PSA (Prostate-Specific Antigen) for Prostate Cancer Diagnosis

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Introduction

Prostate-Specific Antigen (PSA) is a biomarker used to indicate early prostate cancer in men[1,2]. PSA is easily detected in blood[3]. High PSA levels might indicate either prostate cancer or another prostate disease other than cancer[1]. A High PSA test result does not necessarily mean the patient is likely to have prostate cancer, but rather motivates additional tests and examinations of the prostate such as the Digital Rectal Examination (DRE)[4].

PSA is also known as gamma-seminoprotein, kallikrein-3 (KLK3), or P-30 antigen. Specifically, PSA is a glycoprotein enzyme which is encoded in humans by the KLK3 gene[5]. PSA is secreted by epithelial cells within the prostate gland[5,6].

Evidence Supporting the use of PSA

PSA is a useful, but imperfect biomarker for prostate cancer. PSA testing over the past few decades has resulted in a significant increase in the rate of prostate cancer detection accompanied by an increase in how early the prostate cancer is detected within a patient[7]. The combined use of a PSA test and a digital rectal examination (DRE) has led to an increase in the detection of treatable, localized prostate cancer and a decrease in the detection of incurable, advanced cancer[8,9]. PSA is not specific for prostate cancer and has a very high false positive rate when used to screen for prostate cancer[10,11]. Despite these shortcomings, PSA testing remains a valuable tool for detecting prostate cancer.

Biomarker Precision

PSA's precision as a biomarker depends heavily on the establishment of an upper limit of normal (ULN). According to Hernandez et al, a universally-accepted optimal upper limit of "normal" for PSA as a prostate cancer biomarker has not been established[7].

Early in the history of PSA use as a prostate cancer biomarker, a PSA value of 4.0ng/mL[12] was considered the ULN (upper limit of normal). A large Prostate Cancer Prevention Trial (PCPT) involved 2,950 patients [13] and was conducted in 2004. The study's control group never had a PSA level greater than 4.0 ng/mL, and PSA levels between 0 and 4.0 ng/mL had a positive predictive value of 6.6% - 26.9%. In this study, 14.9% of men with prostate cancer had advanced disease, and for men with a PSA level between 3.1ng/mL and 4.0ng/mL, 25% had advanced, "high-grade" disease[13].

As these results indicate, the precision of PSA as a prostate cancer biomarker is strongly influenced by the selected ULN value.

There are several factors known to impact the measured PSA levels in men which are unrelated to prostate cancer and are responsible for false positive results[14,15]. Additionally, elevated PSA levels are not specific to prostate cancer. PSA levels can also be elevated in patients with other types or cancer and even unrelated diseases[16]. PSA levels are known to be higher in older men compared to their younger counterparts[9,11,17,18]. This age trend should be considered when evaluating a patient's PSA levels. There are also documented racial differences, with PSA levels (and also PSA 'density') among African-American men being significantly higher than other populations among those without prostate cancer[19].

How this example corresponds with the biomarker ontology and data model

Table 1: *LOINC codes and related lab test information for PSA prostate cancer biomarkers within the Biomarkers project data model*

LOINC Code	Lab Name, Details	Protein
10886-0	Prostate Specific Antigen (PSA) Free Kallikrein 3	Kallikrein-3
12841-3	Prostate Specific Antigen (PSA) Free Percent Kallikrein 3	Kallikrein-3
2857-1	Prostate Specific Antigen (PSA) Kallikrein 3	Kallikrein-3

How additional illumination could improve their clinical value

Additional illumination of PSA as a prostate cancer biomarker could involve pairing PSA with one or more other known biomarkers or metabolites to create new assays that produce less false-positive results. There are several emerging candidates for new prostate cancer biomarkers such as microRNAs, circulating tumor cells, and exosomes[20–22]. Perhaps one or more of these novel prostate cancer biomarkers could be paired with PSA to develop a new panel capable of producing less false-positive results while maintaining specificity to prostate cancer. It is also possible that further illumination of PSA could reveal new, additional shortcomings that discourage its use as a precise, specific biomarker for the early detection of prostate cancer.

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