**BACKGROUND AND PURPOSE**

Prostate cancer has nearly a 100% survival rate if diagnosed early.\(^1\) Though recognized worldwide as the standard prostate cancer screening test, PSA testing is tissue-specific, not cancer-specific, resulting in more chances of a false positive due to non-cancerous conditions such as prostate enlargement, prostatitis, or urinary tract disease—especially with "gray zone" results between 4-10 ng/mL.\(^2,\)\(^3,\)\(^4\)

The diagnostic confirmation of prostate cancer in patients with a PSA in the gray zone is controversial, often leading to unnecessary biopsy.\(^5\) Without consensus guidelines for prostate management in the gray zone, nearly 80% of prostate biopsies performed are negative for cancer,\(^6\) unnecessarily subjecting thousands of men to harmful side effects of overtreatment, including impotence and incontinence.

We developed a new circulating-tumor-cell (CTC) assay for detection of prostate cancer in patients in the PSA gray zone, with the goal to decrease the number of unnecessary prostate biopsies.

**METHODS AND STUDY DESIGN**

A prospective clinical study was conducted in 200 high-risk subjects. All subjects underwent routine prostate screening including PSA testing and digital rectal exam (DRE). 4 mL of blood was drawn and processed for CTC analysis using the CellMax biomimetic platform.\(^7\)

A subset of 84 subjects with PSA levels in the gray zone (4-10 ng/ml) and those diagnosed as ‘diseased’ based on PSA and DRE results also underwent a biopsy for comparison with blinded CTC test results. The CellMax CTC Prostate Test uses a proprietary microfluidic biochip that accurately captures and enumerates CTCs with antibodies to EpCAM, CK18, and PSMA.\(^8\) Multivariate regression models incorporating CTC Prostate Test results were utilized to derive age-adjusted CTC scores predictive of clinical outcomes.

**RESULTS**

84 subjects with PSA levels in the gray zone (4-10 ng/ml) were included in this study. Prostate biopsy results were available for a subset of 42 patients; 10 had confirmed cancer. A CTC score was calculated as a nonlinear weighted combination of the captured CTCs identified with CK18 and PSMA antibodies. After adjustment for age and PSA, the CTC score remained a significant predictor of clinical outcome in the PSA gray zone (likelihood ratio p-value = .013) whereas PSA was not significant.\(^9\) The sensitivity and specificity of the CTC score were 80.0% (95% CI: 44.4%, 97.5%) and 93.8% (95% CI: 79.2%, 99.2%). Negative agreement and Positive agreement were 93.8% (95% CI: 79.2%, 99.2%) and 80.0% (95% CI: 44.4%, 97.5%).\(^9\) Given the observed odds ratio for CTC score in the study, approximately 0.90 (95% CI 0.79, 0.98), the study is appropriately powered.

**CONCLUSIONS**

This study demonstrates the CTC Prostate Test as a valuable new biomarker in prostate cancer, and proves its clinical utility in the PSA gray zone by helping physicians stratify patients who do not need a prostate biopsy. The test has the potential to reduce unnecessary biopsies in gray zone patients by up to 90%. This is one of the first clinical studies to show the utility of CTCs for accurate prostate cancer detection in the PSA gray zone.

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