A novel tumor genomic classification system accurately stratifies patients with metastatic prostate cancer into distinct prognostic groups

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Abstract

Background: Tumor genomic assessment has revolutionized cancer care as identification of specific gene alterations inform prognosis and predict benefit from precision oncology therapies. To date, prognostic assessment of metastatic prostate cancer does not account for single or combinations of genomic alterations frequently identified through comprehensive genetic profiling (CGP).

Methods: A retrospective cross-sectional study of U.S. Veterans treated for metastatic prostate cancer (All subjects had CGP through the National Precision Oncology Program and were followed until death or censoring at the end of data collection. Cox proportional hazard models were used to identify genomic alterations that were associated with survival while accounting for age, comorbidities, and baseline prostate-specific antigen. The alterations were categorized into favorable, intermediate, or adverse risk classification groups and risk of mortality was analyzed in a multivariable Cox model. Performance was determined in the testing set, other cancer states and a non-VA dataset (MSK IMPACT).

Main Outcomes and Measures Overall survival (OS) from the time of first metastasis.

Results: From a cohort of 7,201 veterans with metastatic prostate cancer, 2484 veterans with de novo metastatic hormone sensitive prostate cancer (dmHSPC) and tissue CGP was divided into training (n=1738) and testing (n=746) subsets accounting for age at dmHSPC diagnosis, prostate-specific antigen (PSA) value, and Charlson comorbidity index (CCI). Sixteen genes altered at ≥2% frequency and associated with overall survival were selected by multivariable analysis (*TP53, PTEN, RB1, BRCA2, FGFR1, FGFR3-4, FGFR19, CDK12, RAD21, MYC, CCND1, LYN, AR, PRKCI, SPOP*). The genomic classification was evaluated in multivariable model, where intermediate and adverse classification was associated with increased mortality (aHR 1.75, 95% CI 1.46-2.08; aHR 2.71, 95% CI 2.15-3.42, respectively) compared to favorable classification in dmHSPC. In the test set, areas under the curve (AUCs) of 0.77, 0.72, and 0.71 at 12, 24 and 36 months, respectively, were determined. Similar performance was found in sensitivity analyses that accounted for tumor volume at diagnosis or testing obtained within 12 months of diagnosis. The genomic classification also showed similar performance when derived from liquid biopsy results and/or across metachronous HSPC and castration-resistant prostate cancer (CRPC) clinical states. Genomic classification was validated in an independent, non-VA dataset (n=990), where intermediate (aHR 2.09, 95% CI 1.11-3.94) and adverse (aHR 4.38, 95% CI 2.14-8.97) classifications were associated with increased mortality with AUCs of 0.75, 0.71 and 0.71 at 12, 24 and 36 months, respectively.

Conclusions and Relevance Tumor genomic classification is prognostic for OS in patients with metastatic prostate cancer. The genomic classification produced consistent, robust results in multiple validation datasets across varying clinical metastatic states, CGP analytes and methods, as well as in datasets derived from non-VA patients. This prognostication approach has the potential to guide decision-making related to therapeutic intensity and duration.

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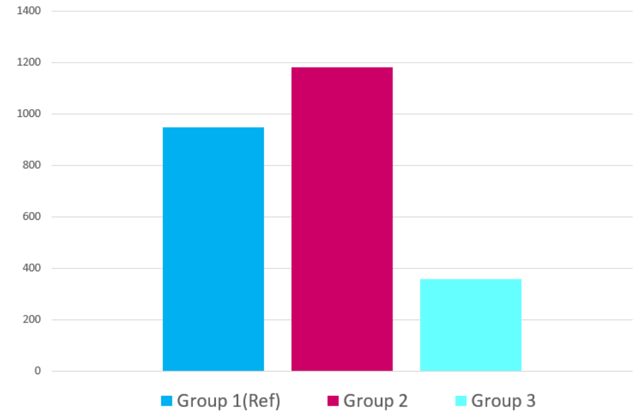
Figure 1:



Group 1 (Favorable Referent)
- ***No Alterations (NULL)***
- ***SPOP only***

Group 2 (Intermediate)
- ***PTEN*** without *TP53 or any group 3*
- ***CDK12*** without *group 3*
- ***BRCA2*** without *any group 3*
- ***TP53 (****without PTEN or any group 3****)***
- ***AR*** *without any group 3*
- **11q13.3 amplified** (represented by any of *CCND1, FGF19, FGF4, FGF3*) *without any group 3*
- **8q amplified *(****represented by any of LYN, MYC, and/or RAD21****)*** *without any group 3*

Group 3 (Unfavorable)
- ***PRKCI, FGFR1***
- ***RB1***
- **TP53 + PTEN**

Figure 2.

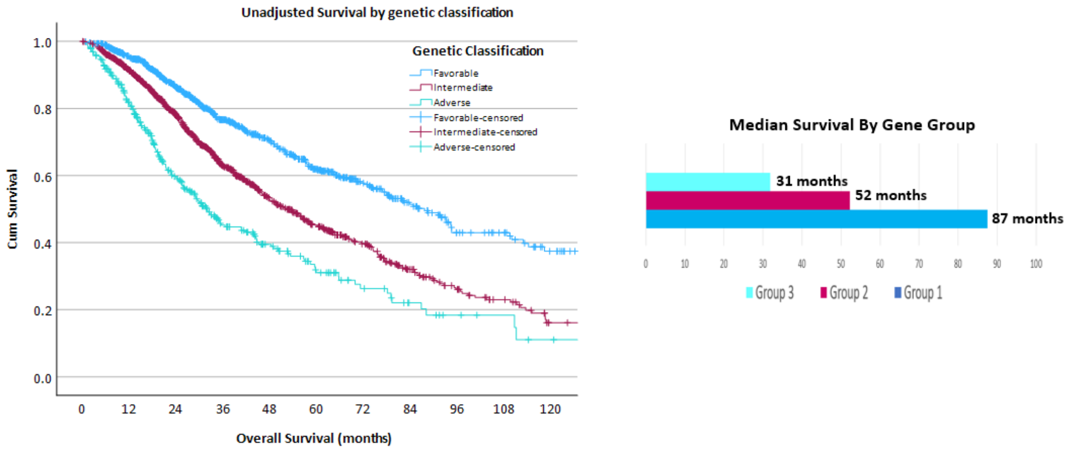
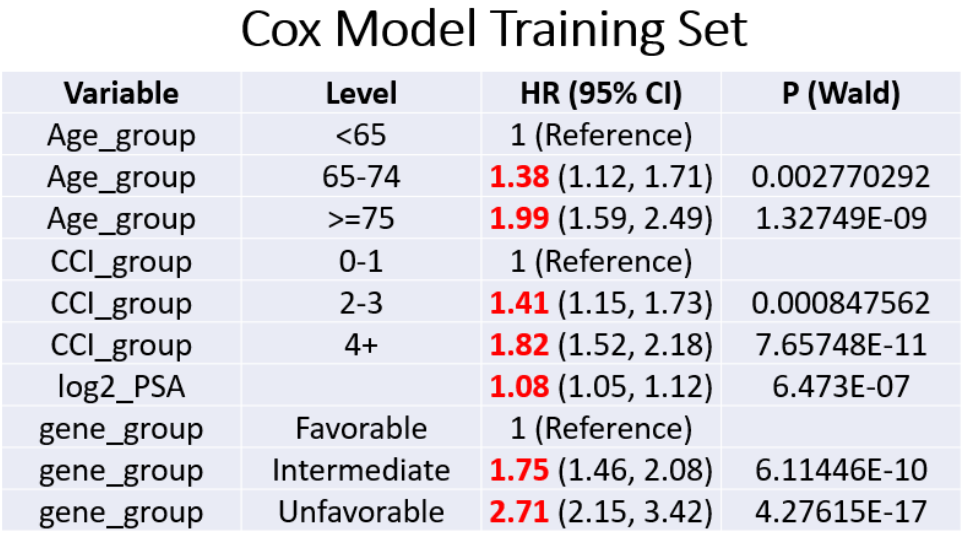


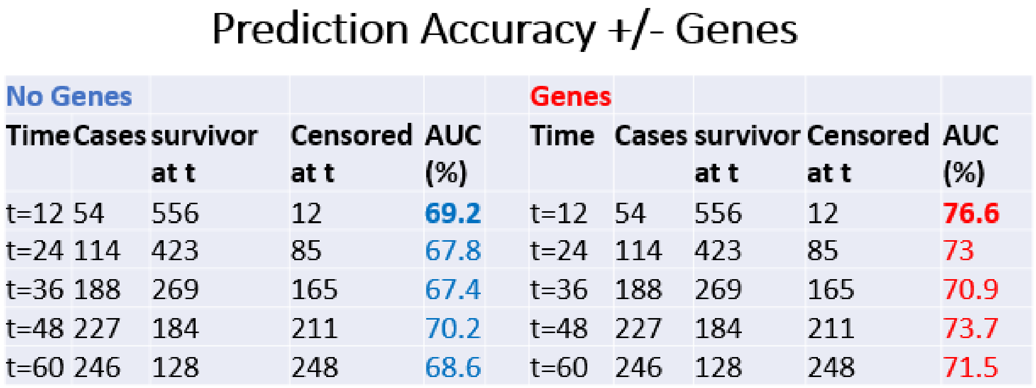
Figure 3:



Cox Model Training Set

Variable	**Level**	**HR (95% CI)**	**P (Wald)**
Age_group	<65	1 (Reference)	
Age_group	65-74	**1.38** (1.12, 1.71)	0.002770292
Age_group	>=75	**1.99** (1.59, 2.49)	1.32749E-09
CCI_group	0-1	1 (Reference)	
CCI_group	2-3	**1.41** (1.15, 1.73)	0.000847562
CCI_group	4+	**1.82** (1.52, 2.18)	7.65748E-11
log2_PSA		**1.08** (1.05, 1.12)	6.473E-07
gene_group	Favorable	1 (Reference)	
gene_group	Intermediate	**1.75** (1.46, 2.08)	6.11446E-10
gene_group	Unfavorable	**2.71** (2.15, 3.42)	4.27615E-17

Figure 4:



Prediction Accuracy +/- Genes

No Genes					**Genes**				
Time	**Cases**	**survivor at t**	**Censored at t**	**AUC (%)**	**Time**	**Cases**	**survivor at t**	**Censored at t**	**AUC (%)**
t=12	54	556	12	**69.2**	t=12	54	556	12	**76.6**
t=24	114	423	85	67.8	t=24	114	423	85	73
t=36	188	269	165	67.4	t=36	188	269	165	70.9
t=48	227	184	211	70.2	t=48	227	184	211	73.7
t=60	246	128	248	68.6	t=60	246	128	248	71.5