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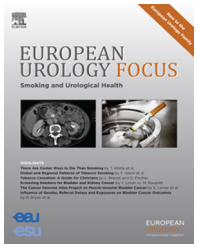


Review – Prostate Cancer

# The Role of Biomarkers and Genetics in the Diagnosis of Prostate Cancer

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## Abstract

***Context:*** Given the pitfalls of prostate-specific antigen (PSA) testing for screening men with asymptomatic prostate cancer (PCa), a number of novel biomarkers have recently been studied that potentially decrease false-positive PSA results and unnecessary biopsies.
***Objective:*** To review the literature on biomarkers with potential diagnostic utility for PCa by guiding the decision for initial or repeat biopsies in patients with elevated PSA.
***Evidence acquisition:*** We conducted a systematic literature review of human clinical studies on diagnostic biomarkers reporting clinicopathologic outcomes. A comprehensive search was performed in the Medline, Scopus, and Web of Science databases for articles from January 2005 through June 2015.
***Evidence synthesis:*** For men presenting with elevated PSA, especially in the 4–10 ng/ml range, who are considered for initial prostate biopsy, two serum-based assays, the Prostate Health Index and the four-kallikrein panel, can help identify patients with an increased risk of significant cancer on biopsy. In the setting of a prior negative biopsy but elevated PSA, urine-based assays detecting prostate cancer antigen 3 and/or transmembrane protease, serine2:v-ets avian erythroblastosis virus E26 oncogene homolog fusion transcript help predict the risk of high-grade cancer on subsequent biopsy. In cases with elevated PSA and an initial negative biopsy, epigenetic analysis can predict cancer diagnosis on subsequent biopsies. The combination of these novel biomarkers with existing nomograms and risk calculators leads to increased predictive accuracy and avoids unnecessary biopsies.
***Conclusions:*** Rapid strides have been made in the discovery of novel biomarkers for guiding biopsy decisions in men suspected of harboring PCa. Although some of them have been approved for specific clinical settings, most of them still await rigorously designed prospective validation studies.
***Patient summary:*** Novel urine-, serum-, and tissue-based biomarkers have been validated for guiding decisions on prostate biopsy in asymptomatic men with elevated prostate-specific antigen. Further exploration in this field may help expand their diagnostic and prognostic roles for prostate cancer.


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## 1. Introduction

Prostate cancer (PCa) is the most common noncutaneous malignancy and the second most common cause of cancer-related deaths in Western men. With an estimated lifetime incidence of 16% in contemporary American men [1], most cases of PCa are diagnosed in the localized stage, due in large part to widespread prostate-specific antigen (PSA) screening. Notwithstanding its relatively indolent nature, PCa still carries a lifetime mortality risk of 3% [1], almost entirely due to metastatic disease. In this context, biomarkers (ie, biological markers) for PCa have three distinct but overlapping roles: *diagnosis* of clinically significant disease (eg, Gleason score [GS] 7–10) that may warrant further treatment, *prognosis* in the pretreatment (allowing risk stratification and treatment selection) and/or post-treatment setting (deciding on the need for adjuvant treatment and tailoring follow-up regimens), and *predicting/monitoring* possible response to secondary therapy. The current review focuses on the diagnostic relevance of biomarkers in PCa.

PSA testing has traditionally been used for screening men with asymptomatic PCa, even in the face of suboptimal sensitivity and specificity, variability in the different commercial assays, and conflicting recommendations on population-based PSA screening. To circumvent this problem, researchers have studied numerous novel biomarkers in an attempt to refine the diagnostic accuracy of PSA in predicting the risk of PCa on future biopsy, especially in the PSA grey zone of 4–10 ng/ml. These markers have primarily been studied in urine, serum, or prostate biopsy specimens. Rapid advances in whole genome sequencing, proteomic analyses, and metabolic profiling of PCa have driven the discovery and further exploration of these biomarkers. Nonetheless, most of these novel biomarkers still remain in the investigational phase absent large-scale validation studies, while some of them have been marketed commercially and approved by the US Food and Drug Administration (FDA) for use in specific clinical settings. Owing to the magnitude of research performed in this area, we have primarily focused on biomarkers studied within the past decade (2005–2015).

## 2. Evidence acquisition

A literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria [2] by two authors (D.D. and F.A.). Figure 1 illustrates the inclusion process of the literature search. Databases including PubMed, Ovid, Scopus, and Web of Science were queried for all articles from January 2005 through June 2015, using the keywords "prostate cancer" AND "biomarkers" AND "diagnosis." The search was further restricted to human studies and those published in English. Studies focusing on clinicopathologic outcomes—presence of any PCa, presence of significant (GS $\geq$7) cancer, clinical stage, and/or number of positive cores on biopsy—and those that have had at least one internal/external validation study were prioritized. Reference lists of selected

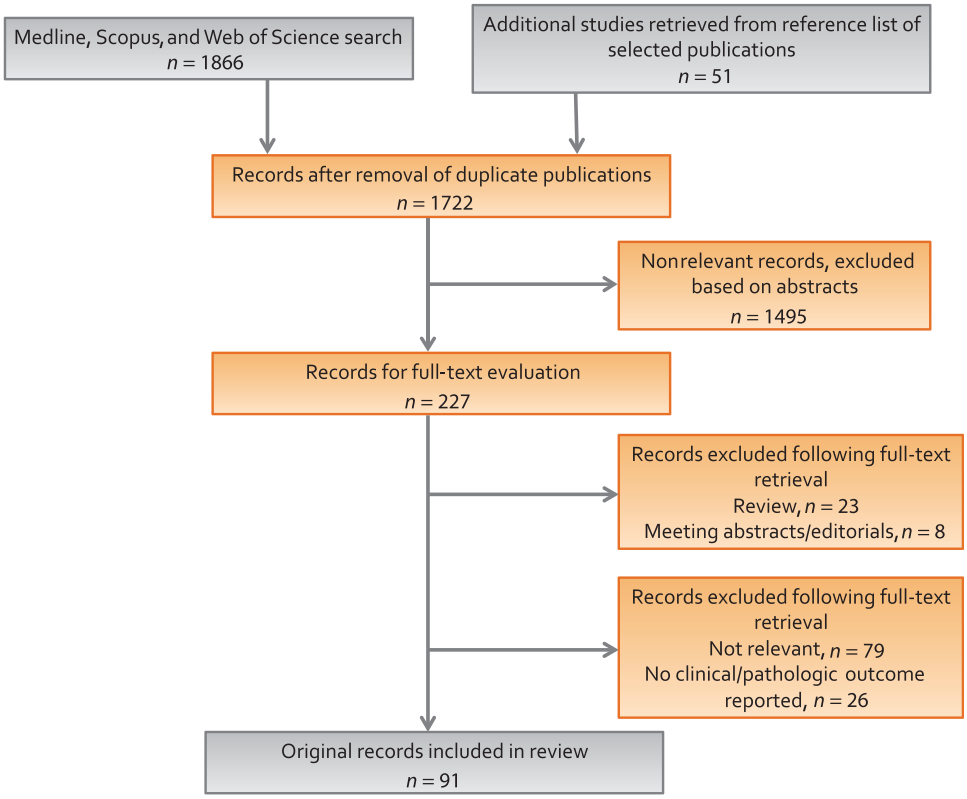


**Fig. 1 – Inclusion process of the literature search.**