4Kscore®

A Precision Test for Risk of Aggressive Prostate Cancer

BioReference LABORATORIES
an OPKO Health Company

How to Evaluate Risk for Prostate Cancer?

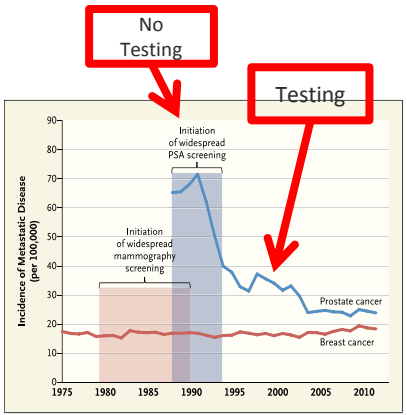
4Kscore

- PSA is a good screening tool
- But abnormal PSA leads to over 1 million prostate biopsies each year
  - **Low yield:** 75% of biopsies show no cancer or indolent cancer[1]
  - **Unnecessary surgical removal of prostate**: 66% of indolent cancers on biopsy are confirmed indolent when the prostate is removed[2,3]
  - **Adverse events:** Hospitalization, bleeding, infections, septicemia[4] - and with therapeutic interventions - complications of surgical removal or radiation
- **Preventative Services Task Force** recently drafted a change in their PSA guidelines, indicating it should be an individual decision for men aged 50-69 years
- **National Comprehensive Cancer Network** updated their guidelines to indicate the increased risk from prostate cancer in African-American men, who may need earlier screening

1.Parekh D et al European Urology 2015; 2. Eggener S et al J Urol 2015; 3.Jalloh M et al. European Urology 67:451, 2015; 4.Nam RK et al J Urol 189:S12, 2013 5. USPSTF: screeningforprostatecancer.org/ 6. NCCN Prostate Cancer Early Detection v. 1.2017

Should we just abandon screening?.... NO

- Prostate cancer remains a lethal disease
- Second leading cause of cancer death in US men

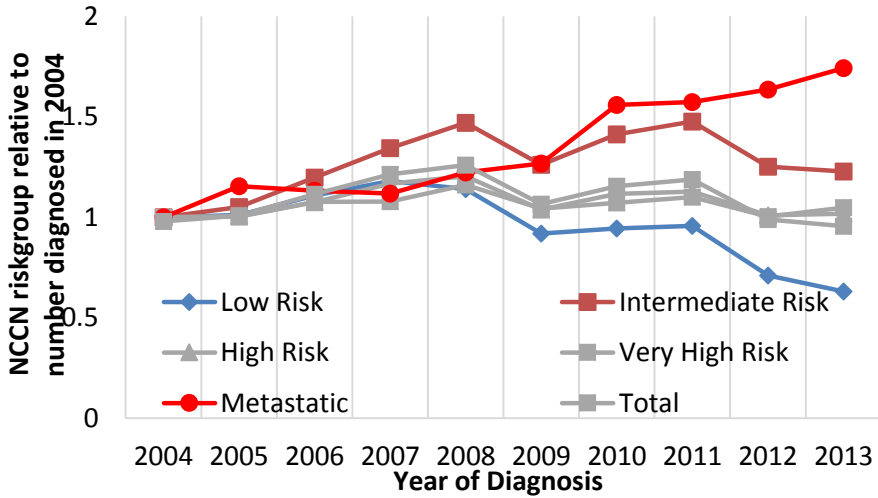


Incidence of Cancer That Was Metastatic at First Presentation, United States, 1975–2012.

Data are for breast cancer (SEER historic stage distant) among women 40 years of age or older and prostate cancer (American Joint Committee Stage IV) among men 40 years of age or older.

- Results of contemporary reductions in screening:

  MORE Metastatic/Lethal disease



1. Welch HG et al NEJM 2015 2. Weiner AB, et al Prostate Cancer Prostatic Dis 2016

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A follow up test to identify risk for high grade, aggressive prostate cancer

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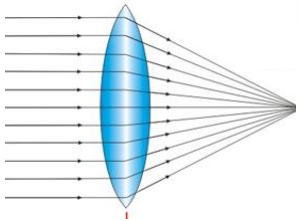
Components

4Kscore Algorithm

- Aggressive cancer: Total PSA, Free PSA, Intact PSA, hK2
- Clinical: + Age, DRE, and prior biopsy status



Results

4Kscore algorithm specifically provides % risk of having high grade prostate cancer on prostate biopsy

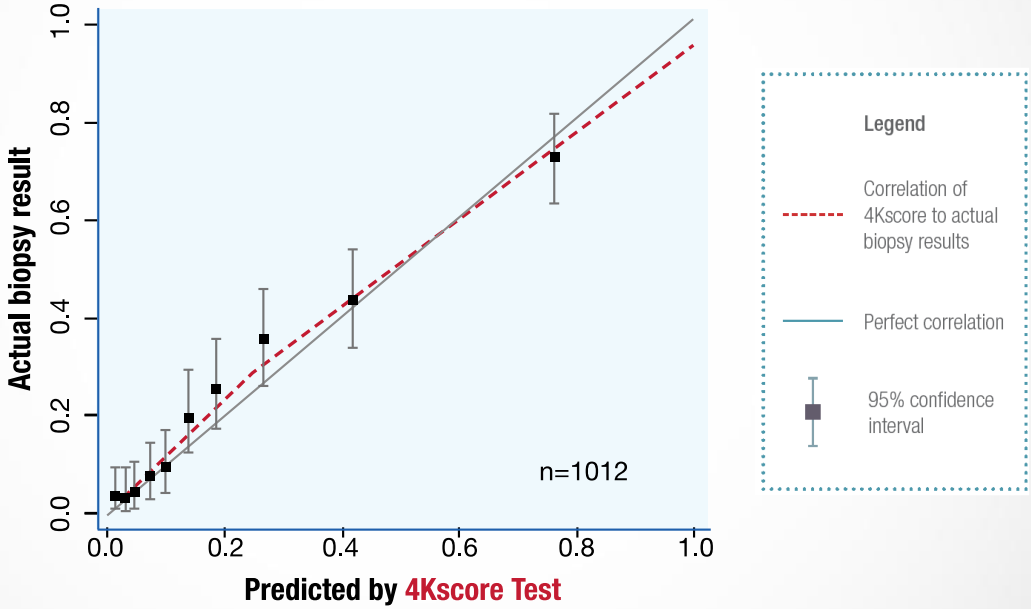
- Commercial, CLIA certified laboratory developed test, included in NCCN Guidelines with a CPT Category I code and Medicare National Price
- Designed to identify risk of aggressive prostate cancer
- OPKO - Intact PSA and hK2 associated with poorly differentiated prostate cancer[1-3]

1. Denmeade et al Prostate 48:1-6, 2001; 2. Avergis et al Biol Chem 393:301-17, 2012; 3. Kontos et al Clin Chem Lab Med 50:1877, 2012.

4Kscore Predicts Risk of Aggressive Prostate Cancer

Validated in a prospective, blinded, multicentre US study of 1012 men using current prostate cancer protocols

4Kscore predicts biopsy results



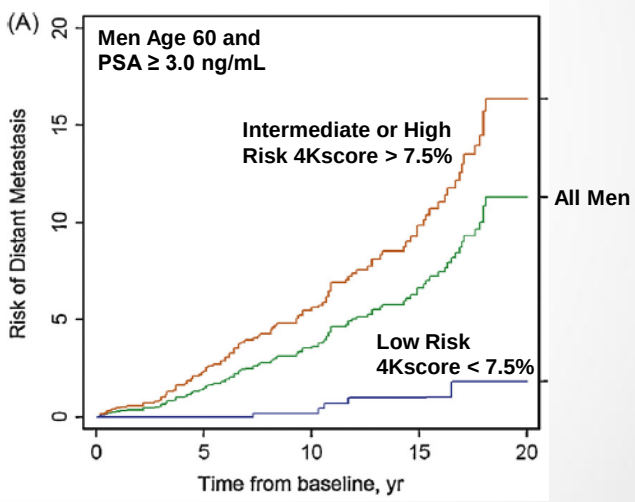
Parekh et al. *Eur Urol.* 2015; 68: 464–470

4Kscore Categorizes Long Term Risk of Developing Distant Metastasis

Men who have a low risk 4Kscore test are at low risk for distant metastasis up to 15-20 years later

Age 50 PSA ≥ 2 ng/mL	10 yr	15 yr	20 yr
4Kscore < 7.5%	0.26%	0.90%	1.25%
4Kscore > 7.5%	2.40%	8.25%	10.68%

Age 60 PSA ≥ 3 ng/mL	10 yr	15 yr	20 yr
4Kscore < 7.5%	0.18%	0.99%	1.82%
4Kscore > 7.5%	5.62%	9.85%	16.36%



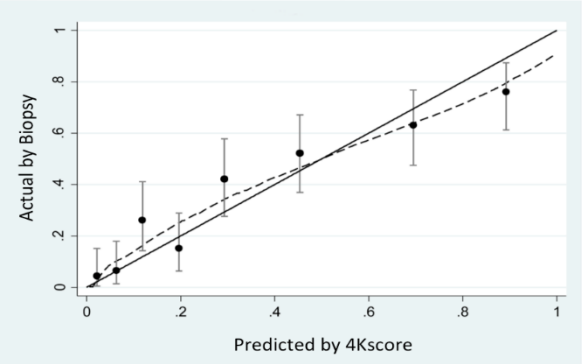
Stattin et al. *Eur Urol*. 2015; 68: 207-213

4Kscore Study in the VA Health System

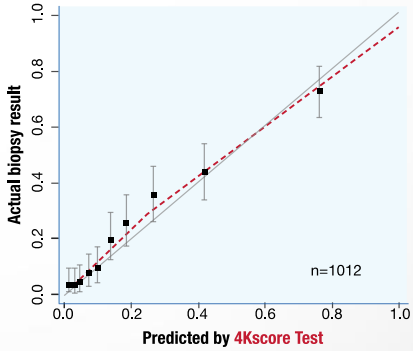
- Multi-institutional, prospective trial involving 8 Veteran's Affairs sites around the nation

- Compared the performance of 4Kscore between African-American and non-African-American men

366 Men prospectively enrolled with 4Kscore and biopsy data
208 (56%) men were African American
131 (36%) men were found to have Gleason 7+ prostate cancer



4Kscore calibration to prostate biopsy in VA Men

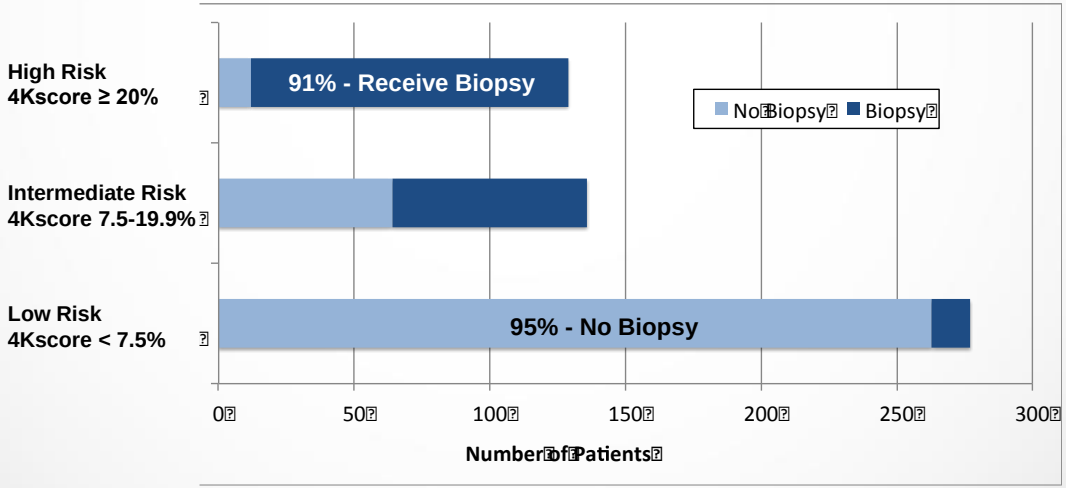


4Kscore calibration in original US validation study

1. Punnen et al. J Urol. 2017 Apr; 197(4)(Suppl.):e1356-e1357. 2. Parekh et al. *Eur Urol.* 2015; 68: 464–470

4Kscore Substantially Reduces Biopsy Rate in Low Risk Patients

- 611 subjects with suspicion of prostate cancer seen by 35 urologists
- Overall biopsy reduction rate = 65%
- 542 (89%) of the biopsy decisions were impacted by the 4Kscore. In this group:
  - 95% of 4Kscore low risk group did not receive prostate biopsy
  - 9% of 4Kscore high risk group did not receive a prostate biopsy



Konety et al. Rev. in Urol. 2015

4Kscore in Clinical Practice

- Reduces uncertainty by providing an accurate risk percentage for aggressive prostate cancer
- Excellent calibration with prostate biopsy results
- VA study group had a majority of African-American men and demonstrated similar accuracy to previous studies
- Predicts risk of distant metastasis for up to 20 years
- Included in National Clinical Guidelines
- Reduces prostate biopsies by up to 65%
- Reduces complications and pain from unnecessary prostate biopsies and potential unnecessary treatment
- Reduces cost of unnecessary procedures

4Kscore Summary

- Paradigm shift
  - Continue screening of men to find aggressive prostate cancer early
  - Avoid immediate biopsy in all men with a suspicious PSA
    - Reduce complications from unnecessary procedures
    - Reduce healthcare cost
- Provide a continuous risk score with risk categories
  - Reduce uncertainty in physician-patient shared decision making
  - Provide actionable, accurate, and easily interpretable results
- Acceptance amongst payors and providers