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MRI Before Biopsy Should be the Standard of Care - Con

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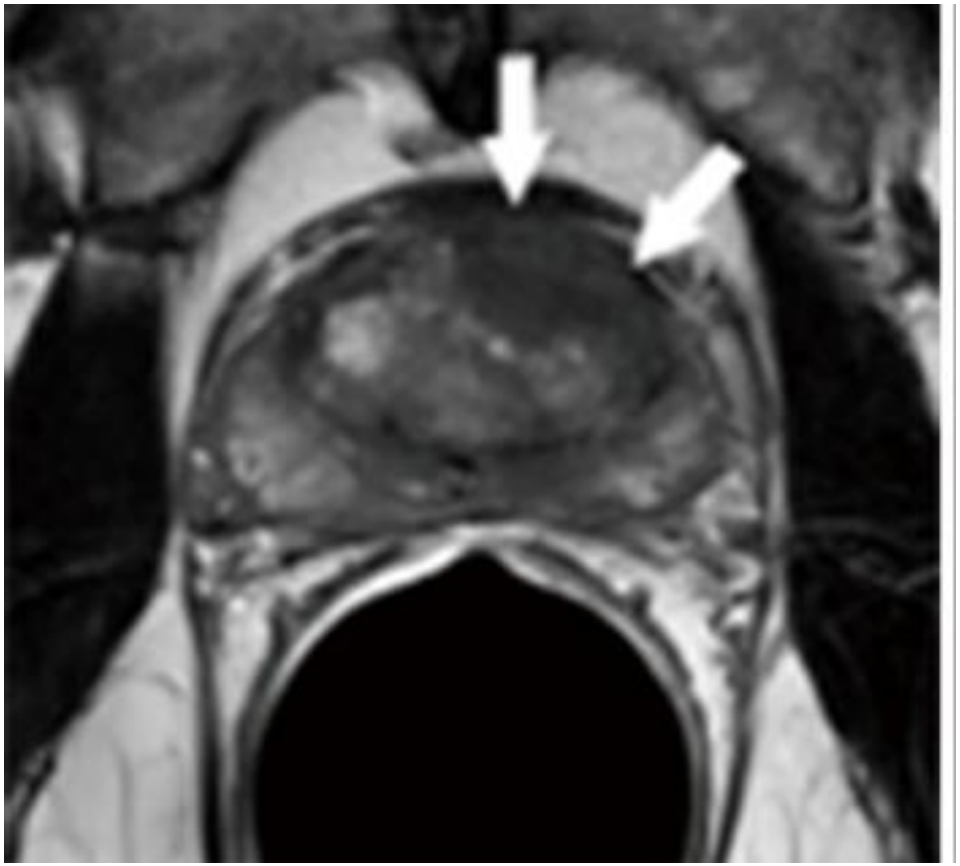
Background

- **To be of value, MRI in biopsy-naïve men followed by TRUS-Fusion biopsy or MRI guided biopsy requires:**
  - MRI with excellent test performance
  - A technology that is generalizable
  - Fusion (regardless of approach) that is accurate in targeting the identified lesion
  - A cancer biology associated with a dominant lesion that is high-grade and visualized by MRI
  - Diminished morbidity
  - Cost effective

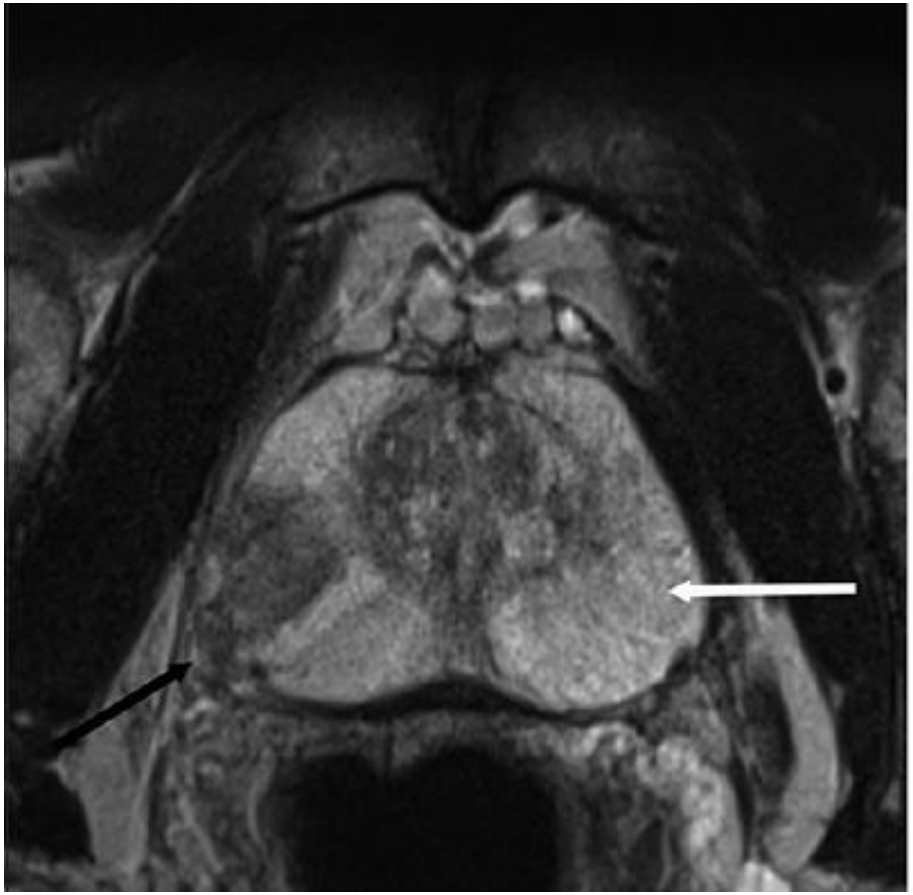
mpMRI Performance

- Test performance varies with setting and the reference
  - Up to 20% of negative MRI have clinically significant prostate cancer (CSPC)
    - Kuru, J Urol 2013, Siddiqui MM, JAMA 2015, Finelli, Haider (CCO Systematic Review 2015)
  - ***The prototypical Anterior Tumour that is always presented, over-represents the situation***

How common is this?



What would MRI add?



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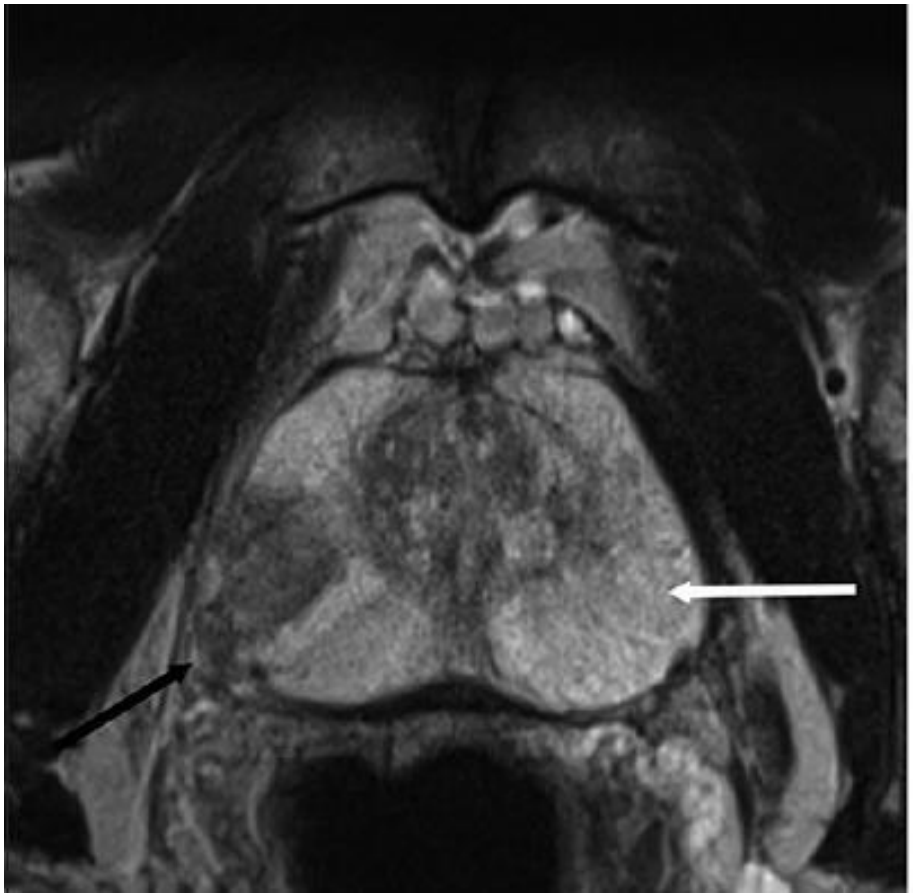


And more importantly, which scenario is more common?

mpMRI Performance

- Biopsy naïve setting
  - MP-MRI fusion TB does **not** significantly improve detection of CSPC
    - Meng X (Taneja S) et al, Euro Urol 2015, Schoots et al, Eur Urol 2015, Finelli, Haider (CCO systematic review 2015)
  - False positive rate of 17%
    - Bains et al, J Urol 2014
- One can not separate the necessity of fusion biopsy if unable to perform MR guided biopsies

And even if you could, MRI Bx results are imperfect!

Review – Prostate Cancer

Magnetic Resonance Imaging–targeted Biopsy May Enhance the Diagnostic Accuracy of Significant Prostate Cancer Detection Compared to Standard Transrectal Ultrasound-guided Biopsy: A Systematic Review and Meta-analysis

Ivo G. Schoots[a,], Monique J. Roobol[b], Daan Nieboer[c], Chris H. Bangma[b], Ewout W. Steyerberg[c], M.G. Myriam Hunink[a,d,e]*

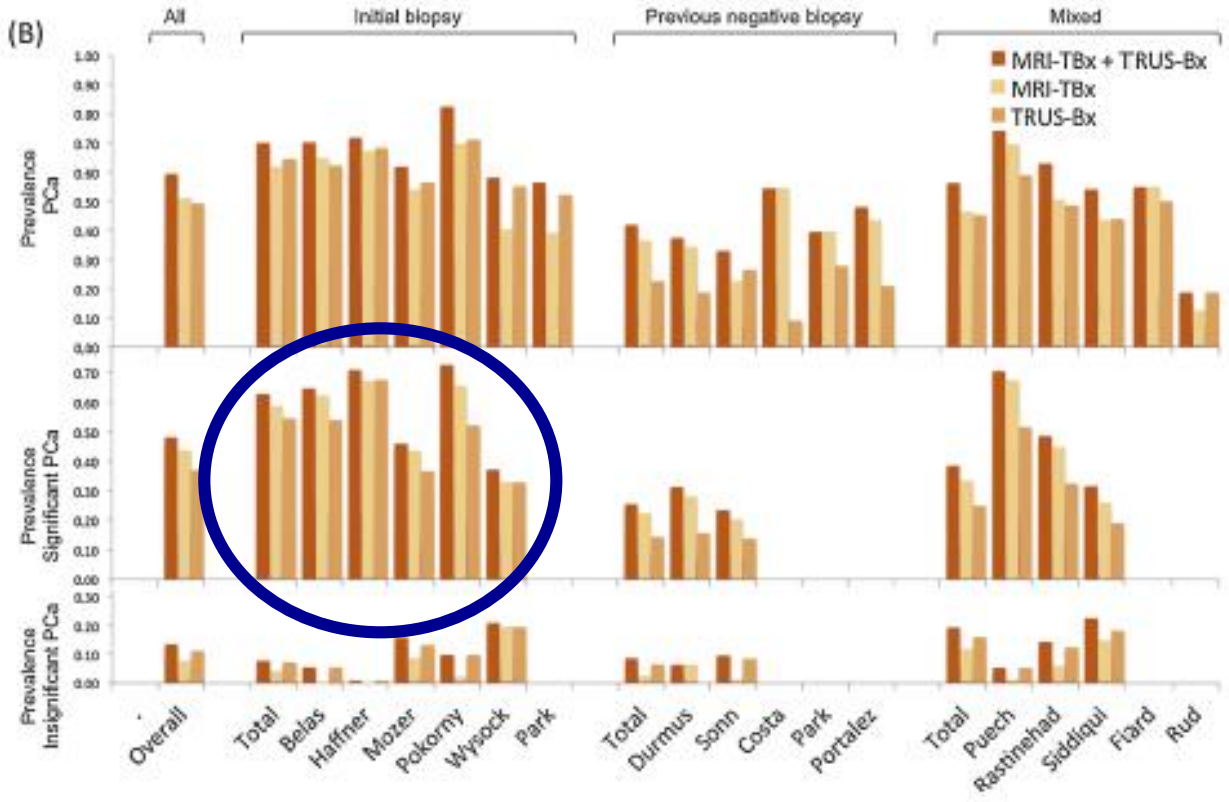
- 16 studies that used both MRI-TBx and TRUS-Bx
- A cumulative total of 1926 men with a positive MRI were included, with prostate cancer prevalence of 59%.
- Detection rates MRI-TBx and TRUS-Bx did **not** significantly differ in overall cancer detection (Sn 0.85, 95% CI 0.80–0.89, and 0.81, 95% CI 0.70–0.88, resp).

Systematic Review and Meta-analysis

- MRI-TBx had a:
  - **higher rate of detection of significant prostate** cancer compared to TRUS-Bx (Sn 0.91 vs 0.76) and a
  - **lower rate of detection of insignificant prostate cancer** (Sn 0.44 vs 0.83).

- Subgroup analysis revealed an improvement in significant prostate cancer detection by MRI-TBx in men with previous negative biopsy, **rather than in men with negative initial biopsy** (relative Sn 1.54, 95% CI 1.05–2.57 vs 1.10, 95% CI 1.00–1.22).

Schoots et al, Euro Urol 2015



Schoots et al, Euro Urol 2015

mpMRI PiRADS 2 Test Performance

- 62 consecutive patients with 116 lesions who underwent mpMRI at 3T with PI-RADSv2 evaluation and subsequent targeted **MRI/TRUS fusion-guided biopsy** (FgBx) and concurrent 12-core systematic prostate biopsy (SBx) between May-Sept 2015.

- Mean lesion size was 1.27cm overall.

- Lesion-based cancer detection rates (CDR) for all tumors and Gleason ≥3+4 tumors at each PI-RADSv2 score were calculated.
  - Mertan FV (Pinto PA) et al, J Urol 2016

mpMRI PiRADS 2 Test Performance

- Based on targeted biopsy on a per lesion basis
- **CDRs for Gleason ≥3+4 tumors was:**
  - **PI-RADS score**
    - 2 – 5.6%
    - **3 – 0**
    - **4 – 21.3%**
    - 5 – 75%
      - Mertan FV (Pinto PA) et al, J Urol 2016

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    - 5 – 75%
      - Mertan FV (Pinto PA) et al, J Urol 2016
- ***Dr. Perlis – will you biopsy PiRAD 3 or only 4 and/or 5?***

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†*

Lancet 2017; 389:815

PROMIS

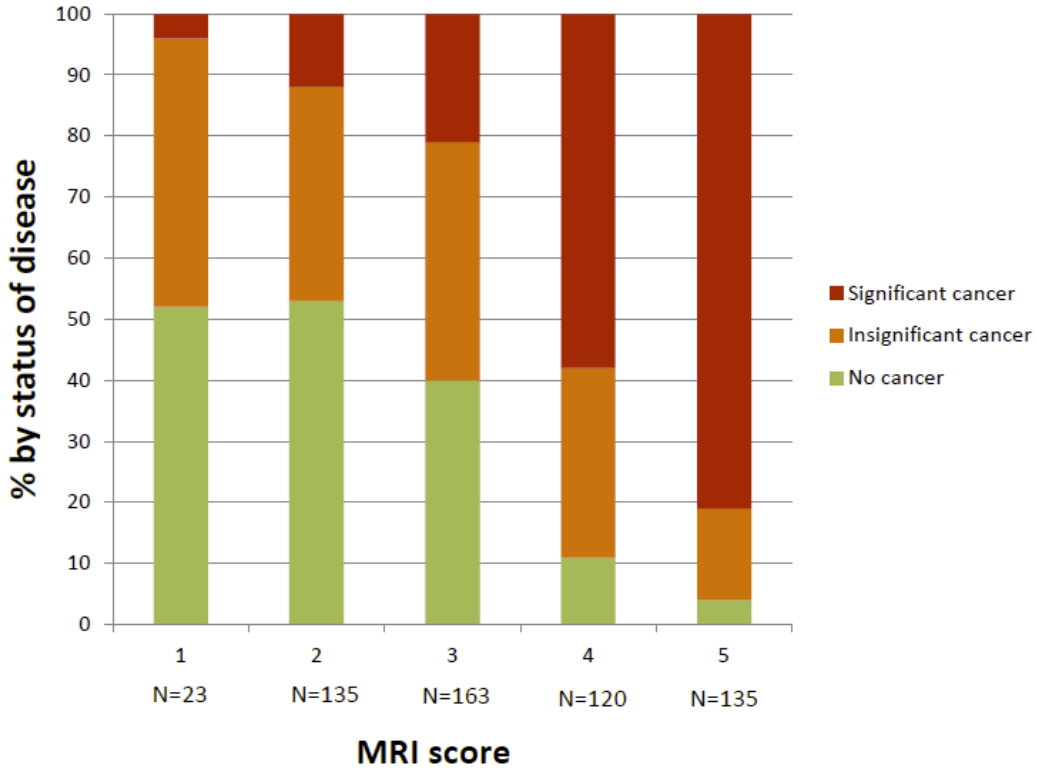
- **Ahmed et al, Lancet 2017;** *(Faria et al, Eur Urol 2018; Brown et al, Health Technol Assess 2018.)*
- **Brief summary and highlights:**
  - Paired validation cohort of patients undergoing mpMRI (index test), TRUS bx (current standard), and template prostate mapping (reference)
  - MRI outperformed systematic biopsy in sensitivity (93%) and negative predictive value (89%)
  - Potentially avoided biopsy in men at low risk of harbouring clinically significant cancer (27% negative MRI), and probable cost-effectiveness

PROMIS – Issues

- **1. No actual MRI guided or MRI targeted biopsies were performed!!!** Instead, PROMIS compared MRI *imaging* results with transperineal template bx assuming that theoretically *MRI = MRI bx*
  - Correct comparison would be MRI bx vs TRUS bx
  - Completely omits the issue of hitting these lesions / accuracy which is subject to centre-specific factors, patient, and learning curve
  - If MRI bx was (performed and) compared, would likely underperform

PROMIS – Issues

- **2. Are these rates of PIRADS 4/5 consistent with our practice?**



PROMIS – Issues

- **3. Reproducibility of MRI results**
  - Assessed by two trained expert uro-radiologists, kappa 0.5 (moderate agreement)
  - Unknown number of “scans of insufficient quality” repeated

PROMIS – Issues

- **4. Cost effectiveness analysis**
  - Minimal difference between “most cost effective threshold” = mpMRI + up to two targeted biopsies (sensitivity 0.95, £807/patient) versus systematic biopsy followed by MRI (sensitivity 0.91, £709/patient)
    - Completely dependent on *assumptions*
  - Cost effectiveness strategy changed between MRI and TRUS based on sensitivity of MRI targeted bx (not assessed in PROMIS)
  - Effect in a Canadian context (vs. UK) unknown

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 10, 2018 VOL. 378 NO. 19

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*

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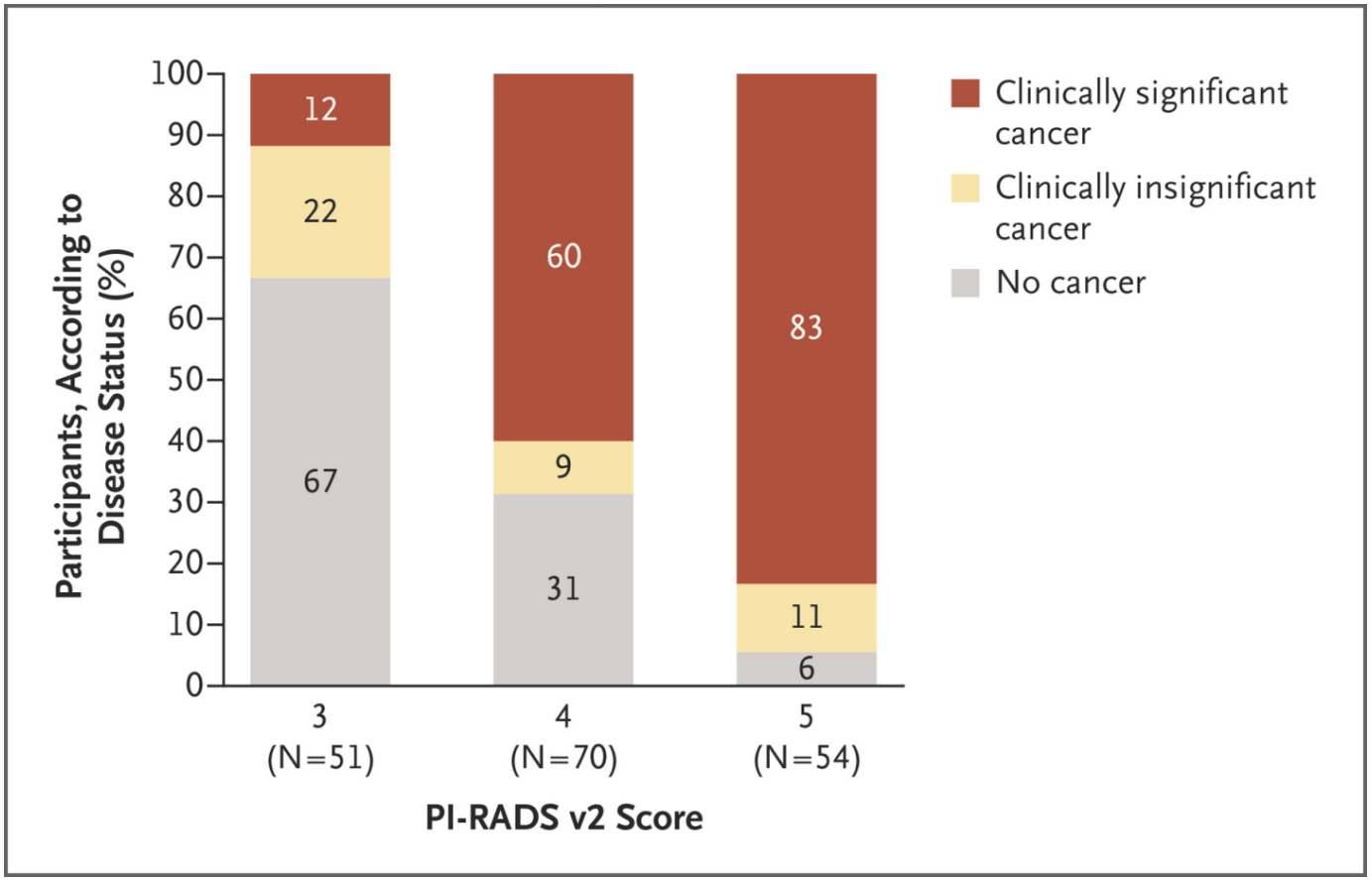
PRECISION is <u>not</u> to be confused with Accuracy

PRECISION

- Multicentre, randomized, non inferiority trial
- 500 men randomized across academic and community sites with 1.5T and 3.0T MRI machines, endorectal coil and without, cognitive and fusion biopsy
- Positive MRI proceeded to targeted biopsy of their lesion and those without were not offered biopsy versus systematic TRUS bx
- MRI increased detection of CSPC 38% vs. 26%
- MRI had fewer clinically insignificant PC 9% vs 22%
- Avoided biopsy in 28%

PRECISION – Issues

- **Are these rates representative of disease in Canada?**



PRECISION – Issues

- ***Did the young Dr. Perlis read the ENTIRE paper??***

PRECISION – Issues

- ***Let's start with Table 1 like every good journal club***

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	MRI-Targeted Biopsy Group (N=252)	Standard-Biopsy Group (N=248)
Age — yr	64.4±7.5	64.5±8.0
PSA level — ng/ml		
Median	6.75	6.50
Interquartile range	5.16–9.35	5.14–8.65
Family history of prostate cancer — no. (%)	48 (19)	40 (16)
Abnormal digital rectal examination — no. (%)	36 (14)	38 (15)

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- ***How many 64 y.o. in your practice with PSA 6.7 at presentation or will you order MRI earlier ?***

PRECISION – Issues

- **How about the Supplementary tables ??**
- **S16**
  - 24/64 (38%) had discordant pathology between local and central review
  - Of these, 14/24 (58%) would have changed management
  - In particular, 5 cases where it was PIRADS 1-2 versus PIRADS 4 on central review
  - Learning curve??

PRECISION – Issues

- **Supplementary table S15, higher rate of discordant pathology (both upgrading and downgrading) in MRI arm versus final RP pathology**

Table S15: Gleason grade concordance with original biopsy after radical prostatectomy

Number of cases	Concordant	Upgraded	Downgraded
MRI±TB arm - no. (%)	19 (63.3)	5 (16.7)	6 (20.0)
TRUS biopsy arm - no. (%)	19 (70.4)	4 (14.8)	4 (14.8)

MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided. Results of radical prostatectomy were available for 30 of the 34 men in the MRI±TB arm and 27 of the 30 men in the TRUS biopsy arm. The remainder were lost to follow up.

MRI in Biopsy-naïve Patients is not ready for primetime

- Test performance is not high enough
  - A great deal of PROMIS with questionable PRECISION and accuracy
  - Generalizeabilty is lacking
- Distribution of PiRAD scores and yield of CSPC unlikely the case in Canada
- High rates of discordance with final pathology remain

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MRI in Biopsy Naïve Patients –

CON Rebuttal

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GU Site Lead, Princess Margaret Cancer Center
GU Cancer Lead, Cancer Care Ontario
Associate Professor, University of Toronto

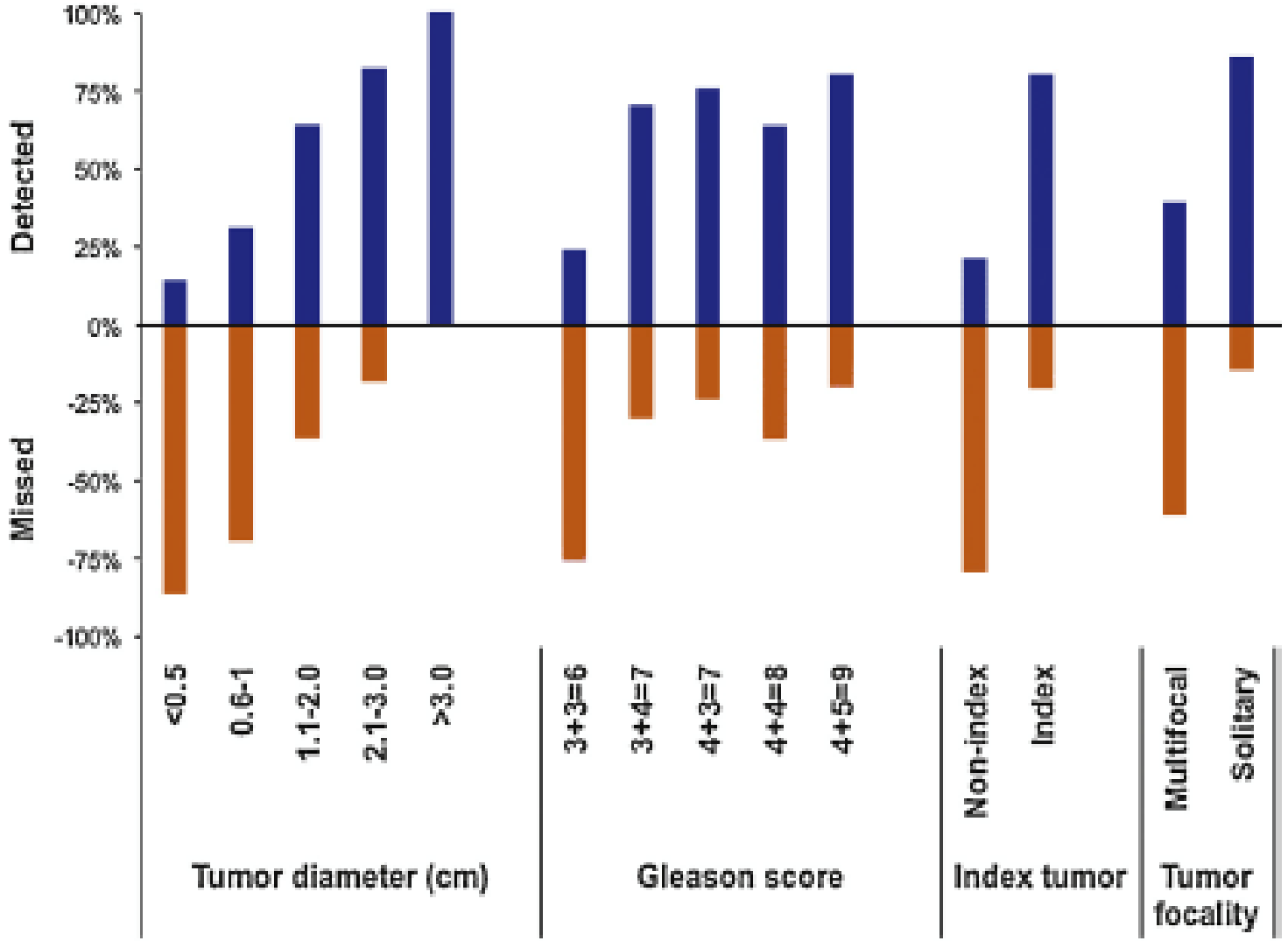
The Impact of Tumor Volume and Multi-focality

- Retrospective study was performed with 122 consecutive men who underwent mp-MRI before RP at a single referral academic center.

- 39/151 (26%) tumours were missed even though they were > 1cm in diameter

- 36/239 (15%) with Gleason 3+4 or higher were missed

  - Le JD et al (Marks L), Euro Urol 2015



239 were multifocal and 44 were solitary

Le JD (Marks L) et al, Euro Urol 2015

The Impact of Tumor Volume and Multi-focality

- Of the 122 cases, 44 (36%) had solitary and 78 (64%) had multifocal tumors.

- Overall mp-MRI sensitivity for tumor detection was 47% (132/283), with increased sensitivity for:
  - larger (102/141 [72%] >1.0 cm),
  - higher-grade (96/134 [72%] Gleason 7) tumors, and
  - index tumors (98/122 [80%]).

Le JD (Marks L) et al, Euro Urol 2015

Other Issues to Consider

- **Learning Curve**
- Prostate cancer detection rate on mpMRI increased from 42% to 81% over series ($P < 0.001$).
  - The prostate cancer detection rate by targeted biopsy increased from 27% to 63% ($P < 0.001$).
  - The negative predictive value of MRI for significant cancer (>Gleason 3+3) was 88.9% later in the series compared with 66.6% earlier.
    - Gaziev et al, BJUI

- **Cost**
  - MRI utilization, Software and expanding indications

Other Issues to Consider

- **Fusion Technique and room for Error**
  - Software Registration versus Cognitive fusion
  - The overall detection rate of cancer is significantly higher in a software fusion cohort (48.1%) compared with both cognitive fusion (34.6% P = .04) and conventional biopsy (32.0%, P = .03).
    - Oberline D et al, Urol 2016
  - ***Is the target registered accurately? Is the target being struck consistently and reliably?.***
- **Morbidity**
  - ***<u>No</u>*** *data to support lower risk of sepsis because of less cores*

Ontario Specific Data

- The wait time for Priority 4 which is what most prostate MRI's for high PSA and non-staging would be coded is a mean of 59 days with a low of 12 and high of 195.

- Number of magnets in Ontario (2017): 74 sites with 120 units - includes private units 8.49/million.
  - **The vast majority of these are 1.5T**

How to follow these patients? What next?

- Natural history of MRI unknown
  - Conversion rate
  - Timing for repeat/confirmatory MRI
  - Rate of upgrading/downgrading

- Wide variability in the progression (regression) of lesions and appearance (disappearance) of new lesions in repeat MRI
  - 70% of patients had progression across median 2 yrs (PI-RADS upgrade, new lesions, increase in size)
  - *Eineluoto et al, PLoS One 2017.*

Who will you order it for?

- *What will be the threshold to prompt MRI in this setting??*

Urologists

- *Isn’t this reminiscent of the screening enthusiasm associated with the introduction of PSA?*

Urologists

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MRI in biopsy-naïve men is not ready for prime time!

Thank You