MRI to reduce overdiagnosis and overtreatment of prostate cancer

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appg on prostate cancer

Disclosures

Grant funding

- National Institute for Health Research
  - NIHR Research Professor
  - Current part-time secondment to DHSC
- Medical Research Council
- Movember
- Prostate Cancer UK (TRANSFORM co-lead)
- Cancer Research UK
- EAU Research Foundation

Commercial funding

- Trial funding Spectracure
- Proctor fees from Sonablate
- Speaker bureau fees from Astellas, Janssen, Bayer

Summary

- MRI is currently used in men with a high PSA
  - 1 in 3 avoid biopsy
  - Detects more clinically significant cancer
  - Halves overdiagnosis
- MRI for active surveillance
  - Reduces anxiety led treatment from 20% to 2%
  - Allows 2 in 3 men to avoid follow up biopsy
- MRI to allow small treatments for small cancers
  - Reduces urine leakage from 1 in 2 to 1 in 50
  - Allows 2 in 3 men to keep natural erections without tablets
- MRI in prostate cancer screening
  - Promising but more data needed

Overdiagnosis and over–treatment

- Overdiagnosis
  - Finding a cancer that would not have caused a problem
  - Many cancers found without MRI don’t need treatment
- Over-treatment
  - Treating a cancer that would not have caused a problem
  - But treatment can cause
    - Urine leakage
    - Bowel problems
    - Difficulties with sexual function

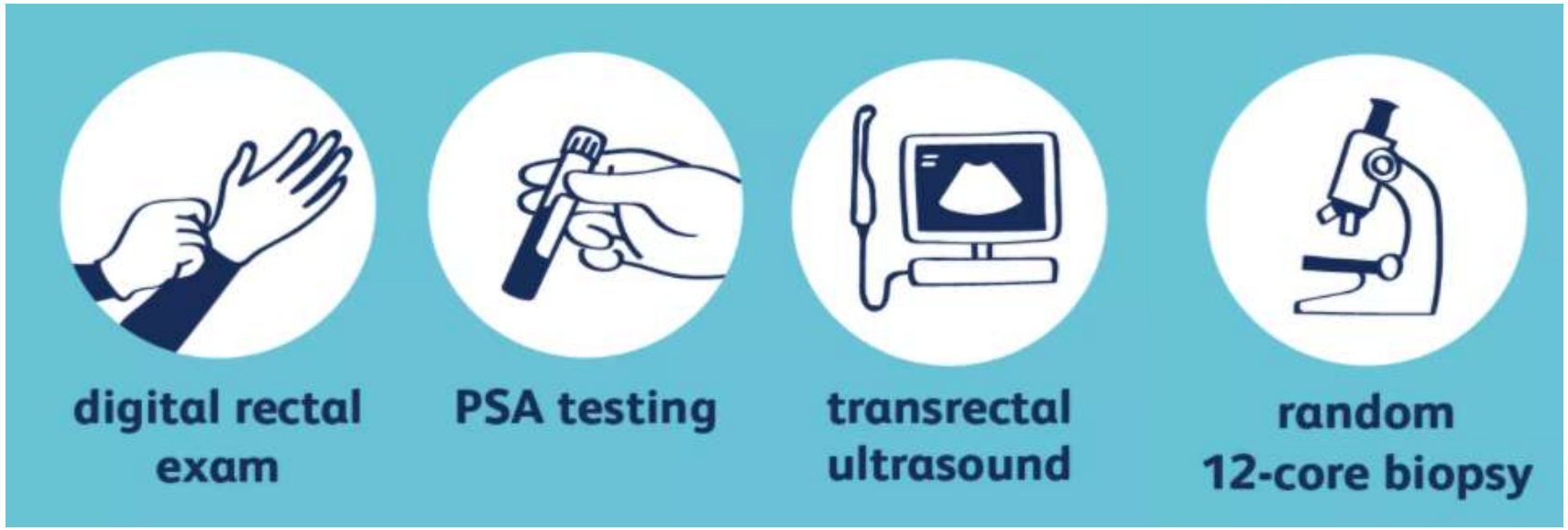
Even with robotic surgery, urine leakage and sexual function are a problem
TrueNTH UK 12 month data (2002 men)

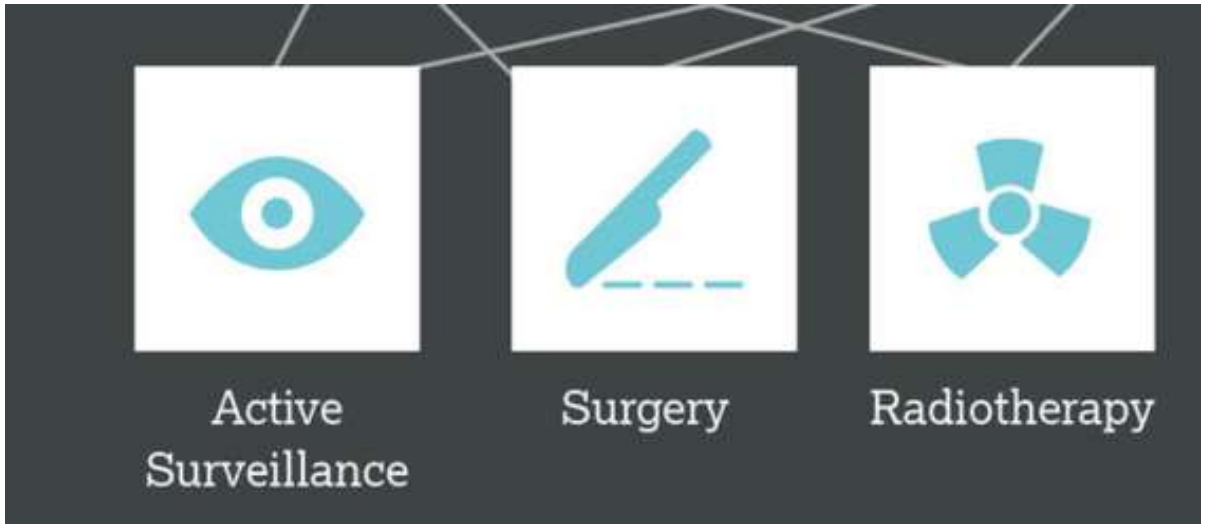
- In men without leakage or pads at baseline:
  - 1 in 3 need pads at 12/12
  - 1 in 2 pad free and leak free
  - Mean EPIC domain score 78
- In men with erections sufficient for intercourse with no assistance
  - 1 in 20 had erections without assistance
  - 1 in 10 had erections with medication or devices
  - 1 in 3 were trying medication or devices and did not have sufficient erections
  - Mean EPIC domain score 34.8

Prostate cancer diagnosis and treatment

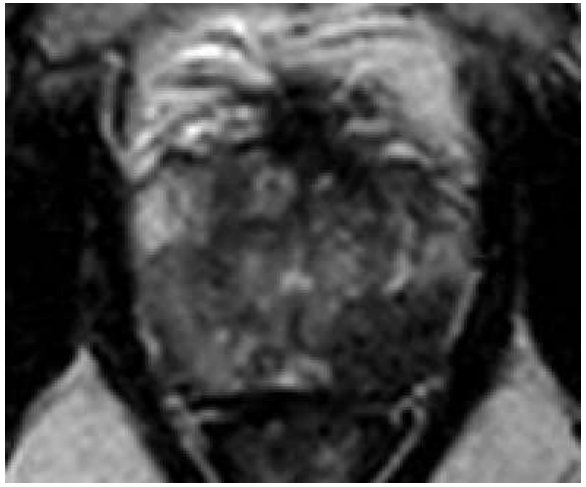
Risk of cancer to life and health

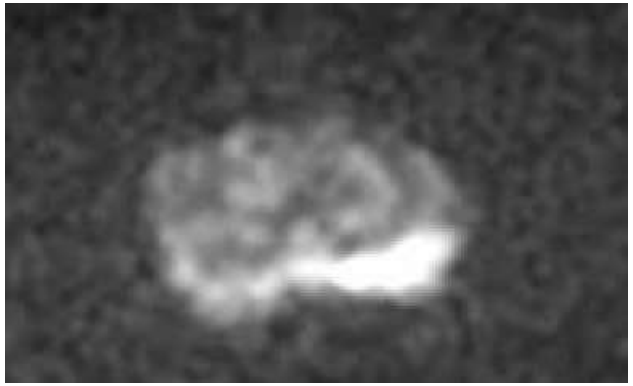
Risks of diagnosis and treatment

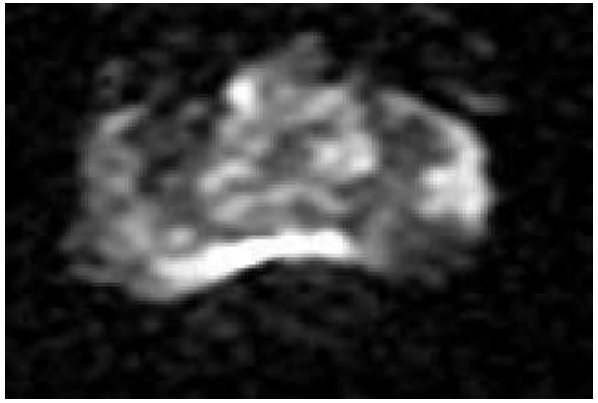

digital rectal exam
PSA testing
transrectal ultrasound
random 12-core biopsy

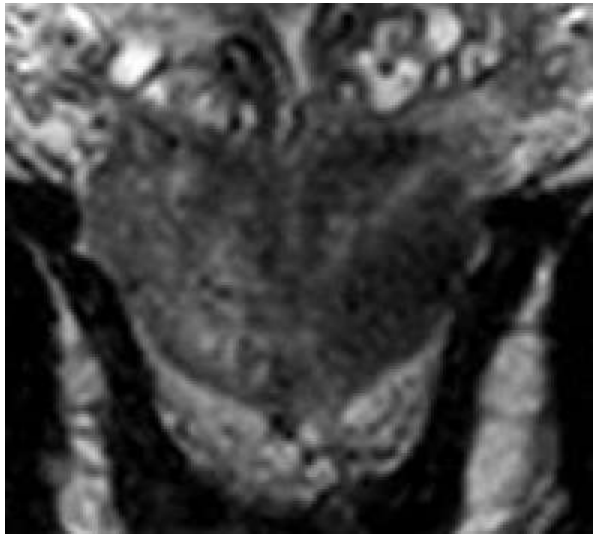

Active Surveillance
Surgery
Radiotherapy

Can MRI help us do better?









We become what we behold. We shape our tools and then our tools shape us.

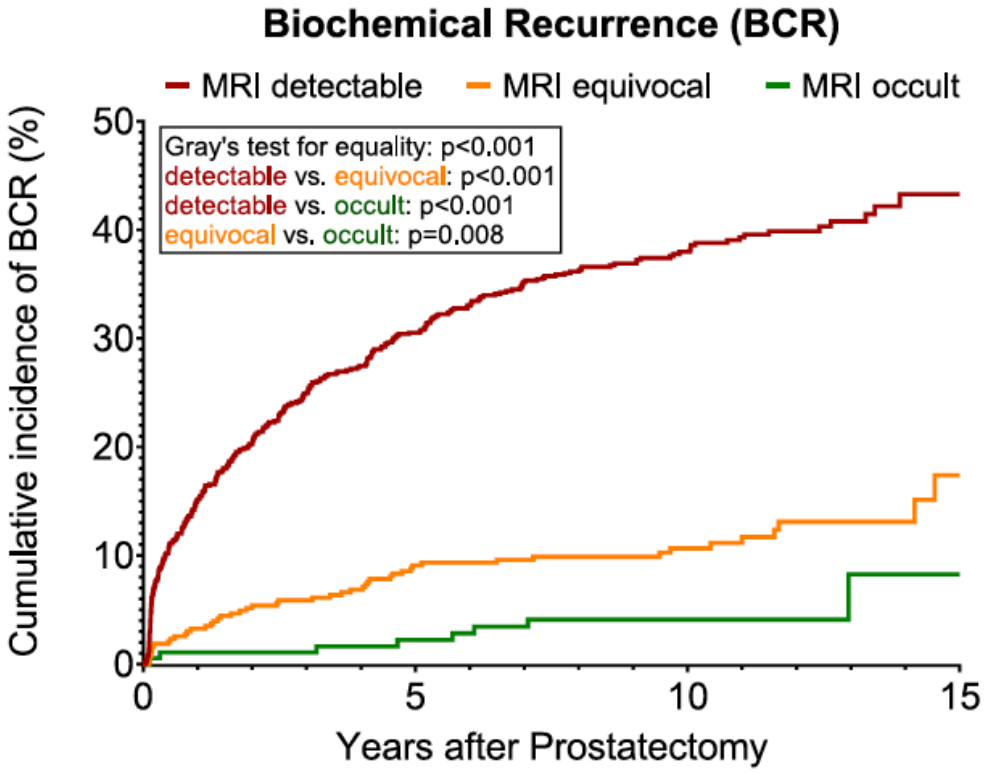
— Marshall McLuhan —

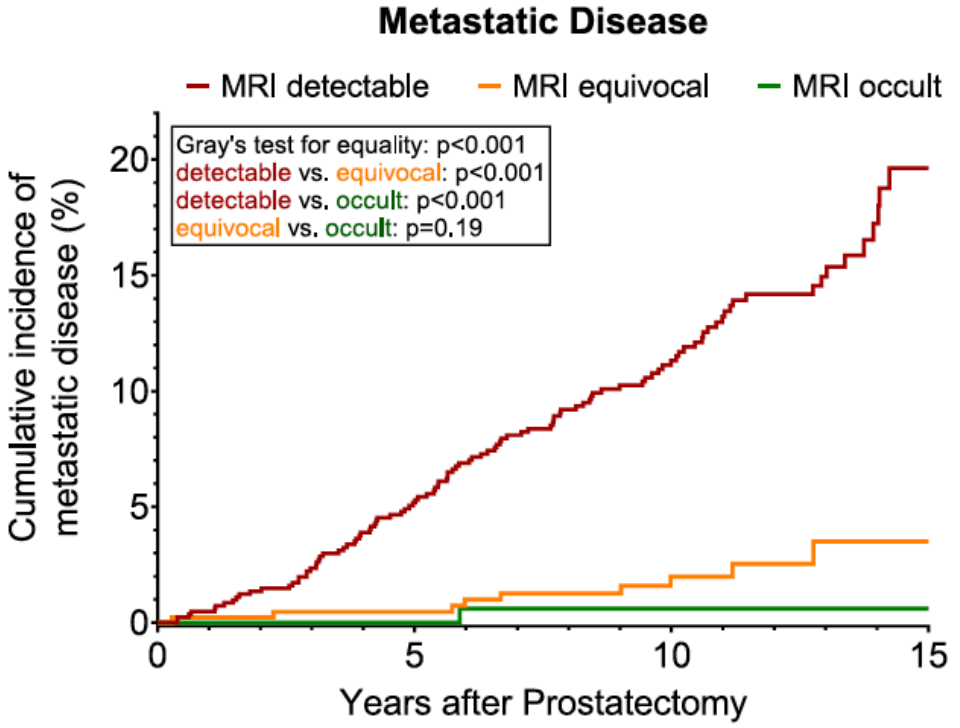
MRI-Detectability of Clinically Significant Prostate Cancer Relates to Oncologic Outcomes After Prostatectomy

Andreas G. Wibmer,[1] Robert A. Lefkowitz,[1] Yulia Lakhman,[1] Joshua Chaim,[1] Ines Nikolovski,[1] Evis Sala,[1,#] Samson W. Fine,[2] Timothy F. Donahue,[3] Michael W. Kattan,[4] Hedvig Hricak,[1,†] Hebert Alberto Vargas[1,†]

- 1449 patients having radical prostatectomy 2002-2006 with cs PCa
- MRI defined as visible (57%) vs equivocal (30%) vs occult (13%)
- Median follow up 11 years
- Outcomes assessed
  - Biochemical recurrence
  - Metastatic disease
  - Prostate cancer specific mortality
  - Overall mortality

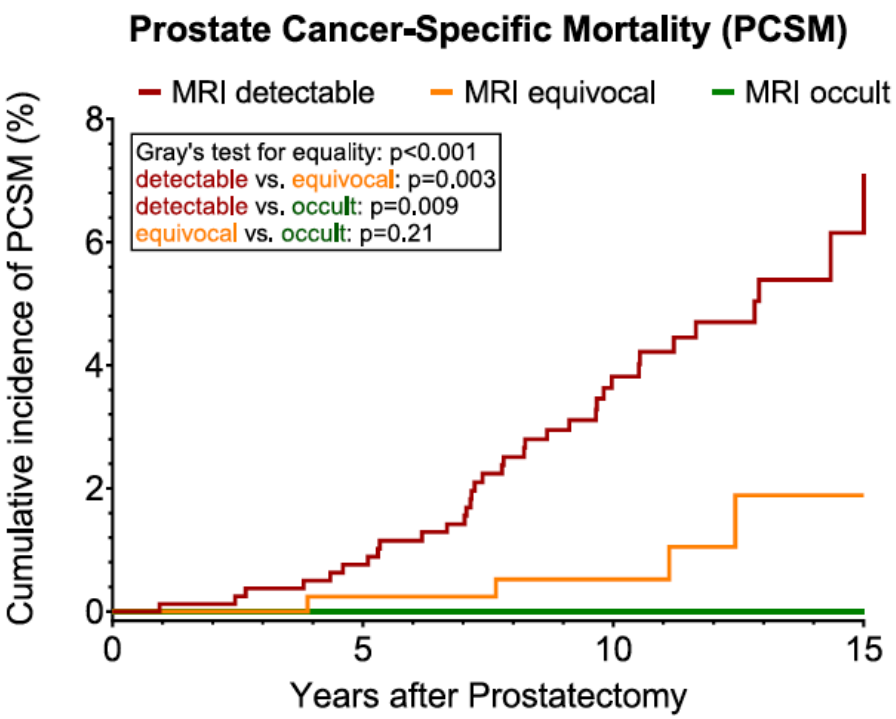
https://doi.org/10.1016/j.clgc.2022.04.001

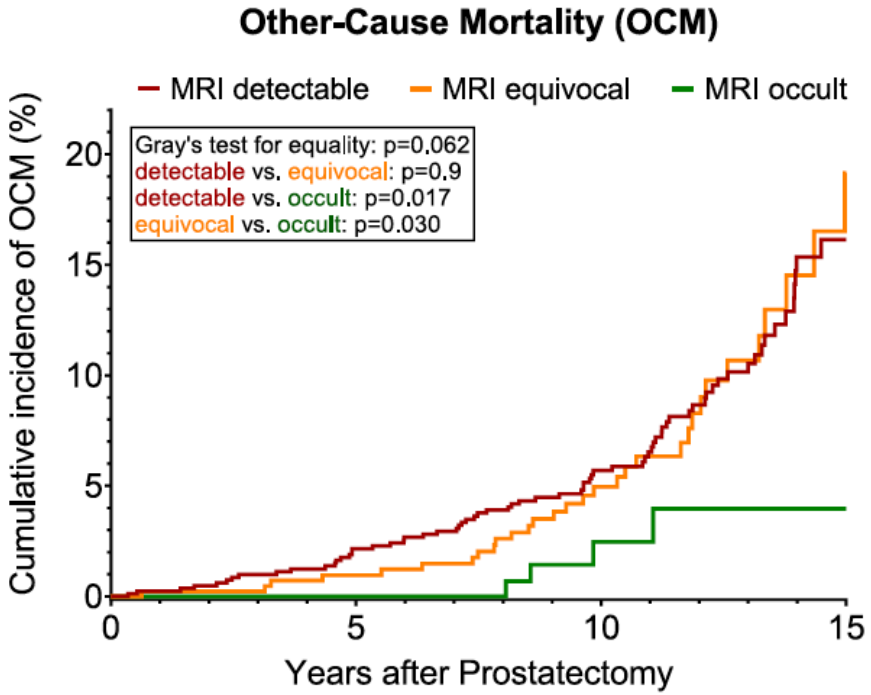




MRI visible disease: 40% have BCR and 20% have metastatic disease at 15 years

https://doi.org/10.1016/j.dgc.2022.04.001





MRI visible disease: 7% prostate cancer mortality at 15 years

https://doi.org/10.1016/j.clgc.2022.04.001

MRI to reduce over-diagnosis in those with a high PSA

Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study

Hashim U Ahmed, Ahmed El-Shater Bosaily*, Louise C Brown*, Rhian Gabe, Richard Kaplan, Mahesh K Parmar, Yolanda Collaco-Moraes, Katie Ward, Richard G Hindley, Alex Freeman, Alex P Kirkham, Robert Oldroyd, Chris Parker, Mark Emberton, and the PROMIS study group†*

- Multi centre UK NHS MRI study

- 576 men had
  - 1.5T MRI
  - 5mm transperineal prostate mapping biopsy
  - 12 core TRUS

- TPM (reference standard)
    - 230 (40%) – clinically significant cancer

- MRI sensitivity 93% (87% for Gleason grade group 2) vs TRUS 48%

www.thelancet.com **Published online January 19, 2017 http://dx.doi.org/10.1016/S0140-6736(16)32401-1**

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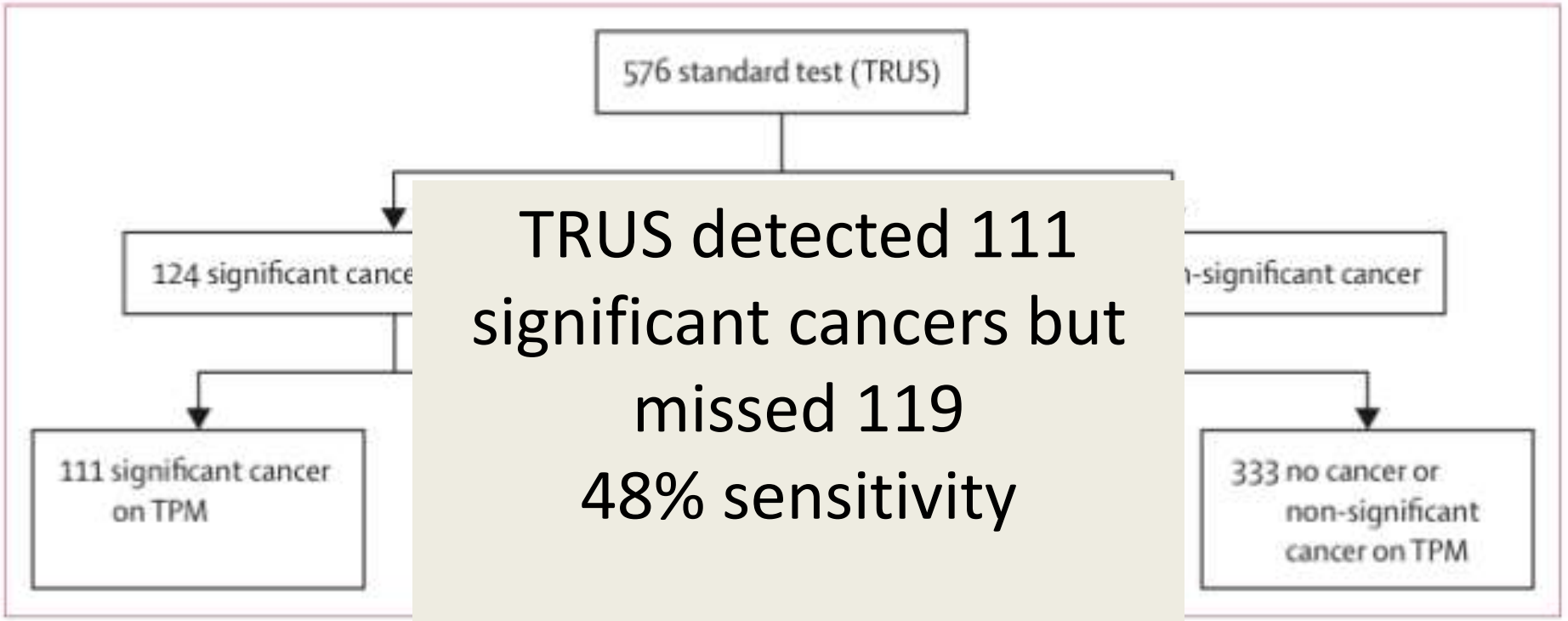

TRUS detected 111 significant cancers but missed 119
48% sensitivity

***Figure 3*: Diagnostic accuracy for detection of clinically significant cancer (primary definition) between TRUS-biopsy and TPM-biopsy**

TRUS-biopsy=transrectal ultrasound-guided prostate biopsy. TPM-biopsy=template prostate mapping biopsy. Sensitivity 48% (95% CI 42–55), positive predictive value 90% (83–94), specificity 96% (94–98), negative predictive value 74% (69–78)

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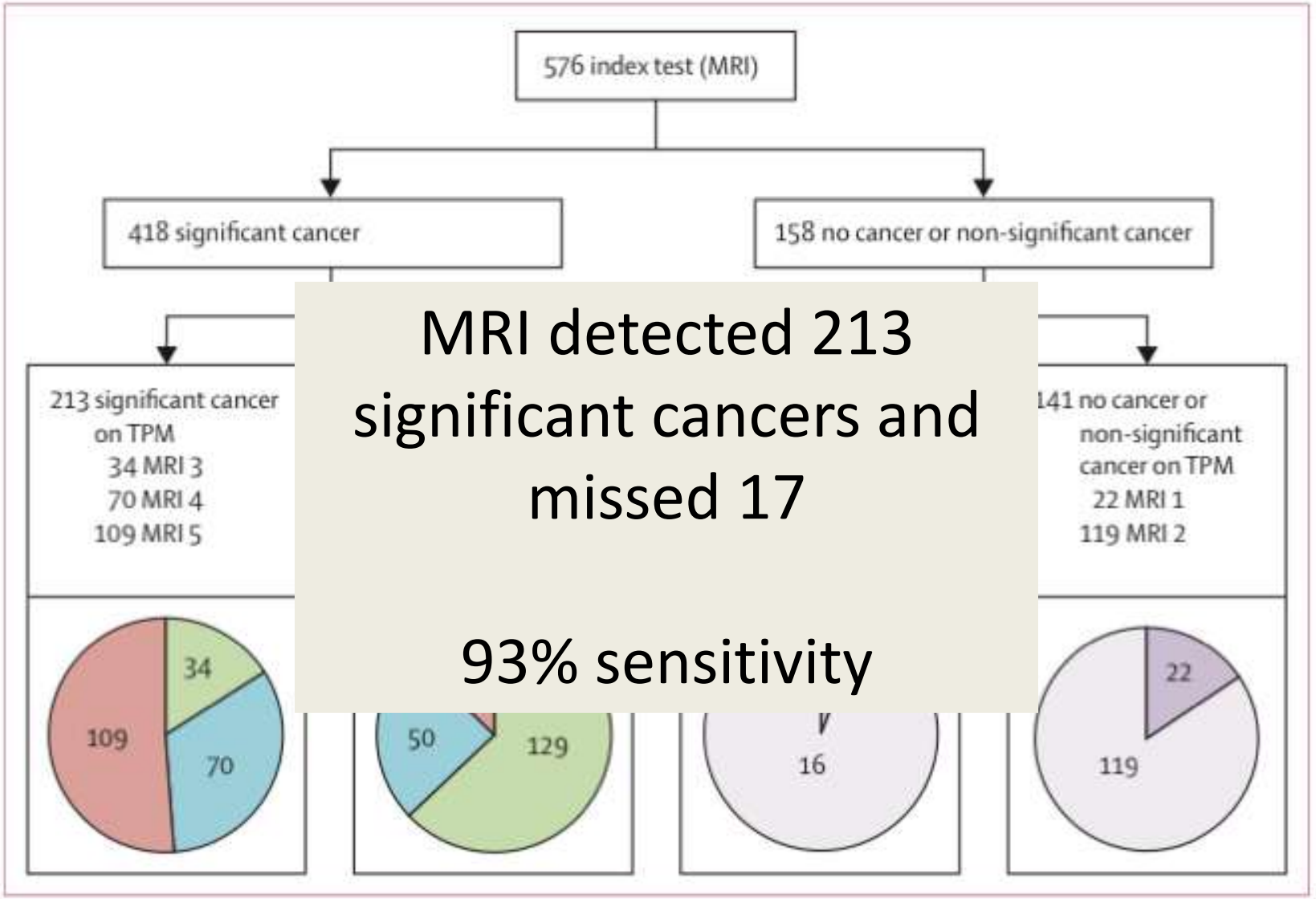


MRI detected 213 significant cancers and missed 17

93% sensitivity

***Figure 2*: Diagnostic accuracy for detection of clinically significant cancer (primary definition) between MP-MRI and TPM-biopsy**

MP-MRI=multi-parametric MRI. TPM-biopsy=template prostate mapping biopsy. Pie charts represent actual MP-MRI scores 1–5. Sensitivity 93% (95% CI 88–96), positive predictive value 51% (46–56), specificity 41% (36–46), negative predictive value 89% (83–94).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasivisvanathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budäus, G. Hellawell, R.G. Hindley, M.J. Roobol, S. Eggener, M. Ghei, A. Villers, F. Bladou, G.M. Villeirs, J. Virdi, S. Boxler, G. Robert, P.B. Singh, W. Venderink, B.A. Hadaschik, A. Ruffion, J.C. Hu, D. Margolis, S. Crouzet, L. Klotz, S.S. Taneja, P. Pinto, I. Gill, C. Allen, F. Giganti, A. Freeman, S. Morris, S. Punwani, N.R. Williams, C. Brew-Graves, J. Deeks, Y. Takwoingi, M. Emberton, and C.M. Moore, for the PRECISION Study Group Collaborators*

Does standard TRUS (10-12 core) or MRI +/- targeted biopsy detect:

- More clinically significant cancer (Gleason 3 + 4)
- Less clinically insignificant cancer
- Using fewer biopsies in fewer men

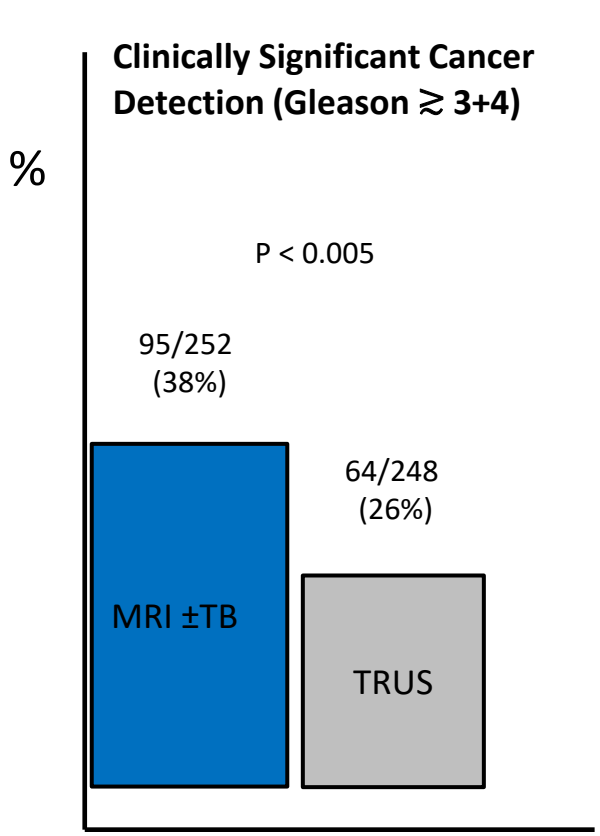
This article was published on March 19, 2018, at NEJM.org.

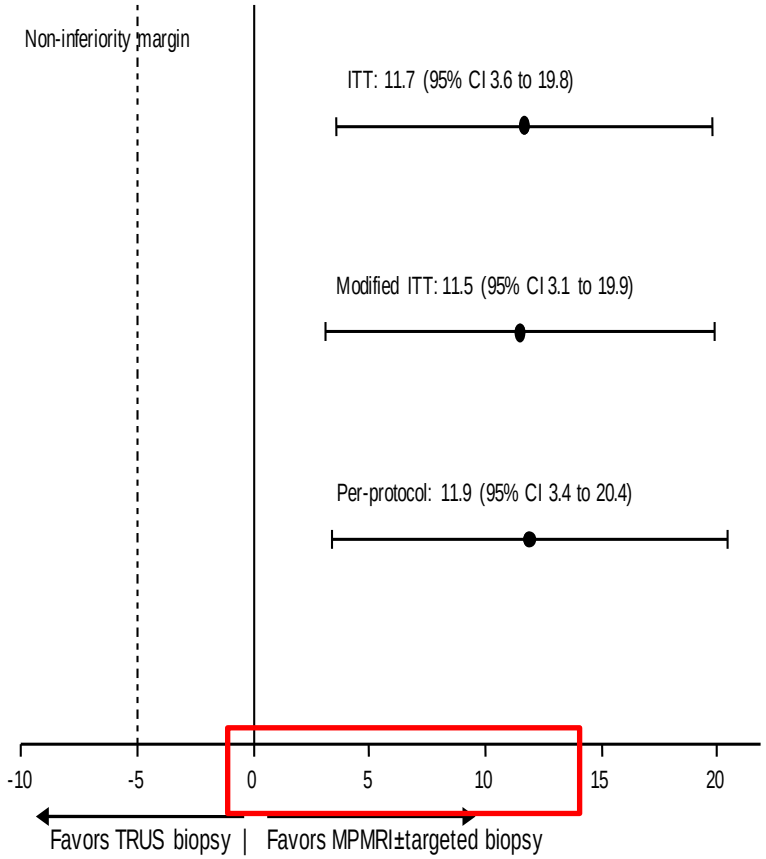
DOI: 10.1056/NEJMoa1801993

Not only was MRI±TB non-inferior to TRUS biopsy, MRI±TB was superior in the detection of clinically significant cancer

71/252 (28%) of men avoided biopsy in the MRI arm

Median 4 cores in MRI ±TB arm versus median 12 cores in TRUS biopsy arm





@mrsprostate

MRI in men with a high PSA

- Allows 1 in 3 men to avoid a biopsy
- Finds more significant prostate cancer than a standard biopsy
- Halves the number of men ‘over diagnosed’ with a low risk prostate cancer
- Is offered as part of routine care across the NHS

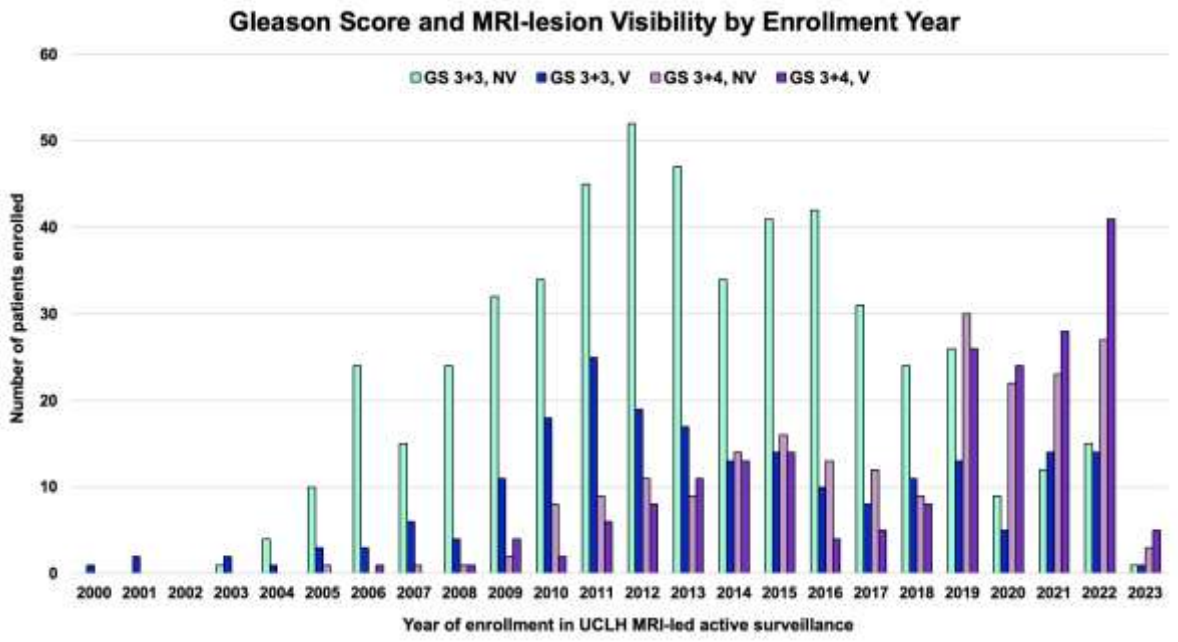
MRI to reduce overtreatment in men diagnosed with prostate cancer

Active surveillance using traditional tools

- Single protocol for follow up across a spectrum of risk of progression
- Uptake of surveillance varies internationally & locally
  - 95% suitable men in UK
  - 60% suitable men US
  - Up to 70% suitable men Switzerland
- Protocols suggest regular biopsies but they are not always done
- 1 in 4 men with no clinical change choose radical treatment as they don't like surveillance
- Men on active surveillance are 10 x as likely to die from heart disease than prostate cancer

UCLH MRI-led active surveillance

- Use PSA and MRI
- Biopsy during surveillance if
  - Change on MRI suggests a change in risk
  - PSA rising and not explained by growth of the whole prostate on MRI



MRI led active surveillance

- Follow up biopsies reduced from routine practice every 1-3 years to only 1 in 3 men needing a follow up biopsy
- Men choosing active treatment due to anxiety reduced from 20% to 2%

Focal therapy for prostate cancer

A small treatment for a small cancer

Risk of cancer progression

Risks of radical treatment

Summary of Focal HIFU experience in the UK

Robust, long-term **clinical data**

- Available on NHS
- With focal hemi-ablation
  - <1% pad use for incontinence
  - 1 in 3 need tablets for erections
  - 2 in 3 natural erections
  - Reduction in semen volume in >50% of men
- Registry data (>1700 men)
  - 1 in 5 need a 2nd HIFU by 7 years
  - 1 in 15 need radical treatment by 7 years

Cancer Control Outcomes Following Focal Therapy Using High-intensity Focused Ultrasound in 1379 Men with Nonmetastatic Prostate Cancer: A Multi-institute 15-year Experience

Deepika Reddy[a,b,*], *Max Peters*[c], *Taimur T. Shah*[a,b], *Marieke van Son*[c], *Mariana Bertoncelli Tanaka*[b], *Philipp M. Huber*[d], *Derek Lomas*[e], *Arnas Rakauskas*[f], *Saiful Miah*[g], *David Eldred-Evans*[a], *Stephanie Guillaumier*[h,i], *Feargus Hosking-Jervis*[a], *Ryan Engle*[a], *Tim Dudderidge*[j], *Richard G. Hindley*[k,l], *Amr Emara*[k,x], *Raj Nigam*[m,n], *Neil McCartan*[h,i], *Massimo Valerio*[f], *Naveed Afzal*[o], *Henry Lewi*[p], *Clement Orczyk*[h,i], *Chris Ogden*[q], *Iqbal Shergill*[r], *Raj Persad*[s], *Jaspal Virdi*[t], *Caroline M. Moore*[h,i,u,v], *Manit Arya*[b,h,i], *Mathias Winkler*[a,b], *Mark Emberton*[h,i,u,v,†], *Hashim U. Ahmed*[a,b,v,w,†]

- HIFU Evaluation and Assessment of Treatment (HEAT) registry
- 1379 primary focal patients across 13 UK centres 2005 -2020
- Median follow up 32 m overall
  - For >5 years, median follow up 82 m
- 2nd focal treatment 1 in 5
- Radical treatment 1 in 15
- PSA 3 m for year 1, then 6m
- MRI 1 year and periodically after, biopsy as needed

https://doi.org/10.1016/j.eururo.2022.01.005

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Radical treatment free survival 73% at 7 years

Overall failure free survival 69% at 7 years

Failure defined as

- evidence of cancer requiring whole-gland salvage treatment/ 3rd focal therapy
- systemic treatment
- prostate cancer metastases
- prostate cancer–specific death

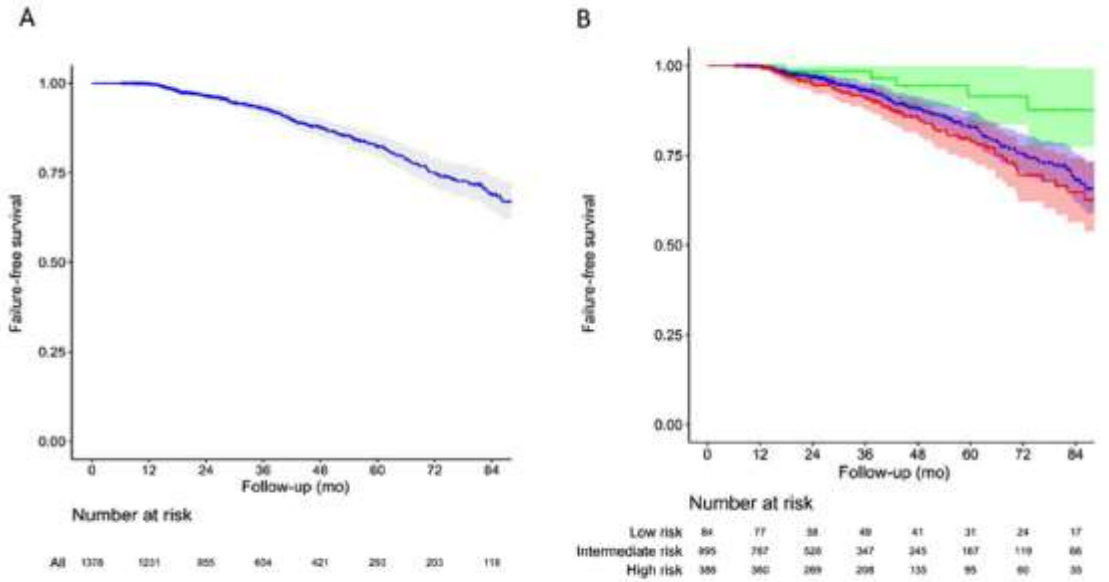


Fig. 1 – Kaplan-Meier curves of failure-free survival (FFS) with 95% confidence intervals. FFS is defined as transition to whole-gland salvage treatment or third focal therapy treatment, systematic treatment, and/or development of prostate cancer metastases and/or prostate cancer–specific death for (A) all patients with at least 6 mo of follow-up and (B) 1365 patients stratified per D'Amico low-risk (green line), intermediate-risk (blue line), and high-risk (red line) group (log-rank analysis of D'Amico intermediate- vs high-risk disease $p = 0.3$).

https://doi.org/10.1016/j.eururo.2022.01.005

Could we use MRI in prostate cancer screening?

How can UK men have a prostate cancer assessment now?

- Ask GP for a PSA blood test
  - Prostate cancer risk management programme
  - Refer men with no symptoms if PSA $\geq$ 3ng/ml
- Assessment of men with problems peeing
  - Refer if PSA higher than expected for age
- Men with a high PSA have an MRI if fit for active treatment
  - Biopsy if MRI shows a higher risk of prostate cancer due to abnormal area or a high PSA for prostate size

Why don’t we have screening now?

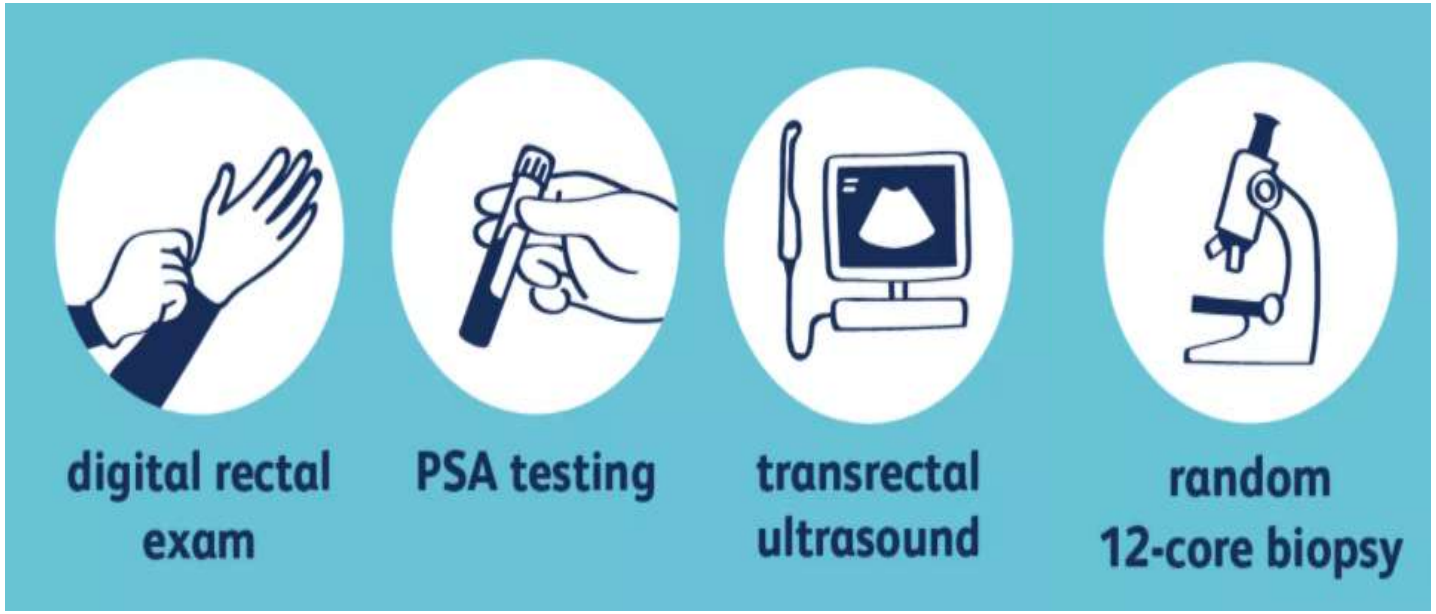
- Screening using traditional methods
  - Reduces prostate cancer death by 20%
- Causes problems
  - Too many men have unnecessary biopsies
  - Too many men diagnosed with low risk cancers that won’t affect them (overdiagnosis)
  - Some of these men have treatment that causes problems with urinary, bowel and sexual function (over treatment)

PROSTATE CANCER UK
TRANSFORM

Why do we need to change?

- Too many men die of prostate cancer
  - Higher prostate cancer death rates than Italy, Spain, France, USA
  - Age-adjusted PCa mortality (per 100 000 person years) for PCa is 50% higher than comparable counties:
    - UK 12.4 vs USA 8.2 , France 8.4, Spain 7.3, Italy 6.9
- Waiting for men to ask for a test means that many men don't ask
- The PCUK risk checker increases men asking for a test
  - But it doesn't reach everyone who might benefit

Traditional assessments use for prostate cancer screening



JAMA | Original Investigation

Prostate-Specific Antigen Screening and 15-Year Prostate Cancer Mortality
A Secondary Analysis of the CAP Randomized Clinical Trial

Richard M. Martin, BM, BS, PhD; Emma L. Turner, PhD; Grace J. Young, MSc; Chris Metcalfe, PhD; Eleanor I. Walsh, MSc; J. Athene Lane, PhD; Jonathan A. C. Sterne, PhD; Sian Noble, PhD; Peter Holding, MSc; Yoav Ben-Shlomo, MBBS, PhD; Naomi J. Williams, PhD; Nora Pashayan, MD, PhD; Mai Ngoc Bui, PhD; Peter C. Albertsen, MD; Tyler M. Seibert, MD, PhD; Anthony L. Zietman, MD; Jon Oxley, MD; Jan Adolfsson, MD; Malcolm D. Mason, MD; George Davey Smith, DSc; David E. Neal, MD; Freddie C. Hamdy, MD; Jenny L. Donovan, PhD; for the CAP Trial Group

- **Men aged 50 to 69 years at 573 primary care practices in England and Wales**
- **Patients enrolled 2002 – 2009 with follow up to 2021**
- **Randomised to invitation for single PSA test (195, 912) or no invitation (219,445)**
  - Standard TRUS biopsy recommended if PSA $\geq$ 3ng/ml
- **98% of participants in control group were white**
- **Rate of low risk cancer increased in intervention group (2.2% vs 1.6%)**
- **Rate of high risk cancer reduced from 1.3% to 1.2% in intervention group**

JAMA. 2024;331(17):1460-1470. doi:10.1001/jama.2024.4011
Published online April 6, 2024.

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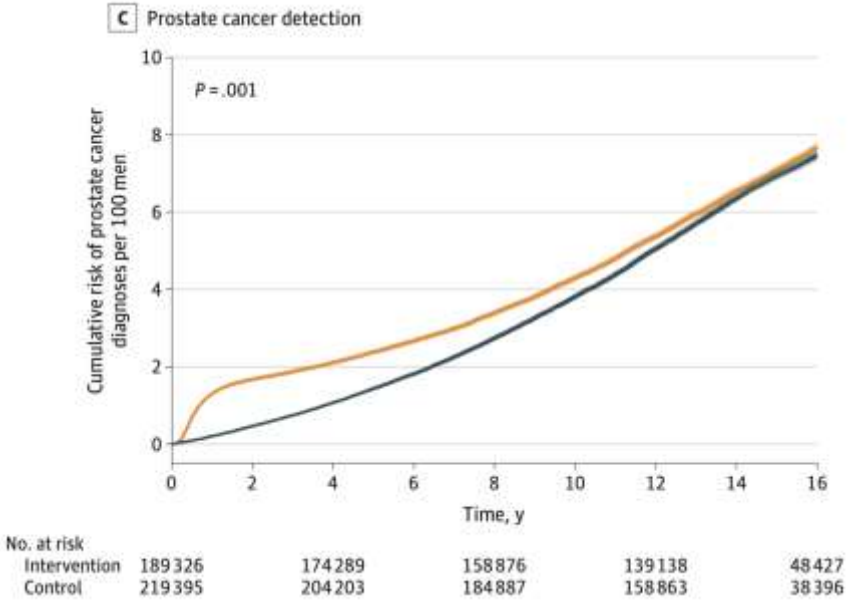
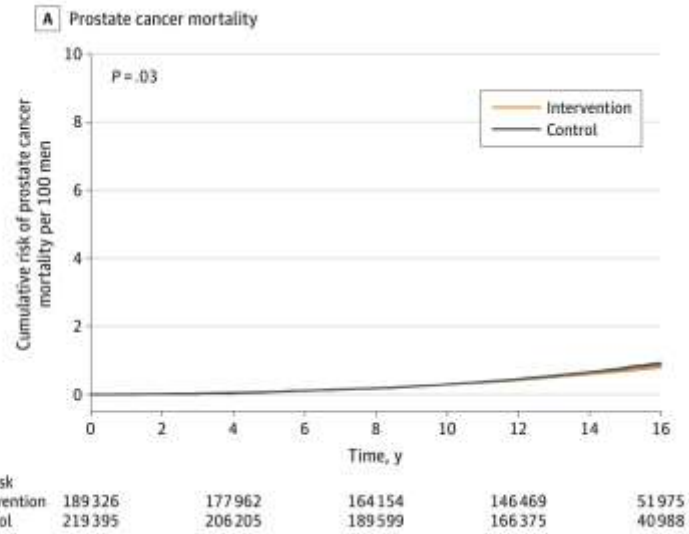
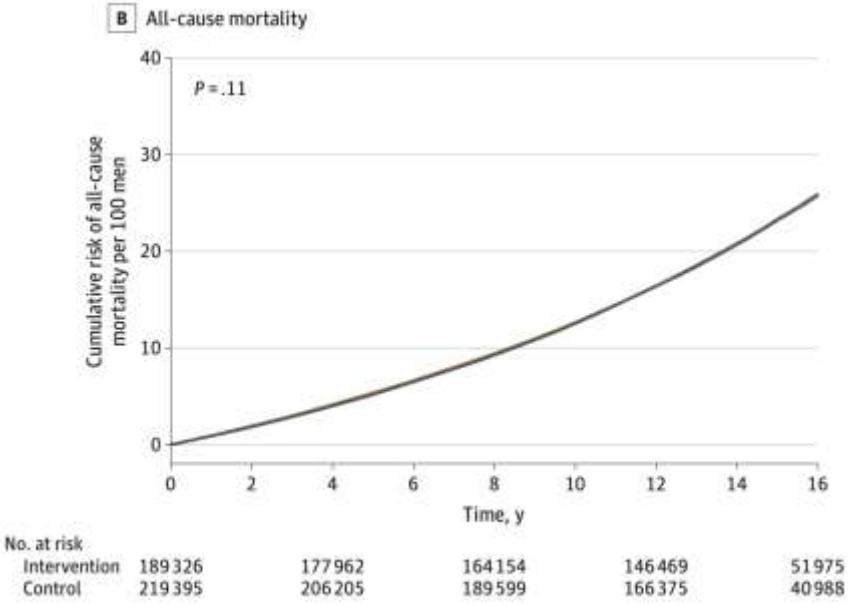


A single PSA test is not adequate for screening for prostate cancer





A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer

Jonas Hugosson [a,], Monique J. Roobol [b], Marianne Månsson [a], Teuvo L.J. Tammela [c], Marco Zappa [d], Vera Nelen [e], Maciej Kwiatkowski [f,g], Marcos Lujan [h], Sigrid V. Carlsson [a,i], Kirsi M. Talala [j], Hans Lilja [k,l,m,n,o], Louis J. Denis [p], Franz Recker [f], Alvaro Paez [q], Donella Puliti [d], Arnauld Villers [r], Xavier Rebillard [s], Tuomas P. Kilpeläinen [t], Ulf H. Stenman [u], Rebecka Arnsrud Godtman [a], Karin Stinesen Kollberg [a], Sue M. Moss [v], Paula Kujala [u], Kimmo Taari [t], Andreas Huber [w], Theodorus van der Kwast [x], Eveline A. Heijnsdijk [y], Chris Bangma [b], Harry J. De Koning [y], Fritz H. Schröder [b], Anssi Auvinen [z], on behalf of the ERSPC investigator*

- ERSPC 16 year
  69 yrs)
- PCa mortality
- To prevent one
  - Invite 560 t
  - Diagnose 1
- But 3 in 4 biop
- Over half of diagnoses low risk disease

Regular PSA testing followed by TRUS biopsy

Reduces mortality in those who have a PSA

But at too high a cost

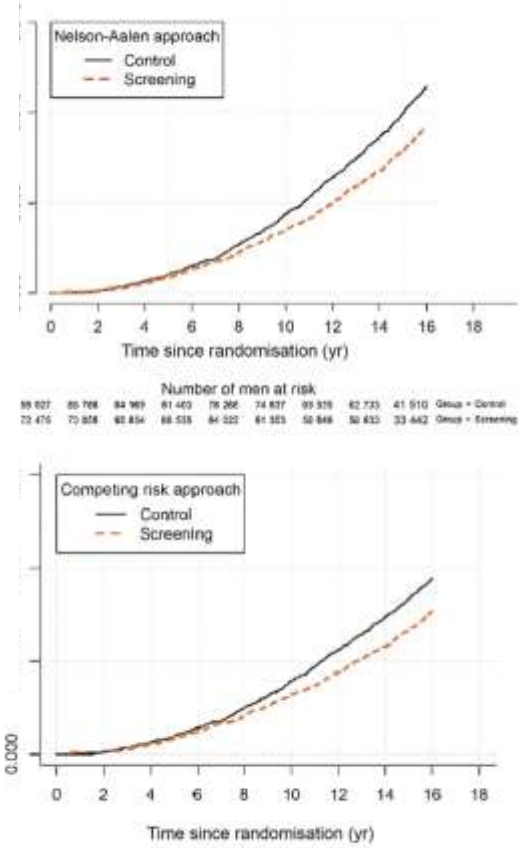
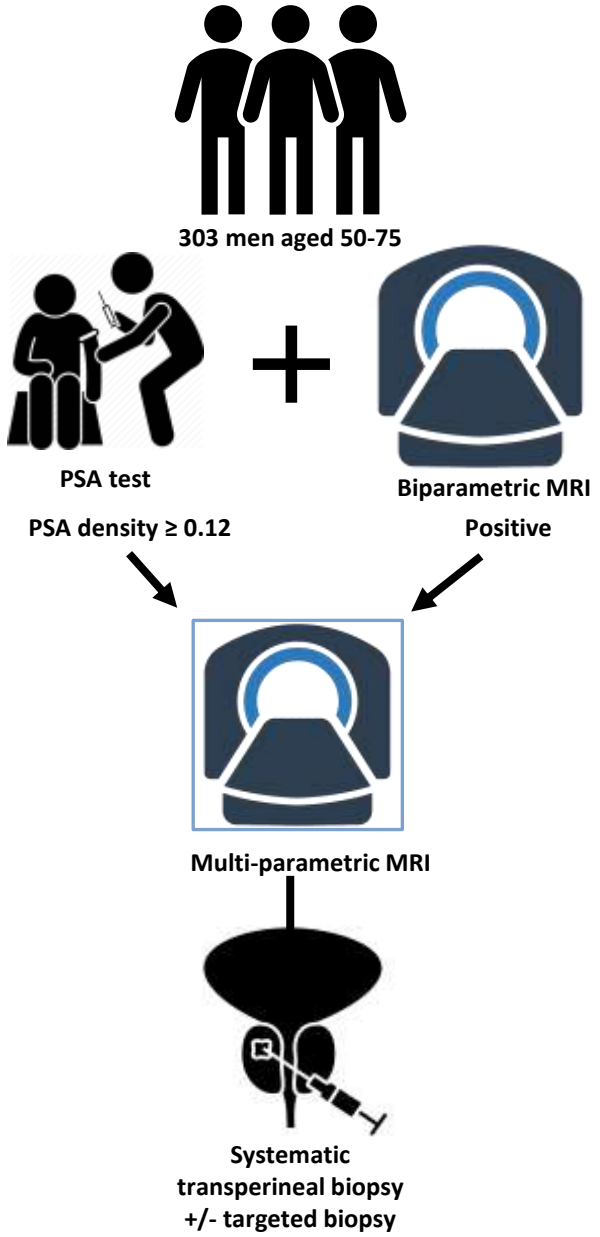


Fig. 2 – Prostate cancer incidence estimated by (A) the Nelson-Aalen approach and (C) the competing risk approach, and prostate cancer-specific mortality estimated by (B) the Nelson-Aalen approach and (D) the competing risk approach. PC = prostate cancer.

MRI to reduce over-diagnosis in screening

relimagine

Design:	• Men invited for screening MRI and blood test • 1 study centre (UCL) & 2 NHS centres (UCLH & Royal Free)
Participants:	• 6 primary care practices • 2096 men aged 50-75 years invited for screening • 303 completed both tests
Screening Tests:	• MRI positive or negative • PSA density : ≥ 0.12ng/ml^2 • Referred for NHS assessment if screened positive
Reference test:	• Transperineal targeted + systematic cores • Clinically significant disease: Any Gleason ≥3+4
Blinding:	• Reporters blinded to other tests • Discussion with clinic nurse about biopsy with results



relimagine

PSA density

0.12 ng/ml

1 in 20 (16/303) had raised PSAD alone
1 in 4 clinically significant prostate cancer

bp-MRI

Positive

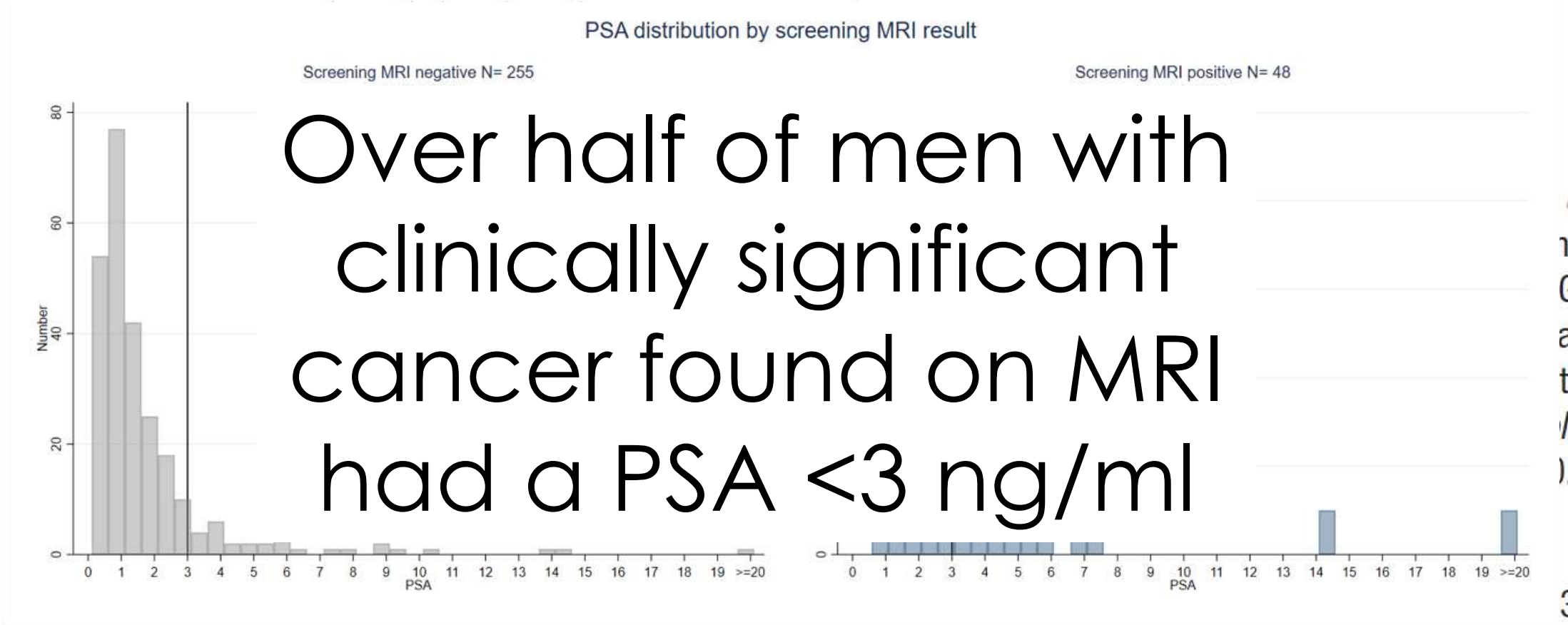
1 in 6 (48/303 or 16%) positive screen
1 in 2 clinically significant prostate cancer

NHS multiparametric MRI before biopsy decision

Open access Original research

BMJ Oncology

Prevalence of MRI lesions in men responding to a GP-led invitation for a



Over half of men with clinically significant cancer found on MRI had a PSA <3 ng/ml

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Accepted 04 June 2023

Response rates

	London population N= 797, 062	ReIMAGINE
Ethnicity		
White		
Black		
Asian		
Mixed		
Other		

Men aged 65-70 most likely to respond

Black men had 20% the response rate of white men

1: Missing ethnicity data 490/2097 (23%) in the ReIMAGINE invited individuals
2: Missing ethnicity data 83/457 (18%) in the ReIMAGINE respondents

Our invitation profile matched the ethnicity profile of London

Our response rate was significantly lower r in black men

UK National Screening Committee

UK NSC requires robust evaluation to recommend that the UK government invests in national prostate cancer screening programme….. this means:

- **Randomised controlled trial across the UK**
- **Making sure diverse population offered screening**
- **Making sure Black men who are at higher risk are represented**
- **Adequate proportion of those invited taking up the offer of screening**
- **Evaluating which is the best screening test**

PROSTATE CANCER UK
TRANSFORM

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Head of Specialist Surgery
Chair & Professor of Urology
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Professor Rosalind Eeles

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Professor Caroline Moore

Head of Urology
NIHR Research Professor
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TRANSFORM: 3 stage design

PROSTATE CANCER UK TRANSFORM

1

Stage 1 (3 years)

- Pilot 4 screening interventions
- Evaluate how to deliver pivotal trial assessing key processes and assumptions
- Short-term outcomes
- Develop bio-digital twin protocols

16,500 men

2

Stage 2 (6 years)

- Main trial of optimal intervention
- Medium-term clinical outcomes
- PROMS: quality of life.
- Costs and resources
- Create bio-digital twin

TRANSFROM Discovery

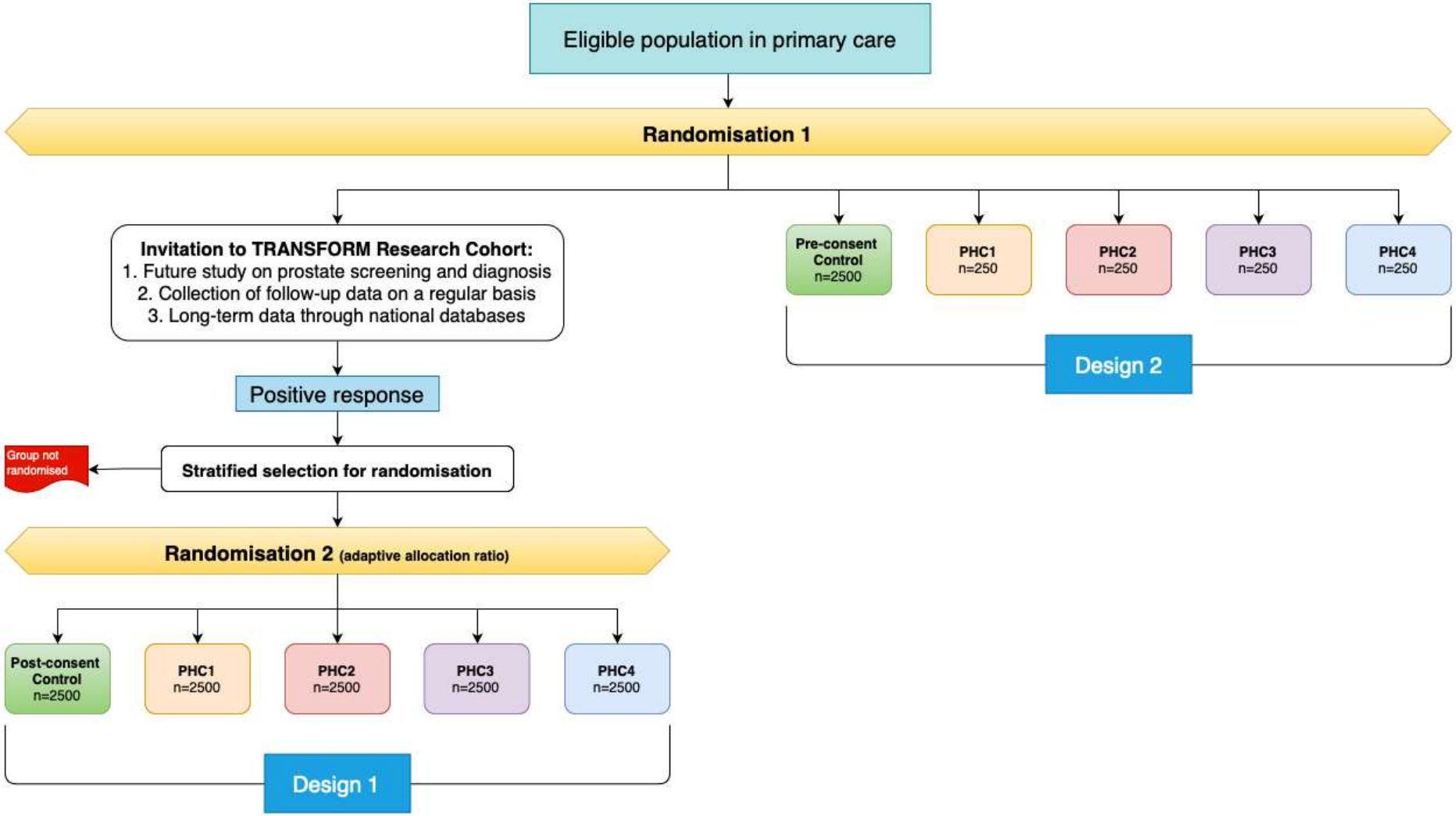
180,000– 500,000 men

3

Stage 3 (10 years)

- Evaluate long-term primary outcomes through linkage to national databases

Stage 1 trial design OVERVIEW



IMPERIAL Queen Mary University of London ICR The Institute of Cancer Research UCL

TRANSFORM Prostate health checks

Arm 1: PSA 3 + MRI

PSA ≥ **3**ng/ml

Prostagram™

Targeted biopsy

Arm 2: PSA 1 + MRI

PSA ≥ **1**ng/ml

Prostagram™

Targeted biopsy

Arm 3: MRI-only

Any PSA level

Prostagram™

Targeted biopsy

Arm 4: PRS

PRS ≥ **3.5%**

Prostagram™

Targeted biopsy

Summary

- MRI is currently used in men with a high PSA
  - 1 in 3 avoid biopsy
  - Detects more clinically significant cancer
  - Halves overdiagnosis
- MRI for active surveillance
  - Reduces anxiety led treatment from 20% to 2%
  - Allows 2 in 3 men to avoid follow up biopsy
- MRI to allow small treatments for small cancers
  - Reduces urine leakage from 1 in 2 to 1 in 50
  - Allows 2 in 3 men to keep natural erections without tablets
- MRI in prostate cancer screening
  - Promising but more data needed

Any questions?

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