995.** The 95% confidence interval is extremely narrow and is not shown here.

**excess cases of PC by uncritical use of PSA:**

| Age | |
|---|---|
| 45-49 | 1.3% |
| 50-54 | 5.7% |
| 65-69 | 58.1% |
| 70-74 | 83.3% |

Vickers A et al. British Medical Journal 2014

# PROBASE

Die Deutsche Prostatakrebs Screening Studie

Risk-adapted **pro**state cancer (PCa) early detection study based on a “**base**line” PSA value in young men – a prospective multicenter randomized trial (**PROBASE**)

**> 46,000 participants**

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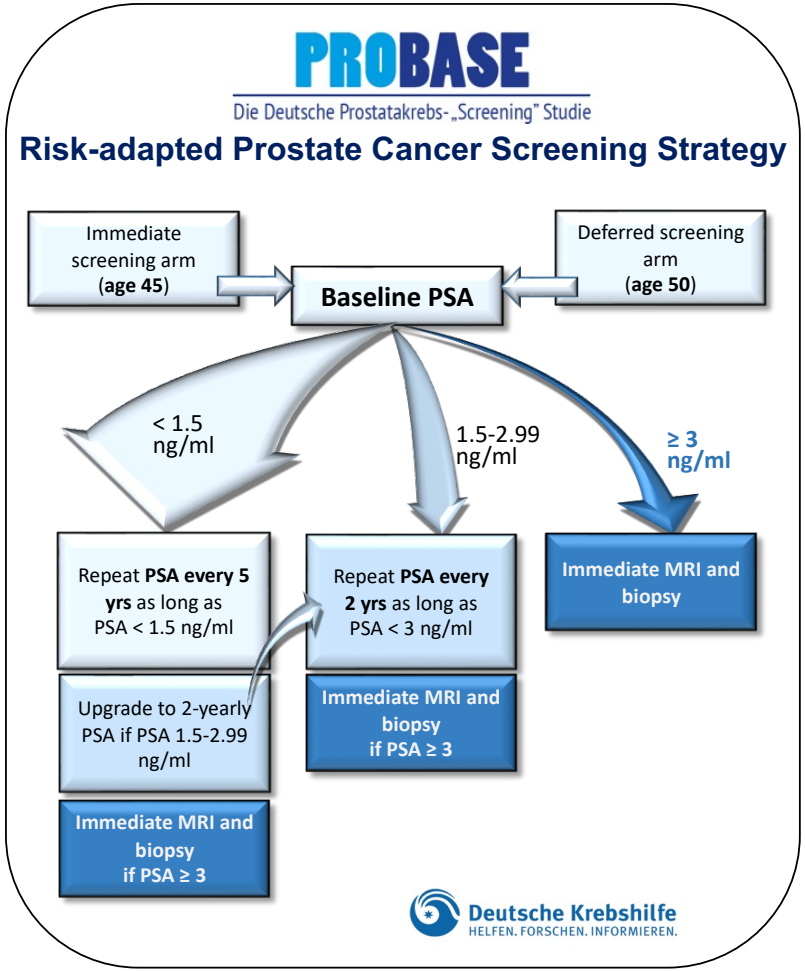
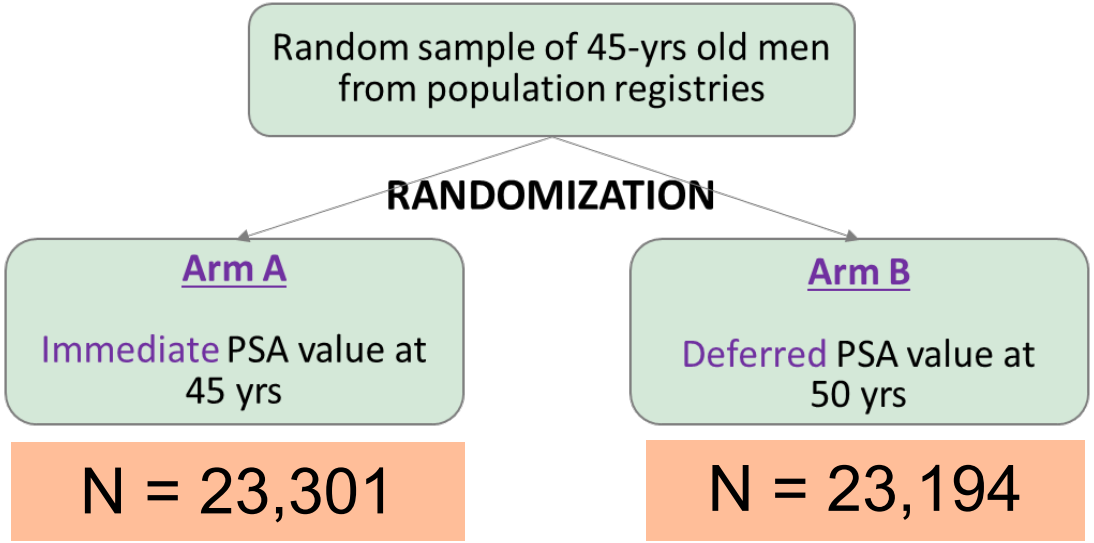



## PROBASE trial (N = > 46,000 participants)

Arsov C et al. Int J Cancer 2022 / Krilaviciute A et al. Int J Cancer 2023

# PROBASE accrual

PROBASE
Die Deutsche Prostatakrebs-„Screening" Studie




total accrual 46,495

Arsov C et al. Int J Cancer 2022

# PROBASE Study Sites

PROBASE
Die Deutsche Prostatakrebs-„Screening" Studie

**Düsseldorf** **N = 12777**
Peter Albers
Jale Lakes
Jan Philipp Radtke

**Heidelberg** **N = 9509**
Jürgen Debus
Stefan Koerber

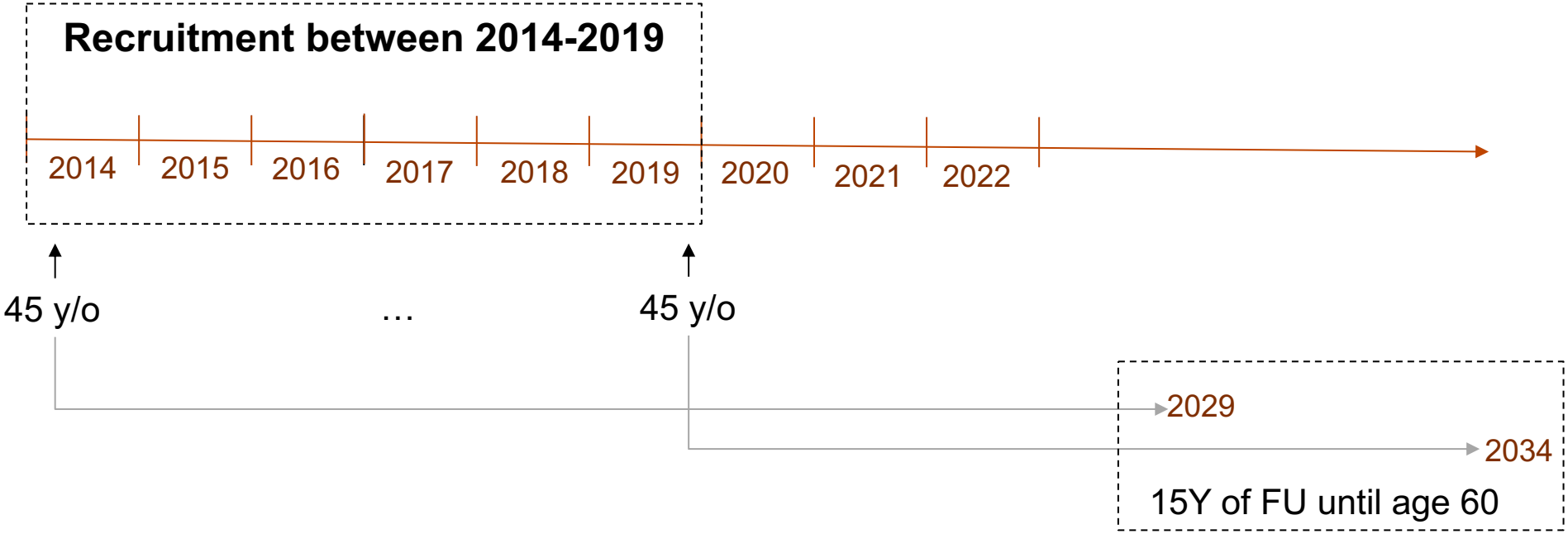
dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Rudolf Kaaks
Peter Albers
Nikolaus Becker
Agne Krilaviciute
Axel Benner

**Hannover** **N = 10860**
Markus Kuczyk
Nina Harke
Inga Peters

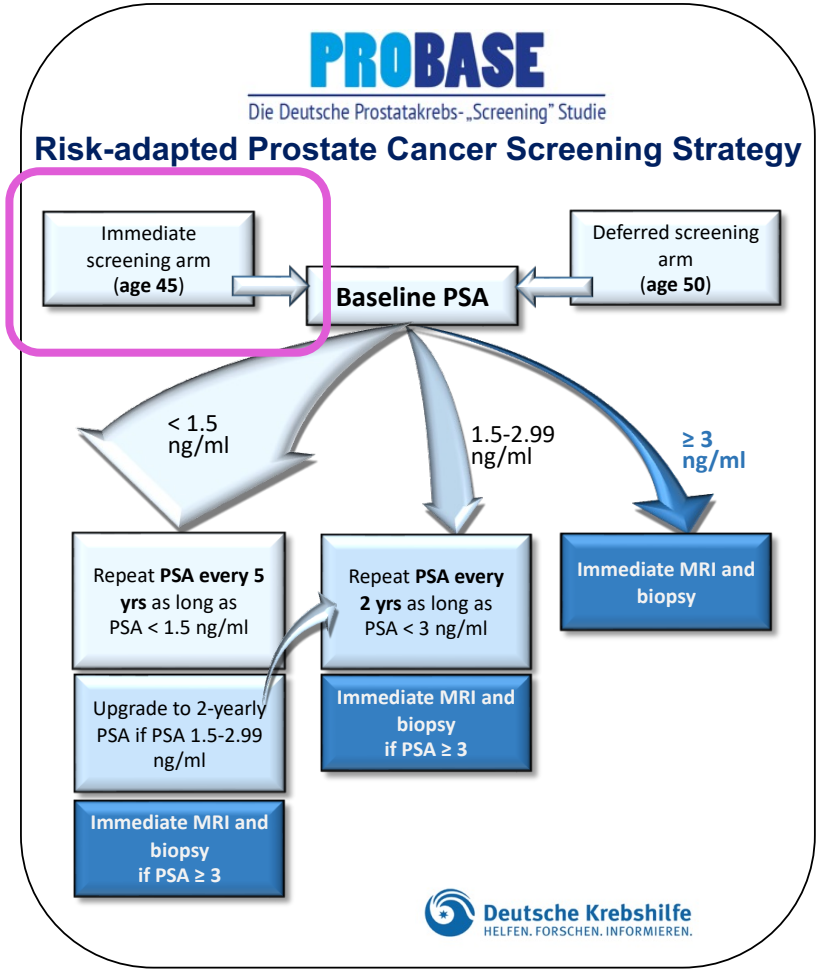
**Munich** **N = 13496**
Jürgen Gschwend
Kathleen Herkommer

PROBASE
Die Deutsche Prostatakrebs-„Screening" Studie




*composite endpoint = non-inferiority in the sensitivity to detect metastasis and superiority in the specificity to detect PCa
null hypothesis: rTPF(B,A) ≥ 1.2 , i.e. the sensitivity in study arm B regarding metastatic PCa is at least 20% higher than in study arm A. rFPF(A,B) ≥ 1.0, i.e. the specificity in study arm B is not superior to that in study arm A.

**prostate cancer metastases***



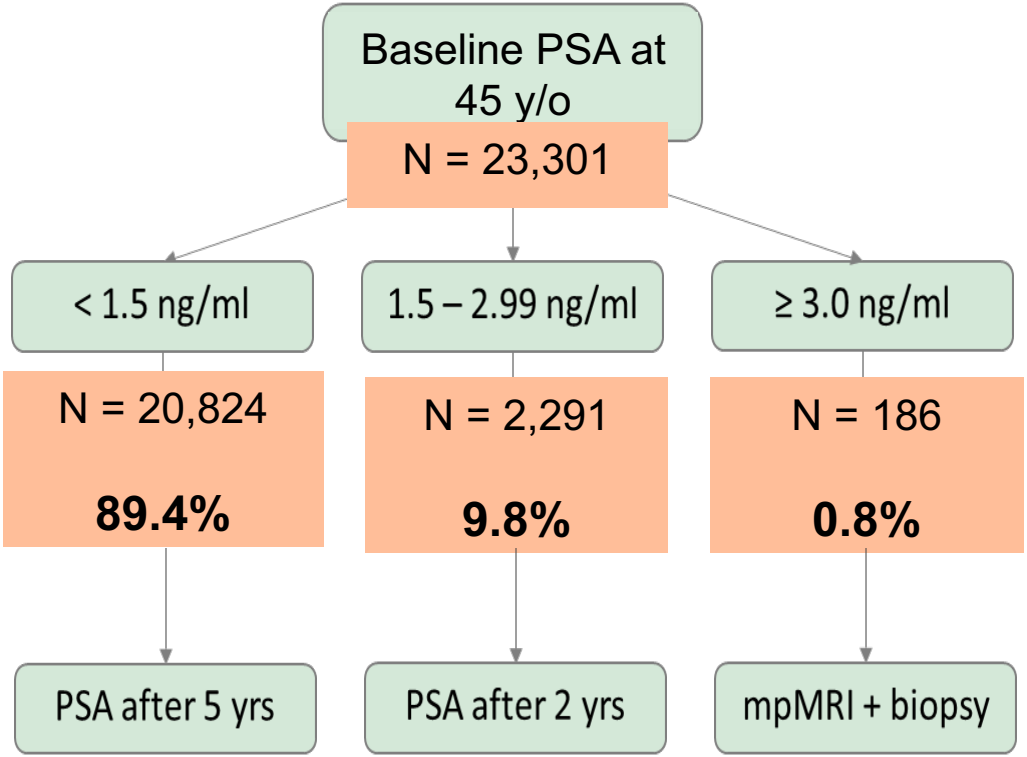

## Immediate screening arm:

## baseline PSA at 45 yrs

Arsov C et al. Int J Cancer 2022 / Krilaviciute A et al. Int J Cancer 2023

# Results of PSA screening at age 45 – immediate screening

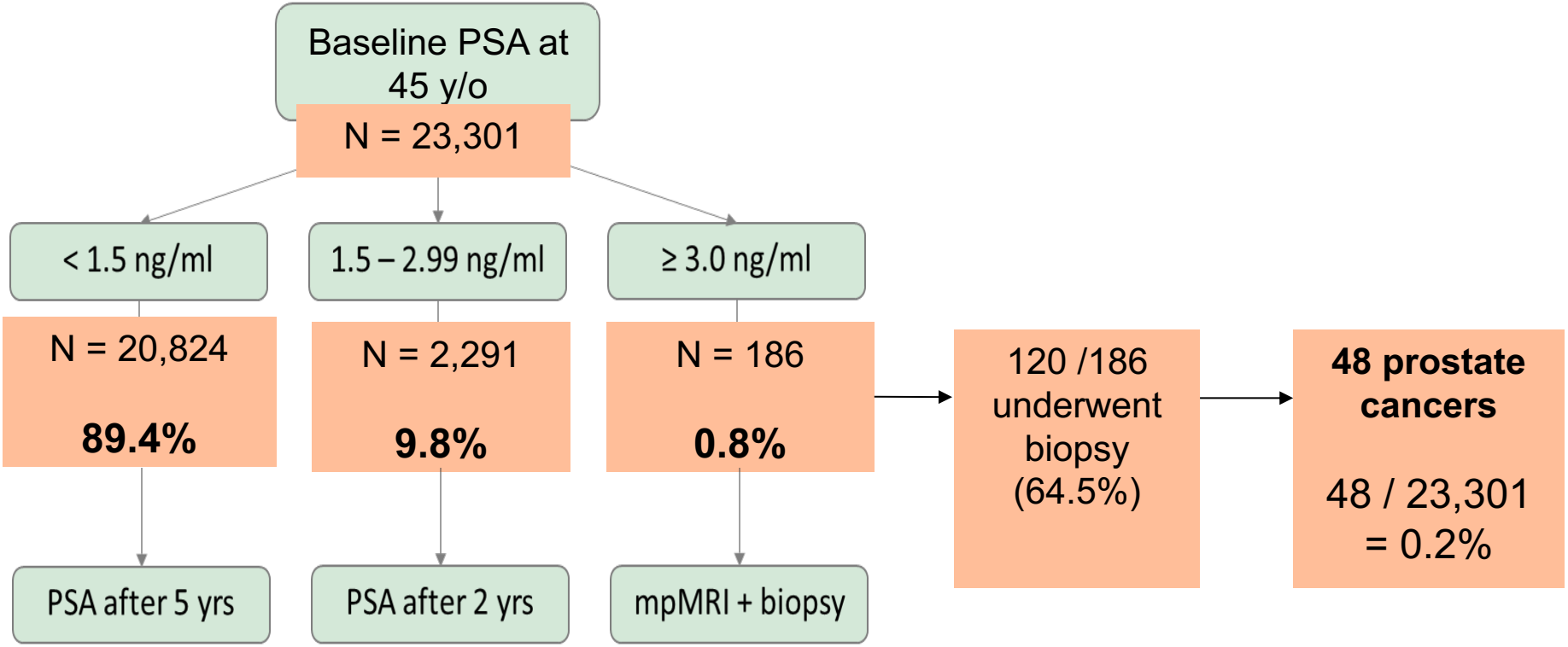
PROBASE
Die Deutsche Prostatakrebs-„Screening" Studie




Arsov C et al. Int J Cancer 2022

# Results of PSA screening at age 45 – immediate screening

PROBASE
Die Deutsche Prostatakrebs-„Screening" Studie

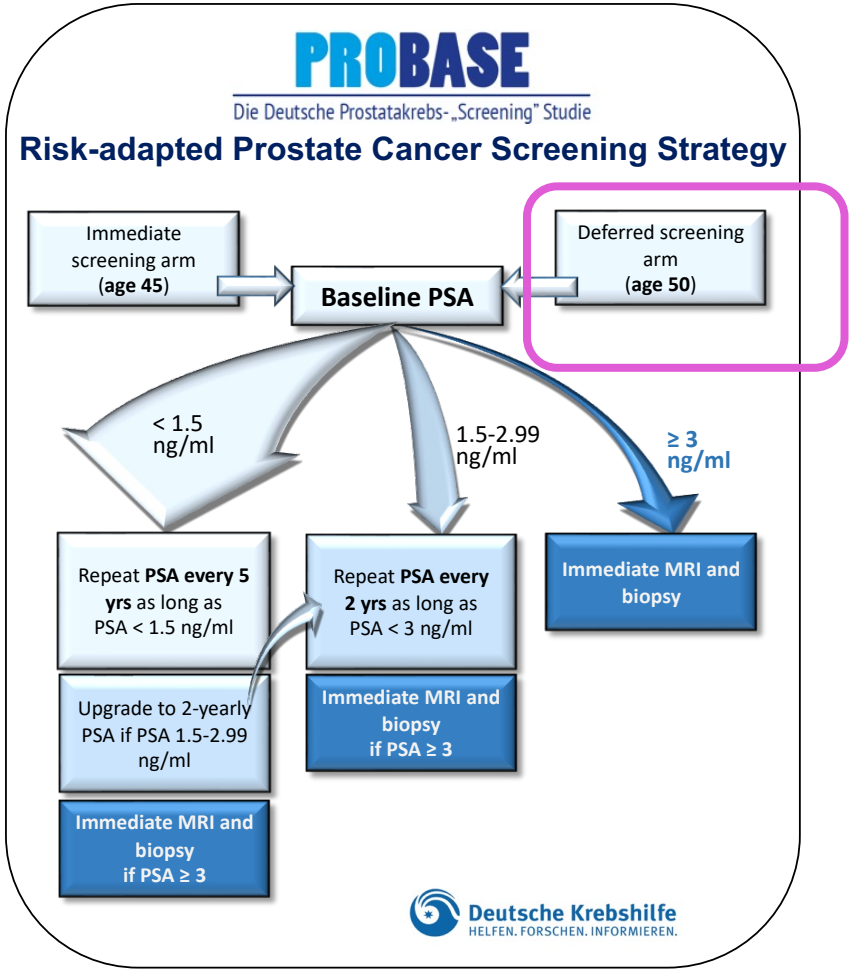



Arsov C et al. Int J Cancer 2022

# Biopsy results of the 1st screening round

| (C) Results of histopathological analysis of biopsies | | | |
|---|---|---|---|
| ISUP 1 | 15 | 31% | 91% |
| ISUP 2 | 29 | 60% | |
| ISUP 3 | 2 | | 9% |
| ISUP 4 | 1 | | |
| ISUP 5 | 1 | | |
| Total | 48 | | |
| | 100% | | |

Arsov C et al. Int J Cancer 2022




**Deferred screening arm:**

**baseline PSA at 50 yrs**

**offer: DRE**

**(statutory German early detection)**

Arsov C et al. Int J Cancer 2022 / Krilaviciute A et al. Int J Cancer 2023

# Digital Rectal Examination (DRE) is not a useful screening test

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EUROPEAN UROLOGY ONCOLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

## Digital Rectal Examination Is Not a Useful Screening Test for Prostate Cancer

*Agne Krilaviciute [a,†], Nikolaus Becker [a,†], Jale Lakes [b], Jan Philipp Radtke [b], Markus Kuczyk [c], Inga Peters [c,‡], Nina N. Harke [c], Jürgen Debus [d,e], Stefan A. Koerber [d], Kathleen Herkommer [f], Jürgen E. Gschwend [f], Valentin H. Meissner [f], Axel Benner [g], Petra Seibold [a], Glen Kristiansen [h], Boris Hadaschik [i,j], Christian Arsov [b,§], Lars Schimmöller [k], Frederik Lars Giesel [l], Gerald Antoch [k], Marcus Makowski [m], Frank Wacker [n], Heinz-Peter Schlemmer [o], Rudolf Kaaks [p,||], Peter Albers [a,b,||,*]*

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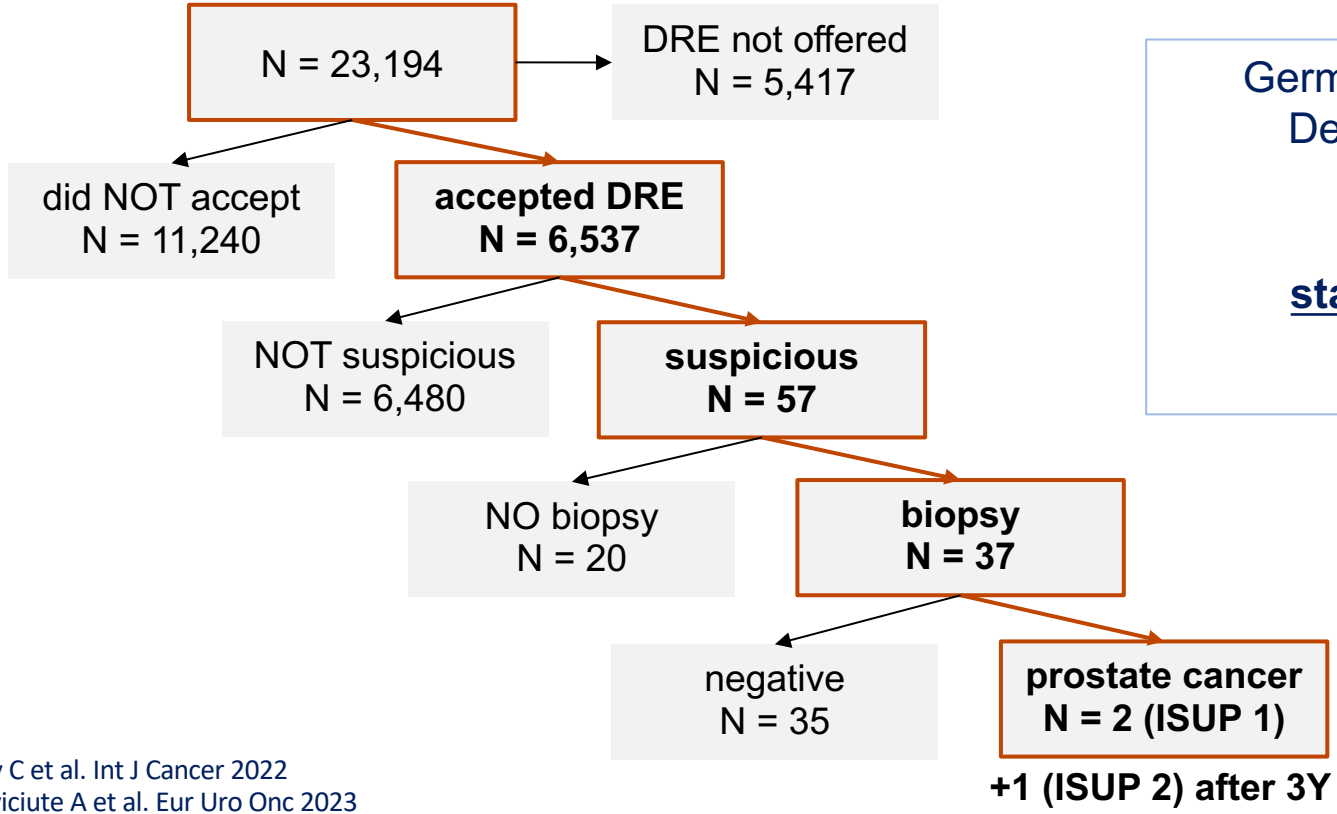
Krilaviciute A et al. Eur Urol Onc 2023

dkfz.

# Digital Rectal Examination (DRE)

PROBASE
Die Deutsche Prostatakrebs-„Screening" Studie




German Statutory Early Detection Program

**annual DRE**

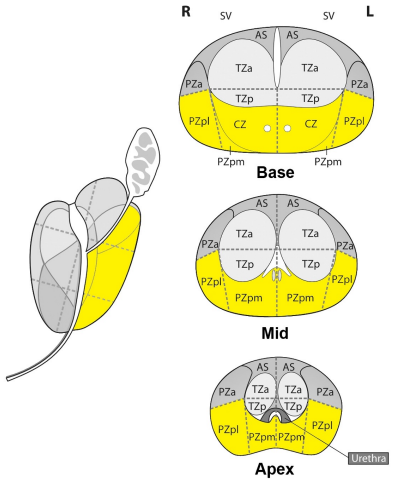
**starting at age 45**

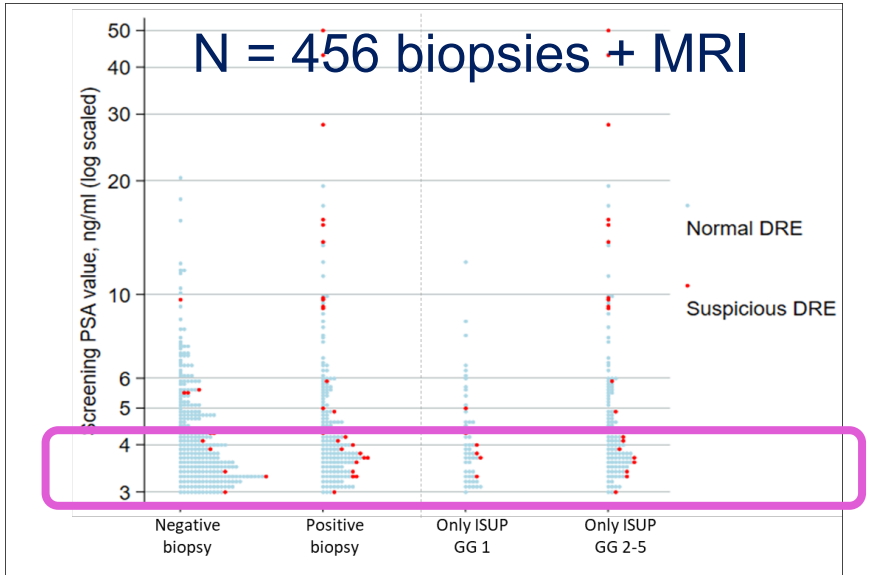
since 1971

**Cancer detection rate**
**3 / 6,537 = 0.05%**

Arsov C et al. Int J Cancer 2022
Krilaviciute A et al. Eur Uro Onc 2023

# DRE in men with histologically confirmed tumors

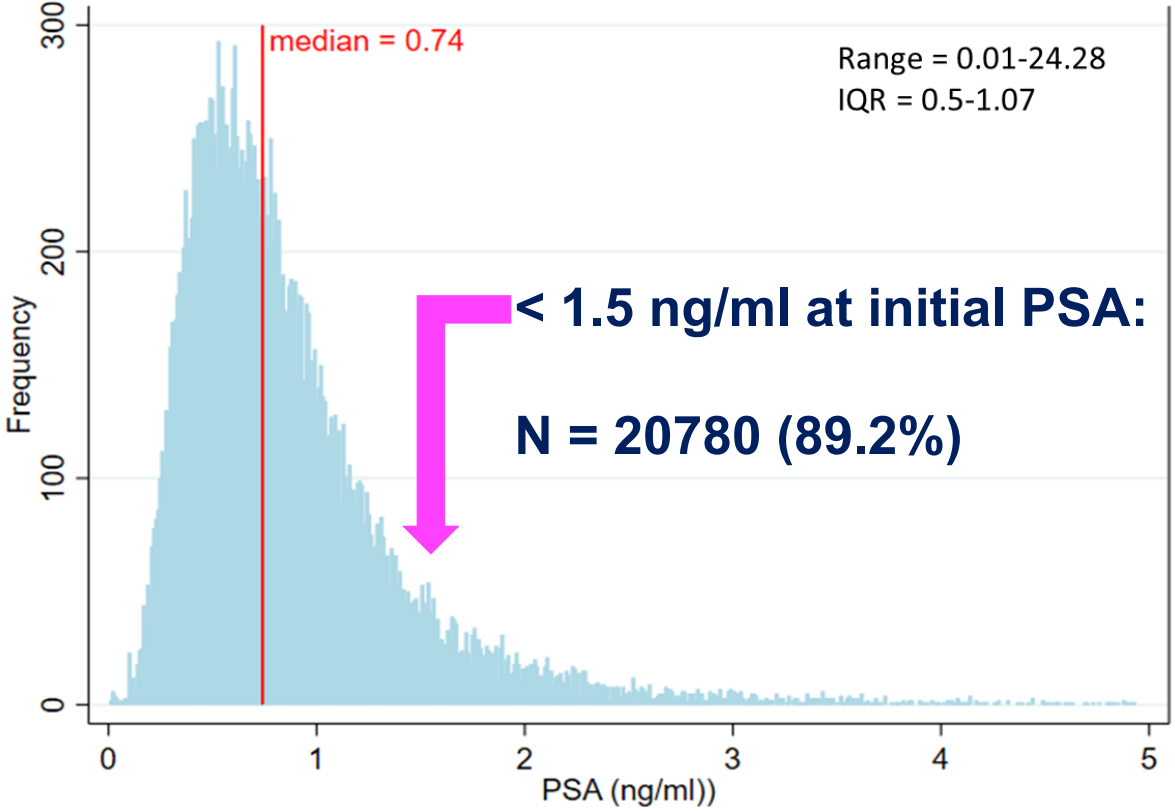



**Tumor not palpable: 86% (154 / 180)**

Krilaviciute A et al. – Eur Urol Onc 2023

# Ongoing Analysis



- **PSA at age 45:** 1% at high risk (confirmed PSA > 3 ng/ml)

  40% of whom will have prostate cancer

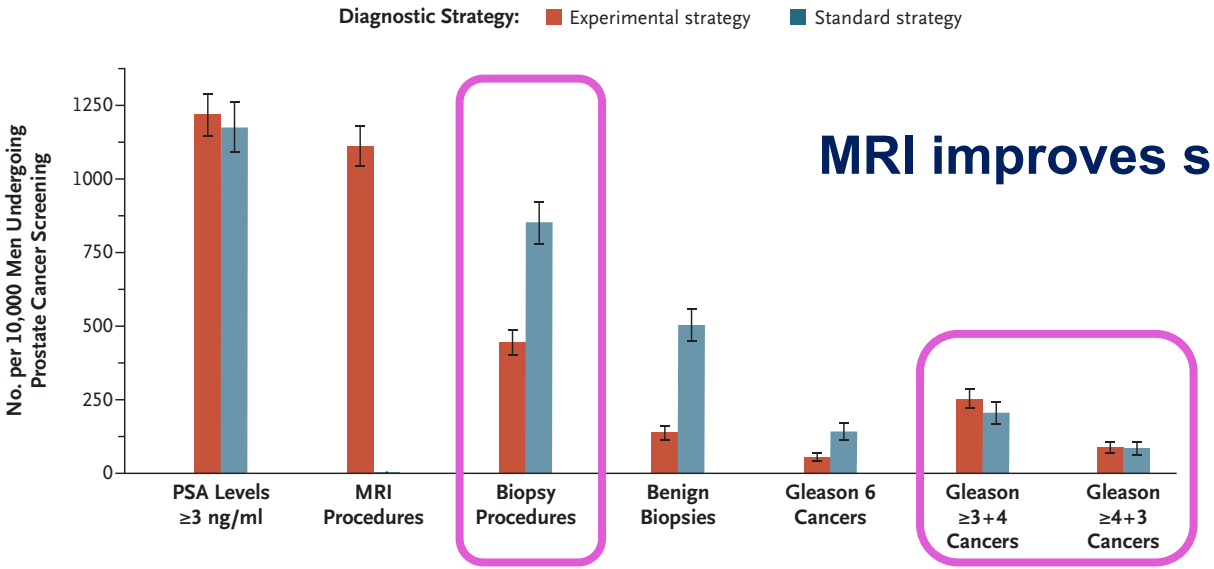
  90% of screen-detected PC are low grade

  90% of men are at low risk (5 yrs confirmation)

- **questions:** what is the additional value of MRI to PSA?
  what is the value of genetic risk factors?
  are there other blood/urine-based biomarkers?

# Research in Imaging

# STHLM3-MRI Trial (Sweden)




## MRI improves specificity

| | PSA Levels ≥3 ng/ml | MRI Procedures | Biopsy Procedures | Benign Biopsies | Gleason 6 Cancers | Gleason ≥3+4 Cancers | Gleason ≥4+3 Cancers |
|---|---|---|---|---|---|---|---|
| Experimental Strategy — no. | 1221 | 1112 | 444 | 138 | 54 | 252 | 88 |
| Standard Strategy — no. | 1175 | 2 | 853 | 504 | 142 | 206 | 84 |
| Absolute Difference (95% CI) — percentage points | 0.5 (–0.7 to 1.6) | — | –4.1 (–5.0 to –3.2) | –3.7 (–4.3 to –3.0) | –0.9 (–1.2 to –0.5) | 0.5 (–0.1 to 1.0) | 0.0 (–0.3 to 0.4) |
| Relative Difference (95% CI) | 1.04 (0.94 to 1.14) | — | 0.52 (0.45 to 0.60) | 0.27 (0.22 to 0.34) | 0.38 (0.26 to 0.55) | 1.22 (0.97 to 1.55) | 1.05 (0.72 to 1.54) |

Eklund M et al. N Engl J Med 2021;385:908-20.

# STHLM3-MRI Trial (Sweden)

## MRI improves specificity and MRI´s can be reduced by STHLM3

| | Elevated tests in 10 000 screened men (95% CI) | Number of procedures (95% CI) | | Prostate biopsy outcome (95% CI) | | | |
|---|---|---|---|---|---|---|---|
| | | MRI | Biopsy | Benign biopsy | Low-grade cancer | Clinically significant cancer | High-grade cancer |
| Standard biopsies in men with PSA of ≥3 ng/mL | 1175 (1088–1264) | 2 (0–6) | 853 (775–925) | 504 (447–561) | 142 (112–175) | 206 (166–245) | 84 (59–108) |
| MRI-targeted biopsies in men with PSA of ≥3 ng/mL | 1221 (1145–1293) | 1112 (1042–1181) | 444 (398–489) | 138 (112–164) | 54 (39–70) | 252 (219–288) | 88 (68–109) |
| MRI-targeted biopsies in men with Stockholm3 of ≥0·11 | 1342 (1264–1416) | 1224 (1151–1296) | 526 (475–576) | 162 (134–190) | 66 (49–84) | 298 (263–337) | 95 (74–118) |
| MRI-targeted biopsies in men with Stockholm3 of ≥0·15 | 789 (652–1019) | 716 (587–927) | 409 (361–470) | 112 (89–143) | 45 (30–60) | 252 (223–294) | 88 (69–111) |

Data are n (95% CI). The table shows results from the intention-to-treat analysis. Low-grade prostate cancer was defined as a Gleason score of 3 + 3 clinically significant prostate cancer was defined as a Gleason score of 3 + 4 or higher, and high-grade prostate cancer was defined as a Gleason score of 4 + 3 or higher. PSA=prostate-specific antigen.

***Table 3:*** **Number of men with elevated PSA or Stockholm3 tests, procedures done, and detected cancers in 10 000 men undergoing blood testing for detection of prostate cancer in a screening-by-invitation setting**

Nordström T et al. Lancet Oncol 2021;22:1240-49.

# Göteborg-2 Trial (Sweden)

**Table 2.** Prostate Cancer Detection Analyses and Outcomes.

| Analysis and Outcome | Reference Group (N = 5994)* | | Experimental Group (N = 11,986) |
|---|---|---|---|
| | MRI-Targeted and Systematic Biopsy | Systematic Biopsy | MRI-Targeted Biopsy |
| **Primary analysis†** | | | |
| PSA ≥3 ng/ml — no. (%) | 405 (6.8) | 405 (6.8) | 796 (6.6) |
| Biopsy indication — no. (%) | 405 (6.8) | 405 (6.8) | 335 (2.8) |
| Biopsy performed and PSA ≥3 ng/ml — no. (%) | 348 (5.8) | 347 (5.8) | 301 (2.5)‡ |
| Any prostate cancer — no. (%) | 140 (2.3) | 131 (2.2) | 176 (1.5) |
| Clinically insignificant cancer — no. (%) | 72 (1.2) | 73 (1.2) | 66 (0.6) |
| Clinically significant cancer — no. (%) | 68 (1.1) | 58 (1.0) | 110 (0.9) |
| Clinically insignificant cancer, with correction for missing biopsy data — no. (%)¶ | 80 (1.3) | 81 (1.4) | 75 (0.6) |

## MRI improves specificity

Hugosson J et al. N Engl J Med 2022;387:2126-31

# MRT Analysis in PROBASE

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EUROPEAN UROLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer
*Editorial by XXX on pp. x-y of this issue*

## Multiparametric Magnetic Resonance Imaging in Prostate Cancer Screening at the Age of 45 Years: Results from the First Screening Round of the PROBASE Trial

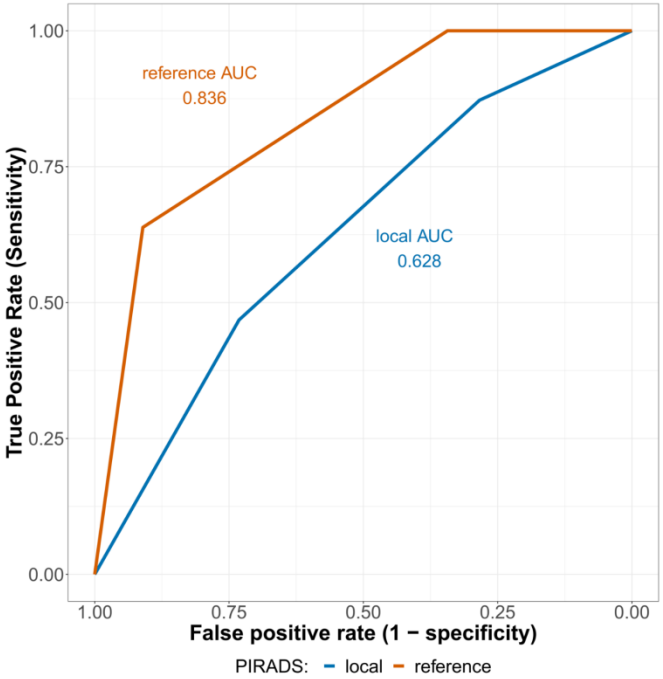
*Matthias Boschheidgen [a], Peter Albers [b,c], Heinz-Peter Schlemmer [d], Susanne Hellms [e], David Bonekamp [d], Andreas Sauter [f], Boris Hadaschik [g], Agne Krilaviciute [c], Jan Philipp Radtke [b], Petra Seibold [c], Jale Lakes [b], Christian Arsov [b,h], Jürgen E. Gschwend [i], Kathleen Herkommer [i], Marcus Makowski [f], Markus A. Kuczyk [j], Frank Wacker [e], Nina Harke [j], Jürgen Debus [k], Stefan A. Körber [k], Axel Benner [l], Glen Kristiansen [m], Frederik L. Giesel [n], Gerald Antoch [a,o], Rudolf Kaaks [p], Nikolaus Becker [c], Lars Schimmöller [a,q,*]*

Boschheidgen et al. Eur Urol 2023

# PROBASE: improved cancer detection at age 45 by PIRADS 4-5

…but only with expert reading

(> 10,000 readings per expert*)




*Lars Schimmöller
(radiologist, Düsseldorf University)
*Heinz-Peter Schlemmer
(radiologist, German Cancer Research Center, Heidelberg)

in submission

# MRT Analysis in PROBASE

**Table 3 – Comparison of PC detection by PI-RADS score on local and reference reading**

| Parameter | PI-RADS score (*n*) | | | | Total |
|---|---|---|---|---|---|
| | 1–2 | 3 | 4 | 5 | |
| **Local reading** | | | | | |
| PC negative | 19 | 30 | 17 | 1 | 67 |
| PC positive | 6 | 19 | 15 | 7 | 47 |
| csPC positive | 5 | 10 | 13 | 5 | 33 |
| GG 1 | 1 | 9 | 2 | 2 | 14 |
| GG 2 | 5 | 8 | 13 | 3 | 29 |
| GG 3–5 | 0 | 2 | 0 | 2 | 4 |
| Total | 25 | 49 | 32 | 8 | 114 |
| **Reference reading** | | | | | |
| PC negative | 23 | 38 | 6 | 0 | 67 |
| PC positive | 0 | 17 | 20 | 10 | 47 |
| csPC positive | 0 | 7 | 17 | 9 | 33 |
| GG 1 | 0 | 10 | 3 | 1 | 14 |
| GG 2 | 0 | 6 | 16 | 7 | 29 |
| GG 3–5 | 0 | 1 | 1 | 2 | 4 |
| Total | 23 | 55 | 26 | 10 | 114 |

csPC = clinically significant PC; GG = International Society of Urological Pathology grade group; PC = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System, v2.1

## Radiology Report

| | local | expert |
|---|---|---|
| PIRADS 1-2 with tumor | 6 | 0 |
| PIRADS 3 | 43% | 48% |

Boschheidgen et al. Eur Urol 2023

# MRT Analysis in PROBASE

**Table 4 – PI-RADS performance for detection of csPC (ISUP ≥ 2) on local and reference reading according to two different biopsy cutoff values**

| Parameter | Biopsy cutoff | |
|---|---|---|
| | PI-RADS ≥3 | PI-RADS ≥4 |
| **Local reading** | | |
| Indication for biopsy, % (*n*) | 78 (89) | 35 (40) |
| Sensitivity, % (95% CI) | 85 (68–95) | 55 (36–72) |
| Specificity, % (95% CI) | 25 (16–36) | 73 (62–82) |
| PPV, % (95% CI) | 32 (22–42) | 45 (29–62) |
| NPV, % (95% CI) | 80 (59–93) | 80 (69–88) |
| Accuracy, % (95% CI) | 42 (33–52) | 68 (58–76) |
| **Reference reading** | | |
| Indication for biopsy, % (*n*) | 80 (91) | 32 (36) |
| Sensitivity, % (95% CI) | 100 (89–100) | 79 (61–91) |
| Specificity, % (95% CI) | 28 (19–40) | 88 (78–94) |
| PPV, % (95% CI) | 36 (26–47) | 72 (59–83) |
| NPV, % (95% CI) | 100 (85–100) | 91 (84–95) |
| Accuracy, % (95% CI) | 49 (40–59) | 85 (77–91) |

CI = confidence interval; PI-RADS = Prostate Imaging Reporting and Data System v2.1; PPV = positive predictive value; NPV = negative predictive value.

## Detection of ISUP GG ≥ 2 (experts)

| | cut-off P 3 | | cut-off P 4 |
|---|---|---|---|
| sensitivity | 100% | | 79% |
| specificity | 28% | → | 88% |
| accuracy | 49% | → | 85% |

- PIRADS 3 cut-off: all csPCs detected, 20% less bx
- PIRADS 4 cut-off: 7/49 csPCs missed (6 x GG2, 1 x GG 3), 68% less bx

Boschheidgen et al. Eur Urol 2023

# Research in Familial Prostate Cancer

Deutsche Krebshilfe
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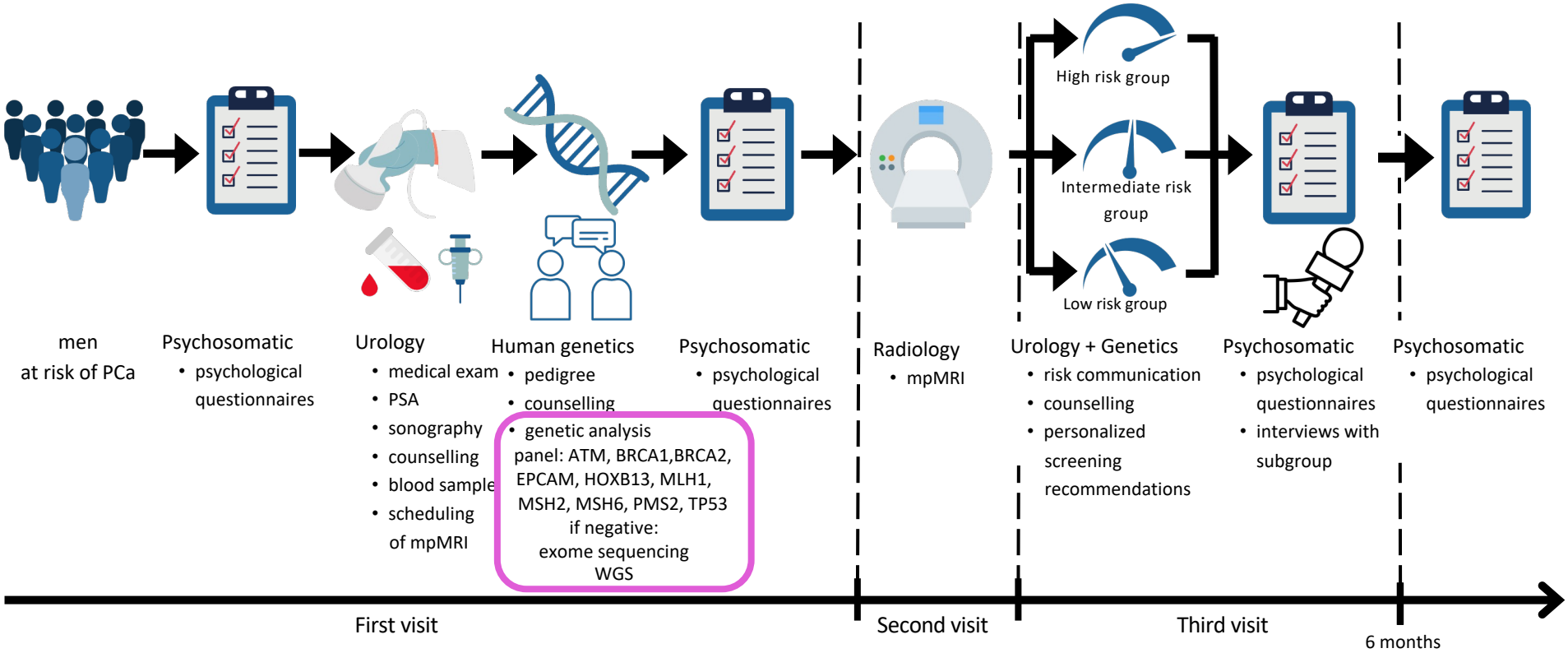
PROFAM-RISK
Prevention Center for Familial Prostate Cancer

# ProFam-Risk: personalized genetic diagnostics in familial PC




profamrisk@med.uni-duesseldorf.de

## PROBASE summary 2023

- confirmation of PSA > 3 ng/ml makes sense
- risk categories are confirmed with 5-yrs follow-up
  (< 1.5 ng/ml = low risk = 90% of population at age 50)
- adherence to suggested f/u investigations is high (75-80%)
- MRI reading is difficult at age 45 with high rates of PIRADS 3
- all in all: risk-adapted concept works !

# Thanks to the participants and the PROBASE team

**Düsseldorf**
Peter Albers
Jale Lakes
Jan Philipp Radtke

**Hannover**
Markus Kuczyk
Nina Harke
Inga Peters

**Heidelberg**
Jürgen Debus
Stefan Koerber

**München (TU)**
Jürgen Gschwend
Kathleen Herkommer

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HELFEN. FORSCHEN. INFORMIEREN.

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Agne Krilaviciute
Peter Albers
Nikolaus Becker
Rudolf Kaaks
Axel Benner

**Clinical Trials Office**
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Sabrina Stebe-Frick

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Thank you for your attention!

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**Further information on www.dkfz.de**