4Kscore for Prostate Cancer Risk Assessment

Introduction

4Kscore testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
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What is prostate cancer

Definition

Prostate cancer is the most common cancer among men, with over 164,000 new cases identified each year in the United States.\(^1\,2\,3\)

Prevalence

The median age at diagnosis is 66 years.\(^3\) Older men are more likely to be affected than younger men, and African American men have higher rates compared to men of other ethnic backgrounds.\(^3\) It is more likely to occur in men with a family history of prostate cancer.\(^3\,4\)

Diagnosis

Screening programs for prostate cancer allow for its early detection. Screening is typically performed by prostate-specific antigen (PSA) test and digital rectal examination (DRE).\(^2\)

Diagnosis is confirmed by prostate biopsy.\(^4\,6\) Biopsy is typically performed by a collection of approximately 12 needle biopsy cores.\(^6\)

Poor detection with biopsies

Initial biopsies only detect 65-77% of prostate cancers and repeat biopsies are frequently performed.\(^7\,8\) The false negative rate of biopsy may be as high as 25%.\(^9\)
Test information

Introduction

The 4Kscore Test (OPKO Lab) is an assay that determines an individual's risk of aggressive prostate cancer.10

4Kscore test

4Kscore uses a blood sample to measure total PSA, free PSA, intact PSA, and Human Kallikrein 2. These measurements in combination with patient age, digital rectal exam, and negative previous biopsy status are used to come up with a risk score.10

Results

The 4Kscore test is reported as a percent between <1% to >95%. This corresponds to the chance of having aggressive cancer in a prospective biopsy.10

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to 4Kscore testing.

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (2019) Clinical Practice Guidelines for Prostate Cancer Early Detection state the following:6

• “Those patients with negative prostate biopsies should be followed with DRE and PSA. Tests that improve specificity in the post-biopsy setting - including percent-free PSA, 4Kscore, PHI, PCA3, and ConfirmMDx - should be considered in patients thought to be higher risk despite a negative prostate biopsy.”

• “Biomarkers that improve the specificity of detection are not, as yet, mandated as first-line tests in conjunction with serum PSA. However there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or physician wish to further define the probability of high-grade cancer. A percent-free PSA <10%, PHI >35, EPI score greater than 15.6, or 4Kscore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone a biopsy or after negative biopsy; a PCA3 score >35 is potentially informative after a negative biopsy. The predictive value of the serum biomarkers discussed above has not been correlated with that of MRI. Therefore it is not known how such tests could be applied in optimal combination.”

• “The panel consensus is that [4Kscore] can be considered for patients prior to biopsy and for those with prior negative biopsy who are thought to be at higher risk
for clinically significant prostate cancer. It is important for patients and urologists to understand, however, that no optimal cut-off threshold has been established for the 4Kscore.”

American Urological Association

The American Urological Association issued a Guideline Statement: Early Detection of Prostate Cancer (Reviewed and confirmed in 2018) stating:11

- “Multiple approaches subsequent to a PSA test (e.g., urinary and serum biomarkers, imaging, risk calculators) are available for identifying men more likely to harbor a prostate cancer and/or one with an aggressive phenotype. The use of such tools can be considered in men with a suspicious PSA level to inform prostate biopsy decisions.”

American Joint Committee on Cancer

The American Joint Committee on Cancer (2017) states:12

- “The AJCC will continue to critically analyze emerging prostate cancer biomarkers and tools for their ability to prognosticate and guide treatment decision making with the highest level of accuracy and confidence for patients and physicians.”

Peer-Reviewed Literature

A number of peer-reviewed expert-authored studies that evaluate the clinical validity and utility of the 4Kscore test for detection of aggressive prostate cancer are available.13-25 Most of these studies demonstrate the potential for the assay to help urologists accurately discriminate between indolent and aggressive prostate cancer, reduce overtreatment, and reduce the burden of cost on patients with suspicion of aggressive prostate cancer. Limitations were noted across the studies and include retrospective study design, small sample sizes, and lack of randomization and blinding.

Criteria

Introduction

Requests for 4Kscore testing are reviewed using these criteria.

Criteria

- No previous 4Kscore testing performed after the most recent negative biopsy when a result was successfully obtained, AND
- No previous ConfirmMDx testing on the most recent negative biopsy when a result was successfully obtained, AND
- Member is not under active surveillance for low stage prostate cancer, AND
• Negative prostate biopsy within the past 24 months, AND
• Member is considered at higher risk for prostate cancer by one or more of the following:
  o Family history of 1st degree relative with prostate cancer diagnosed younger than age 65 years,\textsuperscript{6,26-28} and/or
  o Family history of two or more first-degree relatives with prostate cancer diagnosed at any age,\textsuperscript{27} and/or
  o African American race,\textsuperscript{6,26-28} and/or
  o Known mutation in a gene associated with increased risk of prostate cancer (e.g. BRCA1/2, HOXB13 (G84E mutation carriers), MLH1, MSH2, MSH6, PMS2, EPCAM),\textsuperscript{6,26,29} and/or
  o PSA level of greater than 10 ng/ml,\textsuperscript{30} and/or
  o PSA level increase of greater than 0.35 ng/ml/year if PSA level less than or equal to 10 ng/ml,\textsuperscript{6,31} and/or
  o PSA doubling time of less than 3 years, when initial PSA level is greater than or equal to 4 ng/ml and other causes of rising PSA (i.e., infection, inflammation) have been ruled out for individuals whose PSA doubling occurred in less than 2 years\textsuperscript{32,33}

References

Introduction

These references are cited in this guideline.


10. 4Kscore website. Available at: http://4kscore.opko.com/


