PROGNOSTIC AND CLINICAL UTILITY CAPABILITIES OF CELL CYCLE PROGRESSION TESTING, PROSTATE IMAGING-REPORTING AND DATA SYSTEM SCORING, AND CLINICOPATHOLOGIC DATA IN MANAGEMENT OF LOCALIZED PROSTATE CANCER

David Morris, MD[1]; J. Scott Woods, FNP-BC[1]; Lauren Lenz, MS[2]; Jennifer Logan, PhD[2]; Todd Cohen, PhD[2]; Steven Stone PhD[2]

1.Urology Associates, PC, Nashville TN 37209 2.Myriad Genetics, Inc., Salt Lake City, UT 84108

BACKGROUND

- For men with newly diagnosed, localized prostate cancer (PrCa), determining whether it is safe to pursue active surveillance (AS) requires precise risk stratification.
- Multiparametric magnetic resonance imaging (mpMRI) with Prostate Imaging and Reporting and Data System (PI-RADS) scoring and the cell cycle progression (CCP) molecular prognostic test both have emerged as important tools for improving PrCa risk discrimination.
- We compared the prognostic and clinical utility capabilities among CCP testing, mpMRI with PI-RADS, and clinicopathologic data in selected medical management scenarios. We assessed:
  - Distributions of CCP scores, clinical cell-cycle risk (CCR) scores, and clinicopathologic data relative to PI-RADS.
  - Ability to predict tumor grade post-radical prostatectomy.
  - Impact on the decision to pursue AS or curative therapy.

METHODS

COHORT

- This was a retrospective, observational analysis of data from sequential patients (N=223, across two cohorts) from a single Urology community practice (January 2015-June 2018).
- Inclusion criteria: diagnosed with localized PrCa; had a PI-RADS version 2 score derived from mpMRI-ultrasound fusion targeted biopsy; and a concomitant biopsy CCP test result.
- Cohort 1 (n=157): Men newly diagnosed with localized PrCa, either with or without a previous negative biopsy.
- Cohort 2 (n=66): Men with localized PrCa who had initiated AS without CCP testing, but who subsequently received the test, with medical management informed by the result.

ANALYSIS

- The CCP test measured the expression of 31 CCP genes and 15 housekeeper genes in FFPE tissue using RT-PCR.
- The CCP score was calculated as the normalized expression of 31 CCP genes and was combined in a validated model with the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score (0.57×CCP + 0.39×CAPRA) (Cuzick et al., *Br J Cancer,* 2015).
- Likelihood-ratio tests were used to determine predictor significance in both univariate and multivariate models.

RESULTS

Table 1. Patient Characteristics

	Cohort 1 Newly Diagnosed		Cohort 2 On AS		Combined Cohorts 1 + 2	
	N	Median (IQR) or Frequency	N	Median (IQR) or Frequency	N	Median (IQR) or Frequency
Age at Biopsy Collection	157	68 (61, 72)	66	69 (63.75, 73)	223	68 (62, 72)
CCP	157	-0.40 (-0.90, 0.00)	66	-0.60 (-1.18, -0.10)	223	-0.50 (-0.90, 0.00)
CAPRA						
Low (0 – 2)	47	29.9%	34	51.5%	81	36.3%
Intermediate (3 – 5)	82	52.2%	28	42.4%	110	49.3%
High (6 – 10)	28	17.8%	4	6.1%	32	14.3%
CCR	157	1.10 (0.55, 1.94)	66	0.80 (0.21, 1.38)	223	1.00 (0.38, 1.63)
Below AS threshold (≤0.8)	58	36.9%	33	50.0%	91	40.8%
Above AS threshold (>0.8)	99	63.1%	33	50.0%	132	59.2%
PI-RADS						
2/3 (low/ intermediate)	50	31.8%	24	36.4%	74	33.2%
4/5 (high/ very high)	107	68.2%	42	63.6%	149	66.8%
Prostate volume (cm^3)	157	41 (31, 50.3)	66	35.8 (29.0, 50.4)	223	39.5 (29.4, 50.5)
PSA (ng/mL)	157	8.2 (5.8, 12.4)	66	6.6 (4.9, 8.8)	223	7.5 (5.4, 11.7)

AS, active surveillance; CAPRA, UCSF Cancer of the Prostate Risk Assessment; CCP, cell cycle progression; IQR, interquartile ratio; PI-RADS, Prostate Imaging and Reporting Data System; PSA, prostate-specific antigen

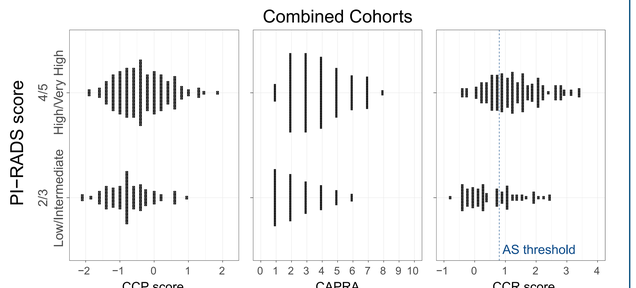
- On multivariate analysis, CCP was a significant predictor of higher-grade tumor (Gleason score ≥4+3) after radical prostatectomy, with the resected tumor approximately four times more likely to harbor a higher-risk Gleason score with every one-unit increase in CCP score (Table 2).
- In combined Cohorts 1+2, weak but significant correlations were observed between PI-RADS and CCP, CAPRA, or CCR, suggesting that much of the prognostic information captured by these measures is independent (Figure 1).

Table 2. Prediction of Gleason Score Category: Multivariate Analysis

Post-RP			Diagnostic Biopsy		
Cohort 1, Newly Diagnosed (n=56/157)			**Cohort 1, Newly Diagnosed (n=157)**		
Predictor	**Odds Ratio (95% CI)**	**p-value**	**Predictor**	**Odds Ratio (95% CI)**	**p-value**
CCP	4.39 (1.62, 14.81)	**2.8×10^{-3}**	CCP	4.09 (2.23, 8.07)	**1.7×10^{-6}**
CAPRA	2.06 (1.24, 3.82)	**3.9×10^{-3}**	PI-RADS	1.94 (0.97, 4.03)	0.060
PI-RADS	0.43 (0.09, 1.67)	0.23	PSA	1.01 (0.95, 1.07)	0.778
Combined Cohorts (n=68/223)			**Combined Cohorts (n=223)**		
Predictor	**Odds Ratio (95% CI)**	**p-value**	**Predictor**	**Odds Ratio (95% CI)**	**p-value**
CCP	4.06 (1.57, 12.69)	**3.0×10^{-3}**	CCP	3.05 (1.83, 5.29)	**1.1×10^{-5}**
CAPRA	2.43 (1.50, 4.45)	**1.1×10^{-4}**	PI-RADS	1.99 (1.07, 3.82)	**0.029**
PI-RADS	0.36 (0.079, 1.32)	0.13	PSA	1.04 (0.99, 1.10)	0.12

CAPRA, UCSF Cancer of the Prostate Risk Assessment; CCP, cell cycle progression; CI, confidence interval; PI-RADS, Prostate Imaging and Reporting Data System; PSA, prostate specific antigen; RP, radical prostatectomy

Figure 1. Distribution of CCP, CAPRA, and CCR Scores Across PI-RADS Score Groups for Patients in Combined Cohorts 1 + 2 (N=223)



Dotted line shows the validated CCR active surveillance (AS) threshold of 0.8 (Lin et al., *Urol Oncol*, 2018). CAPRA, UCSF Cancer of the Prostate Risk Assessment; CCP, cell cycle progression; CCR, clinical cell-cycle risk; PI-RADS, Prostate Imaging and Reporting Data System

Table 3. Impact on Management Selection (Active Surveillance vs. Definitive Treatment) Among Newly Diagnosed Patients (Cohort 1) (N=151)

Predictor	Odds Ratio (95% CI)	p-value
Univariate Models		
CCP	2.47 (1.45, 4.45)	**6.3×10^{-4}**
CAPRA	1.43 (1.15, 1.80)	**8.7×10^{-4}**
CCR	2.31 (1.51, 3.73)	**6.4×10^{-5}**
PI-RADS	1.39 (0.80, 2.45)	0.244
CCP, CAPRA, PI-RADS Multivariate Model		
CCP	1.98 (1.11, 3.67)	**0.020**
CAPRA	1.31 (1.03, 1.69)	**0.030**
PI-RADS	0.98 (0.53, 1.79)	0.938
CCR, PI-RADS Multivariate Model		
CCR	2.33 (1.49, 3.84)	**1.3×10^{-4}**
PI-RADS	0.97 (0.53, 1.77)	0.92

CAPRA, UCSF Cancer of the Prostate Risk Assessment; CCP, cell cycle progression; CI, confidence interval; PI-RADS, Prostate Imaging and Reporting Data System
Multivariate models adjusted for CCP, CAPRA, CCR, and PI-RADS.

- On multivariate analysis, both CCP and CCR were significant and independent predictors of AS versus curative therapy in Cohort 1. Each one-unit increase in score corresponded to an approximately two-fold greater likelihood of selecting curative therapy (Table 3).
- CCR score at or below the AS threshold significantly reduced the probability of selecting curative therapy over AS [OR 0.29 (95% CI 0.14, 0.59), p=6.1×10^{-4}].
- PI-RADS showed no significant association with treatment selection (Table 3).

CONCLUSIONS

- In multiple scenarios, the CCP test was an independent and accurate prognostic measure that aided in risk stratification and medical management of localized PrCa.
- The CCP score was a better predictor of both tumor grade (at biopsy and after radical prostatectomy) and treatment selection than PI-RADS scores.
- A broad portfolio of measures, including targeted biopsy, clinicopathologic measures and molecular biomarker information, remains essential to ensure the most accurate and precise risk assessment to inform treatment selection.

Presented at SUO on December 4, 2019.