Prolaris®

Prostate Cancer Prognostic Test

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CLINICAL SUMMARY

Development and validation of a cell cycle progression signature for decentralized testing of men with prostate cancer

Kuhl V. et al., Biomark.Med. 2022;16, 449–59.

Introduction

The 46-gene Prolaris test, combining individual genomic cell cycle progression information (CCP score) with clinico- pathological features (CAPRA score), is an independent prognostic tool for disease progression and mortality in men with localized prostate cancer. With two clinically validated thresholds, the test can inform tailored treatment decisions for both conservative management (active surveillance) and definitive treatment (single versus multi-modal therapy).

With an increasing requirement or preference for countries to perform in vitro diagnostic testing locally using in-house platforms and/or the need for expedited testing times, traditional centralized testing may present a barrier to access from a physician and patient perspective. The purpose of this study was to develop and validate a kit-based CCP test to allow for decentralized testing in localized facilities, increasing patient access to testing and reducing time to result.

Methods

To develop an assay that could be run effectively as a kit, an abbreviated gene panel was required

- The selection of the abbreviated gene panel for the kit was determined using data from samples previously submitted for Prolaris testing. The genes of the original 46-gene centralised test were ranked and selected according to expression level, specificity, and correlation with CCP score.
- CCP scores were generated from 100 FFPE samples for both tests and their equivalence evaluated to ensure the results of the kit test could be applied clinically in the same manner as the 46-gene test.
- Factors impacting the repeatability and reproducibility of the kit test were evaluated to ensure the test would perform properly in a decentralised setting, using multiple samples, kit lots, operators, and instruments.
- The clinical validity of the kit-based CCP score was assessed via in silico reanalysis of previously published validation cohorts (Cuzick 2012 and 2015).

Results

Gene selection: Ranking and selection of the original 46 genes produced a final 16-gene kit consisting of ten CCP genes and six housekeeping genes.

CCP genes: *ASPM, CDC2, CDCA8, CDKN3, DTL, FOXM1, KIAA101, NUSAP1, PRC1, TK1*

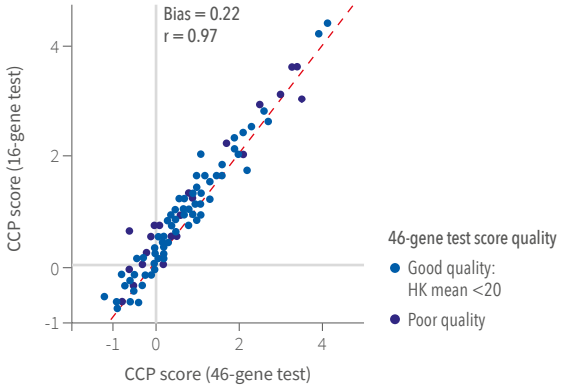
Housekeeping genes: *CLTC, PSMA1, RPL4, RPS29, SLC25A3, UBA52*

Tissue from FFPE localized prostate cancer biopsy was macro dissected in order to extract RNA. All CCP and housekeeping genes in the 16 gene panel had a PCR efficiency within the acceptable range of 90-110%. RNA measurement range was also acceptable showing that RNA input concentration did not affect the CCP score result.

Repeatability / Reproducibility: The CCP score of the 16-gene test was highly repeatable and reproducible (SD 0.085 and 0.115). It was not impacted by the instrument used and was only minimally impacted by test operator and kit lot.

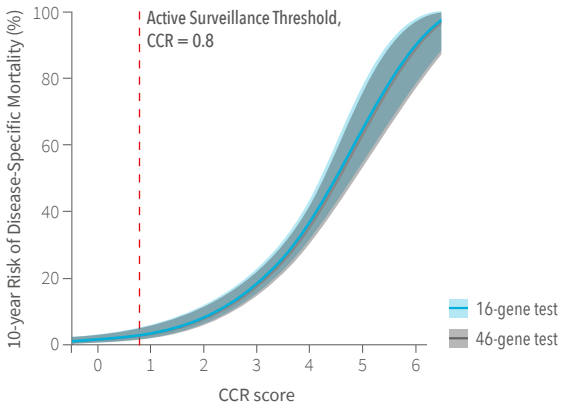
Equivalence: The CCP scores generated from both the 46-gene and 16-gene kit showed high correlation (r=0.97) and comparable results demonstrating analytical equivalence between both versions of the test.

Fig 1. Correlation of cell cycle progression score from 16-gene test with score from 46-gene test.



Clinical validity: In silico reanalysis of previously published clinical validation prostate cancer cohorts showed that the 16-gene test produced a clinical cell cycle risk score (CCR) that was a significant prognosticator of 10-year disease-specific mortality similar to the 46-gene cell cycle risk score:
- 16-gene, HR=2.28, 95% CI 1.93-2.70, p=8.46x10-26;
- 46-gene, HR 2.26, 95% CI 1.93-2.65, p=2.34x10-27.

Fig 2. Risk curves from the 46-gene test report and based on the 16-gene test CCR.



Conclusions

- The 16-gene kit-based CCP signature is an analytically valid test to independently prognosticate the risk of prostate cancer progression, comparable with previous validation of the 46-gene CCP score.
- CCP score produced by the 16-gene test is independent of the input RNA concentration where the PCR efficiency of the genes was acceptable and the minimum tumor content should be >50%.
- CCP scores were highly repeatable and reproducible, with no or limited impact from instrument, kit lot or operator.
- In silico reanalysis of the original 46-gene Prolaris clinical validation studies demonstrated that the CCP scores derived from the 16-gene kit are robust and equivalent to those obtained with the larger gene panel, making the Prolaris kit a reliable solution for countries where local testing is preferred.

Bottom line

- **This is the first prognostic test for prostate cancer that is available in a kit form for decentralized testing; enabling more men with localized prostate cancer to make informed decisions.**
- **As with the 46-gene Prolaris test, the 16-gene Prolaris kit utilizes two validated thresholds: enabling the identification of those patients who are candidates for active surveillance versus definitive treatment and those suited to single versus multi-modal therapy.**

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