Prostate Cancer
Screening & other controversies…

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MEDICLINIC PAARL

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Content

- **Embryology & Physiology**
  - Prostate
  - PSA and derivatives

- **Screening**
  - Overview
  - Controversies
  - Literature review

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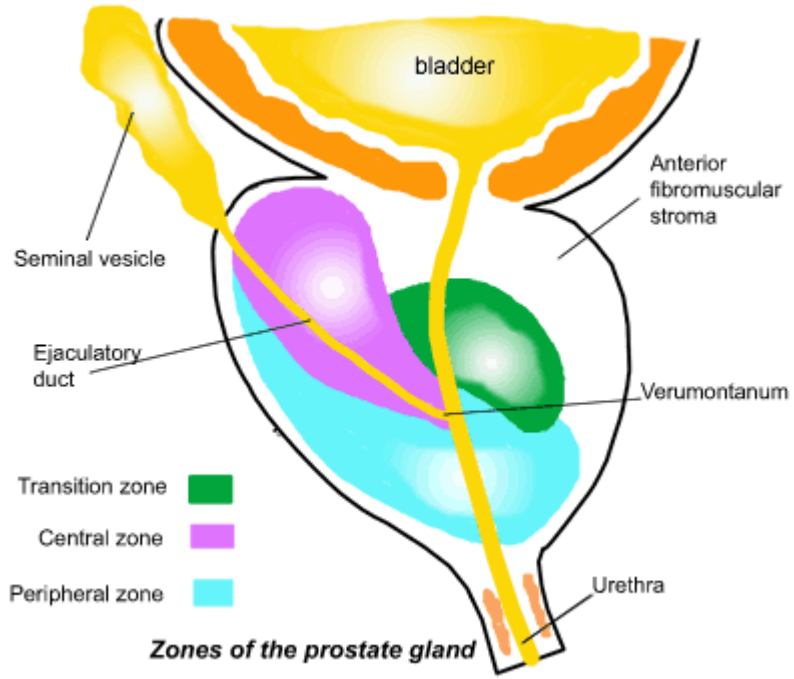
Prostate

- Embryology
  - Develops from 3rd month of gestation
  - Origin Urogenital sinus
  - DHT stimulation dependant

- Zonal anatomy
  - Anterior Fibromuscular stroma
    - 30% prostate weight
    - Smooth muscle only
    - No glandular tissue



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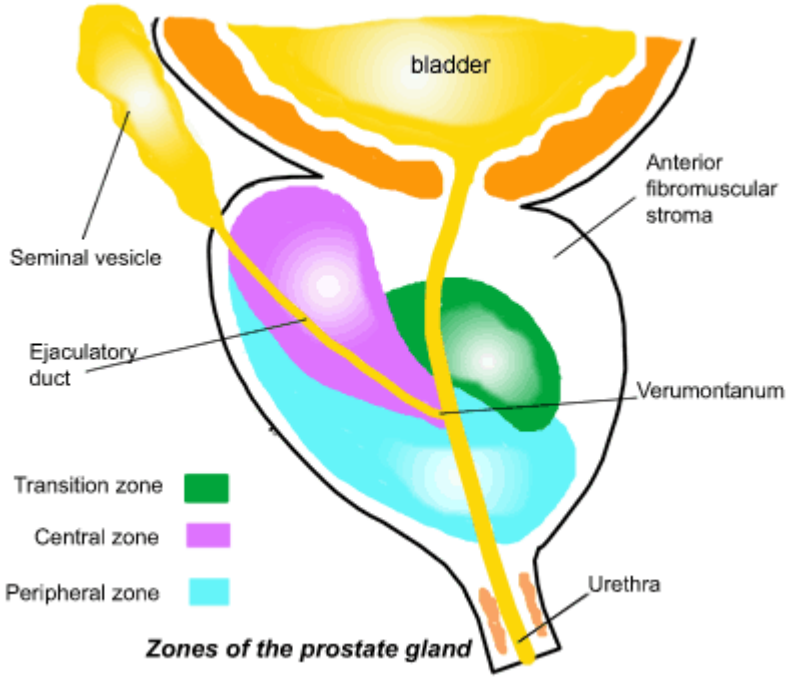
Prostate

- Zonal anatomy
  - Central zone
    - 25% Glandular elements
    - Surrounds ejaculatory ducts
  - Transitional zone
    - Glandular and Stromal elements
    - BPH
  - Peripheral zone
    - Largest zone
    - 75% of glandular elements
    - Usually site of carcinoma



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Prostate

- Integral part of Reproductive system
  - Important role in fertility
  - Anatomical
  - Physiological
- Produces PSA
  - Epithelial cells
- Ejaculate
  - Total volume ~3ml
  - SMV 1.5 - 2ml
  - Prostate 0.5ml

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What is PSA?

- Serine protease / Glycoprotein
- 1st demonstrated in human tissue in 1970 by Richard Ablin
- Widely used as clinical marker for CaP since early 90`s

- Also called Human Kallikrein 3 (hK3)

- First discovered during forensic investigations
  - ejaculate / prostatic fluid
- Free / Complexed forms

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PSA

- Why is PSA important for reproduction?
  - Lyses clotting ejaculate
  - Seminogellin
- Limitation as investigation
  - Organ specific
  - Not disease specific
- Multifactoral elevation
  - Malignancy
    - PSA "leak"
  - BPH / Inflammation / Interventions etc
- 5a Reductase inhibitors

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Screening

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Screening

- What is screening?
  - Asymptomatic patient
  - Normal DRE
  - Aim
    - Early disease pickup

- Who to screen?
  - All men > 50yr
  - Men > 45yr if + Fam Hx / African American
  - Stop when life-expectancy < 15yr

EAU Guidelines 2014 (level 2b)

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Why the controversy…?

- **CaP ideal screening candidate**
- **CaP is common**
  - Most commonly diagnosed visceral cancer in US males
  - 233 000 new cases of CaP expected in US in 2014

UptoDate, March 2014

- **Who is at risk?**
  - Lifetime risk for US male of Dx
    - 17.6% Caucasian
    - 20.6% African American
  - Lifetime risk of CaP death
    - 2.8% Caucasian
    - 4.7% African American

American Cancer Society, 2005

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Incidence…

- **Age matters**
- Age at Dx
  - <0.1% younger 50yr
  - 85% of patients > 65yr
  - Peak incidence 70-74yr
- Microscopic evidence of CaP at AUTOPSY
  - 30% 4th decade
  - 50% 5th decade
  - >75% in 8th – 9th decade

Sakr et al, 1993; Gronberg 2003

- **Lifestyle influence**

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Early detection best…

- **Timing of Dx is important**
  - Tumour extent = Mortality
  - 5yr relative survival of CaP
    - Localized100%
    - Metastatic 31.9%
  - Advanced disease not curable

Ries et al, SEER Cancer Statistics Review, 20007

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So why the controversy...?

- Asymptomatic aggressive local disease
- Early detection
- Improved outcomes...

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So why the controversy…?

- Screening not the problem…
- Screening **tools** are the problem
- Available modalities
  - PSA and derivatives
  - DRE
  - Imaging
  - Genetics (PCA3)

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PSA as screening tool

- Widely adopted early 90`s

- **Clinical** stage migration
  - Increased incidence loco-regional disease
  - Lower incidence metastatic disease

Newcomer et al, 1997

- **Pathological** stage migration
  - Increased incidence organ-confined disease post Rad Prostatectomy

- Nonpalpable cancers (T1c) **75%** of newly diagnosed cases

Derweesh et al, 2004

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PSA as screening tool

- PSA range 0 – 4.0 ng/ml
  - Sensitivity
    - 21% all cancers
    - 51% HG cancers
  - Specificity
    - 91%

UptoDate, March 2014

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PSA as screening tool

- Positive Predictive Values
  - **The proportion of men with elevated PSA who have CaP**

- PSA < 4 ng/ml
  - PPV ~30%
- PSA 4 – 10 ng/ml
  - PPV ~25%

Many negative Biopsies

- PSA > 10 ng/ml
  - PPV 42 – 62%
  - Organ confined < 50%

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Will lowering PSA cut-off help?

- PCP trial
  - PSA 2.1 – 4.0 ng/ml
  - 24.7% CaP / 5.2% Gleason ≥ 7

  - PSA of < 1.1 ng/ml
  - 17% CaP / 5% Poorly diff

PCPT, Thompson et al, 2003

- ? Clinical relevance
- If cut-off 2.5 ng/ml
  - 6 million new abnormal PSA in US alone
  - Overdiagnosis & Overtreatment
  - Improved Sens / Worse Spes

Welch et al, J Natl Cancer Inst, 2005

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PSA & Derivatives

- Free / Total Ratio
- PSA dynamics
  - PSADT
  - PSA velocity
- PSA vs Prostate size
  - PSA density
- Other PSA markers
  - Pro-PSA
  - hK2
  - PSMA (Membrane antigens)

NO CONCLUSIVE EVIDENCE

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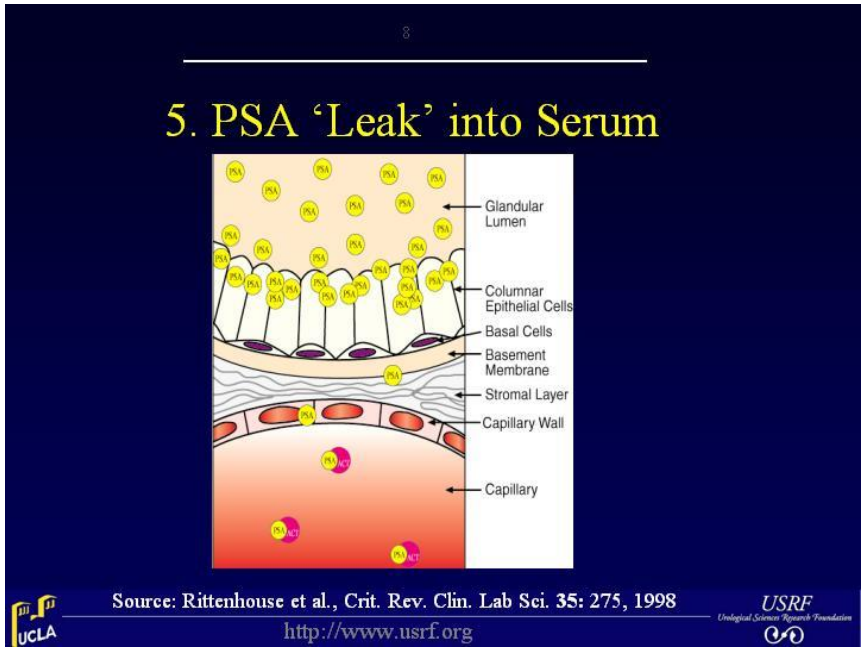
Free / Total Ratio

- Basement membrane disrupted in Ca Prostate
- PSA leak before completed proteolysis of PSA
- More complexed / Bound PSA in serum
- Less Free PSA proportionally

- **LOW RATIO = BAD**



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Other modalities

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DRE only

- Poor correlation of findings between urologists
- Sens & Spes
  - 59% & 94%

Smith et al, Urology, 1995

- PPV
  - 28% if abnormal DRE

Hoogendam et al, Fam Pract, 1999

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PSA & DRE combined

- Marginally improved detection rates
- Multicentre cancer detection screening study
  - 6630 men
  - 3.2% DRE
  - 4.6% PSA
  - 5.8% Combination
- 45% percent of cancers detected PSA only, 18% solely by DRE

Catalona et al, J Urol, 1994

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PSA & DRE combined

- PPV
  - 10% with suspicious DRE / Normal PSA
  - 24% with elevated PSA / Normal DRE

Yamamoto et al, Urology, 2001

- Suggested potential benefit

- **No RCT`s confirming this**

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MRI & Screening

- High sensitivities for locally advanced disease
- No proven benefit as screening tool
- Costs & Resources

Tanimoto et al, J MRI, 2007

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Genetics

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PCA3

- Identified 1999
- mRNA overexpressed in cancer tissue only
- PROGENSA®
- Urine specimen post vigorous DRE
- Costly

- PCA3 score
  - Ratio PCA3 mRNA / PSA mRNA

- Ratio > 25 positive

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PCA3

- Consider when
  - Elevated PSA / ≥ 1 negative Bx
  - Normal PSA / Family Hx
  - PSA 2.5 – 10 ng/ml / No previous Bx
  - Elevated PSA / Concommitant Urinary condition
  - Monitoring of treatment

Schilling et al, BJUI, 2009

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Landmark studies

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Screening studies

- Widely used
- No randomized trials initially
- New evidence disputing PSA screening long term benefits

- Trials
  - European Randomized Study of Screening for Prostate Cancer (ERSPC)
  - Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)

- **Very little to no long term benefit**

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Landmark studies

- ERSPC &PLCO
  - Multicentre
  - Randomized controlled trials
  - Large numbers

- PLCO
  - 7yr study
  - Controversial study design
  - No benefit found
  - Disputed conclusions

Andriole et al, N Eng J Med, 2009

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ERSPC trial

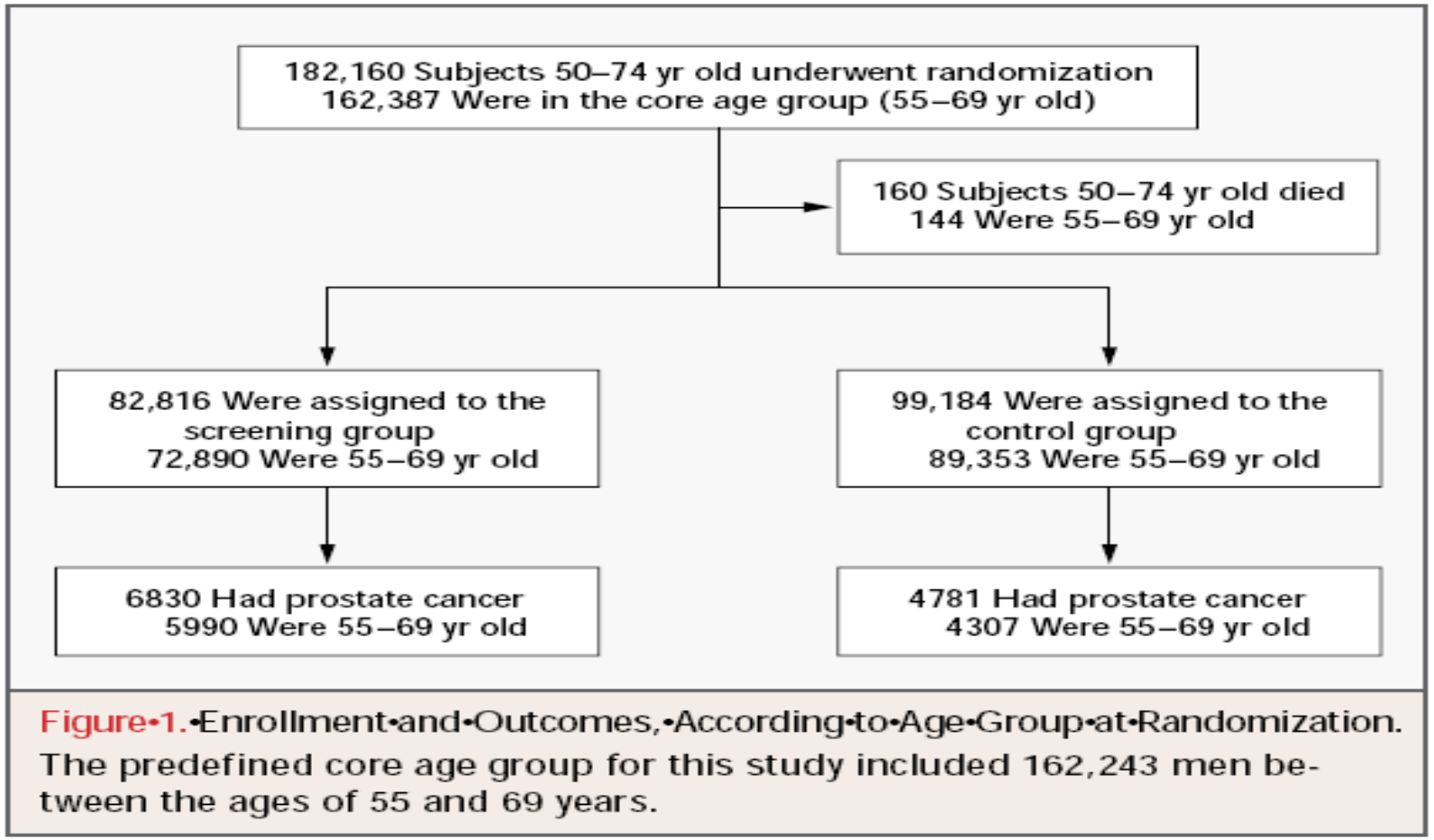

Figure 1. Enrollment and Outcomes, According to Age Group at Randomization.
The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years.

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ERSPC trial

- Median follow-up 11yr
- PSA cut-off for Bx
  - 3 ng/ml
- Screening intervals ~ 4yr
- Primary outcome
  - Rate of death from CaP
- QOL secondary outcome (not all centres)

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ERSPC trial outcomes

- **BENEFIT SHOWN!!**

- 21% improved CSS in **SCREENING** group (55-69yr group)

- Absolute prostate cancer mortality rates
  - 0.39 vs 0.50 per 1000 person / years
  - Absolute reduction of 0.10 deaths / 1000 person years

- Increased numbers CaP in screening group
  - 9.7 vs 6.0 cases / 1000 person years

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ERSPC trial outcomes

- Minimal survival benefit
- **1055 men screened = 37 additional cases = 1 CaP death prevented**
- High risk of overdiagnosis

Schröder et al, N Eng J Med, 2009

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ERSPC trial – Swedish arm

- **Best results**
  - Götenborg, Sweden
  - Cumulative CaP mortality reduction 44% after 14 yrs (95% CI)
  - 55% increase CaP pickup with screening

- First study proving significant survival benefit of screening

- **POSTER BOY FOR SCREENING**

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But…

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Screening = TRUS Bx = DANGER

- Abnormal DRE / PSA
- TRUS Prostate Bx
  - NOT INOXIOUS PROCEDURE
- Post Bx complications
  - **Sepsis**
    - Hospitalization 0.6 – 4.1%
  - **Mortality**
    - 0.1 – 0.3% in 30 days post Bx
  - **Psychological burden**

UptoDate, March 2014

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Critical analysis Swedish arm

- French group
- Actuarial / Statistical evaluation of Bx mortality
- Each CaP death avoided
  - 9.3 yrs life gained

- Death after Bx
  - 17.1 yrs life lost

- **Overall impact on survival net loss of 3.6 years of life / avoided death**

- For real gain require 666 screened / 1 death avoided

Boniol et al, BJUI,2012

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To screen or Not…

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Recommendations

- When in doubt…..follow the guidelines
- EAU guidelines
  - Joint decision with well informed patient
  - Start @ 50yr, unless risk factors
  - Stop when life expectancy < 10yr
- School of thought to risk stratify @ 40yr age

Zhu et al, Eur Urol, 2012

- Watch this space…

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Sources

- www.uptodate.com/contents/screening-for-prostate-cancer, March 2014
- Guidelines on Prostate Cancer, European Association of Urology, 2014
- The Prostate Cancer Gene3 assay: indications for use in clinical practice, *Schilling D et al, BJUI, 2009;105,452 - 455*
- Screening and Prostate-Cancer Mortality in a Randomized European Study, *Schroder et al, N Eng J Med,360;13,2009*
- Mortality results from a randomized prostate-cancer screening trial, *Andriole GL et al, N Eng J Med, 2009;360(13):1310*
- Critical role of prostate biopsy mortality in the number of years of life gained lost within a prostate cancer screening programme, *Boniol et al, BJU,2012:110,1648-1653*
- *Risk-based Prostate Cancer Screening, Zhu et al, Eur Urol, 61(2012)652-661*

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