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Genomic Scores are Independent of Disease Volume in Men with Favorable Risk Prostate Cancer: Implications for Choosing Men for Active Surveillance

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PII: S0022-5347(17)77563-5  
DOI: [10.1016/j.juro.2017.09.077](https://doi.org/10.1016/j.juro.2017.09.077)  
Reference: JURO 15007

To appear in: *The Journal of Urology*  
Accepted Date: 11 September 2017

Please cite this article as: Nyame YA, Grimberg DC, Greene DJ, Gupta K, Kartha GK, Berglund R, Gong M, Stephenson AJ, Magi-Galluzzi C, Klein EA, Genomic Scores are Independent of Disease Volume in Men with Favorable Risk Prostate Cancer: Implications for Choosing Men for Active Surveillance, *The Journal of Urology*® (2017), doi: 10.1016/j.juro.2017.09.077.

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Funding: none

Key Words: Prostate Cancer, Genomic Prostate Score, Disease Volume, Active Surveillance, Favorable Pathology Likelihood

Conflict of Interest: See attached author forms

**Page count:** 13 (including title page)

**Figures, Tables, Video count:** 5

**Word count-** Abstract: 243

Text: 2303

References: 30

**ABSTRACT:**

**Objective:** To determine if disease volume at prostate biopsy correlates with genomic scores among men with favorable risk prostate cancer.

**Methods:** All men with NCCN very low (VLR) and low risk (LR) disease and OncotypeDx Prostate testing at our institution from 2013 to 2016 were identified. Volume of disease was characterized as percent of positive cores, number of cores with >50% involvement, largest involvement of any single core, and PSA density. Nonparametric testing was performed to compare the median genomic prostate score (GPS) and likelihood of favorable pathology (LFP) between quartiles of disease volume.

**Results:** 112 (37.8%) and 184 (62.2%) NCCN VLR and LR men were identified, respectively. Median GPS scores did not differ significantly between disease volume quartiles (all  $p > 0.05$ ); however, median LFP was statistically different between volume quartiles (all  $< 0.05$ ). In total, 7/105 (6.3%) of men with VLR disease were reclassified to LR, and 13/181 (7.2%) with LR disease were reclassified as intermediate risk. Genomic disease reclassification was not dependent on biopsy tumor volume.

**Conclusion:** For patients with NCCN VLR and LR risk prostate cancer, genomic scores did not demonstrate meaningfully significant differences by volume based on clinically established cutpoints. Moreover, genomic scores identified and reclassified men with higher risk disease despite generally acceptable surveillance characteristics in this group by grade and volume. This suggests that for low risk patients, the tumor's biologic potential as measured by genomics, rather than volume, should inform decisions on active surveillance candidacy.

## INTRODUCTION

Disease volume at prostate biopsy has been a key component in defining favorable risk prostate cancer as established by the landmark publication by Epstein et al.<sup>1</sup> Since that time, the definition of very low risk prostate cancer specifies a low volume of disease at diagnosis based on two or fewer involved cores, maximum core involvement < 50 %, and prostate specific antigen density (PSAD) < 0.15 ng/ml/g. This definition, commonly known as the Epstein criteria, are used by many institutions to define candidates for active surveillance,<sup>2</sup> although due to the inherent risk of sampling errors with needle biopsy, the absence of these adverse features at biopsy does not guarantee favorable pathology at eventual radical prostatectomy.<sup>1</sup> Furthermore, despite long term evidence of the safety of active surveillance for most men with pure grade group (GrdGrp) 1 (i.e., Gleason score 3+3) tumors,<sup>3,4</sup> violation of the Epstein criteria based on tumor volume is used to exclude men against the recommendation for surveillance in some provider/institutional protocols.<sup>5</sup>

The diagnostic inaccuracies of biopsy and traditional risk stratification measures create a need for improved methods to identify men at low risk of progression who may avoid initial therapy, a limitation that is being addressed by the growing use of genomic biomarkers<sup>6-8</sup> and multiparametric magnetic resonance imaging as diagnostic tools.<sup>9,10</sup> The OncotypeDX Genomic Prostate Score (GPS)<sup>TM</sup>, is a 17-gene quantitative RT PCR assay of selected genes from four cancer related molecular pathways (androgen signaling, cellular organization, stromal response, and cellular proliferation)<sup>11</sup> that has been analytically<sup>11</sup> and clinically<sup>12,13</sup> validated when measured on prostate biopsies to predict the presence of adverse pathology (GrdGrp 3 or higher or non-organ confined disease), as well as time to biochemical recurrence and metastasis.<sup>14</sup> Further, use of GPS testing in a clinical setting demonstrated an increase in the recommendation for and adoption of active surveillance in patients with newly diagnosed prostate cancer,<sup>15</sup> leading to a recommendation in the current NCCN guidelines to consider the use of such tests when qualifying men for active surveillance.<sup>16</sup>

In this study, we aimed to determine from prostate biopsies GPS scores and accompanying estimates of the likelihood of favorable pathology in men with Gleason grade group 1 (Gleason score 3+3) tumors as a function of tumor volume, to determine if some men not meeting traditional Epstein criteria are safe candidates for active surveillance based on the molecular rather than histological features of their tumors.

## MATERIALS AND METHODS

All men at our institution who had OncotypeDX<sup>TM</sup> GPS testing performed on prostate biopsy samples to aid in clinical decision making were identified from a genomic database. Men were excluded from analysis if they had National Comprehensive Cancer Network (NCCN) intermediate risk disease<sup>16</sup> and 36 men (19 LR and 17 VLR) had core biopsy samples submitted for genomic testing that failed to have enough quality RNA for analysis. In total, 296 men biopsied between 2013 and 2016 were included for analysis. Institutional review board approval was obtained for this study.

### *Clinical Data*

Review of the electronic medical record and a prospectively maintained active surveillance database was performed to obtain all relevant demographic and clinical data including age at biopsy, ethnicity/race, body mass index (BMI), initial PSA, digital rectal exam findings, and length of follow up. Biopsy data including Gleason score, prostate volume at TRUS, total number of cores taken, number of positive cores, number of cores with >50% involvement, and largest percent core involvement were also collected. Men were stratified into NCCN very low and low risk disease based on their baseline data per NCCN guidelines.<sup>16</sup> Volume of disease was defined as (1) percent of positive cores, (2) number of cores with >50% involvement, (3) largest involvement of any single core, and (4) PSA density (PSAD). GPS and associated likelihood of favorable pathology (LFP, estimated probability of low grade (GrdGrp 1 or 2) and organ confined (pT2) disease) were obtained from each patient's OncotypeDX<sup>TM</sup> test result. As aforementioned, the OncotypeDX Genomic Prostate Score (GPS)<sup>TM</sup>, is a 17-gene quantitative RT PCR assay of selected genes from four cancer related molecular pathways (androgen signaling, cellular organization, stromal response, and cellular proliferation). Testing is performed on tissue obtained from core prostate biopsies. LFP is a probability (0 to 99 percent) that was reported in the initial iterations of the OncotypeDX<sup>TM</sup> test result. It was a calculation that predicted the probability of adverse biologic disease compared to men with a similar National Comprehensive Cancer Network risk grouping. Biopsy core number and location were performed according to the preference of the physician and not standardized. All

biopsies were reviewed at our institution by expert genitourinary pathologists in concordance with the current ISUP criteria.<sup>17</sup>

### *Statistical Methods*

Descriptive statistics were performed to characterize the cohort with data presented as medians with interquartile ranges for continuous variables, and frequencies with proportions for categorical variables. The primary endpoint for this study was to compare likelihood of favorable pathology (LFP, organ confined and without any primary Gleason pattern 4 or 5) between patients stratified by disease volume, as estimated with the three aforementioned volume parameters. Secondary endpoints included a sub-analysis to assess the rates of disease reclassification with GPS. Each volume parameter was divided into statistical quartiles with cutpoints at the 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentile. Kruskal-Wallis test was performed to compare the median LFP between quartiles of each volume parameter, and Mann-Whitney U test was used for tests between only two groups. All statistical tests were two-sided, and significance was defined as  $p < 0.05$ . Statistical analyses were performed using Stata 12.1 (StataCorp 2011, College Station, TX) and SPSS 24 (IBM Corp 2016, Chicago, IL).

## **RESULTS**

Baseline clinical and demographic data for the cohort are listed in Table 1. 112 (37.8%) and 184 (62.2%) men in the cohort had NCCN very low and low risk prostate cancer, respectively. Median length of follow-up was 17 months (IQR 8.3-28.2). The median age was 62.5 years (IQR 58.0-66.6), and 13.5% self-identified as African American. The median LFP was 86.0% (IQR 83.0-88.0%) and 78.0% (IQR 73.0-81.0%) for very low and low risk men, respectively. At last follow-up, 214 (72.3%) remained on active surveillance, 44 (14.9%) had radical prostatectomy, 31 (10.5%) had brachytherapy, and 6 (2.0%) had external beam radiotherapy.

The relationship between median GPS score, LFP, and volume quartiles are shown in Table 2. GPS scores did not differ between quartile groups by any of the volume estimates, or by PSA density (Figure 1a-d). There were statistically significant differences between the

median LFP of each quartile group when stratified by percent of positive cores, number of cores  $\geq 50\%$  involvement, maximum core involvement, and PSAD (Figure 2a-d, all  $p < 0.05$ ).

In total, 98 (33%) men had disease risk reclassification following genomic testing (Table 3). Of these men, 7/98 (7.1%) very low risk patients were reclassified to low risk disease, 13/98 (13.3%) of low risk patients were reclassified to intermediate risk disease, and 78/98 (79.6%) low risk men were reclassified to very low risk. The median LFP for men with very low risk disease reclassified to low risk disease was 76.0% (IQR 70.5-77.0%) and 63.0% (IQR 62.0-63.0%) for men reclassified to intermediate risk disease from low risk disease. Conversely, men who were reclassified from low risk to very low risk had a median LFP of 81.0% (IQR 80.0-82.0%). By univariate analysis, disease volume did not correlate with reclassification on genomic testing.

## DISCUSSION

Currently, the NCCN has adopted risk groups for prostate cancer based on relevant clinical and biopsy data adopted from the D'Amico<sup>18</sup> and Epstein<sup>1,19</sup> studies. Specifically, Epstein and colleagues defined histologic findings indicative of clinically significant prostate cancer as a PSAD  $>0.15$  ng/mL, the presence of any Gleason pattern 4 or 5 disease, 3 or more biopsy cores involved with tumor (or  $> 33\%$  positive cores in contemporary series), and any core with greater than 50% involvement by tumor.<sup>1</sup> However, due to the inherent risk of sampling errors with needle biopsy, the absence of these adverse histologic features does not guarantee favorable prostate cancer pathology among men who undergo radical prostatectomy.<sup>1</sup> Initial validation studies of these criteria demonstrated 84% accuracy for predicting "insignificant" (a term intended to define lack of biological potential) tumor<sup>19</sup>; however, accuracy of these criteria now vary from 37-76%<sup>20,21</sup> following the 2005 IUSP changes to the Gleason Grading system.<sup>22</sup> Nonetheless, these criteria have been a key driver of current active surveillance practices, and their use has demonstrated good clinical outcomes in men managed by active surveillance.<sup>2,5</sup>

In an effort to improve accuracy of risk stratification, several new schemes have been proposed to augment or replace the NCCN criteria, including preoperative nomograms such as the MSKCC nomograms and risk calculators such as CAPRA.<sup>23,24</sup> While these tools more accurately characterize risk for individual patients, they are still limited by the lack of biological

data beyond that contained in grade, stage and PSA. Recent studies have shown that several commercially available gene expression assays, commonly referred to as “genomic tests”, can further improve on individual risk classification when combined with traditional clinical criteria.<sup>12,14</sup> As a result, the most recent NCCN guidelines now endorse the consideration of genomic testing when making a decision on eligibility for active surveillance.<sup>16</sup>

Despite the fact that prior studies have shown that tumor volume does not predict for worse outcome in patients with only GrdGrp 1 disease<sup>25,26</sup>, in community practice most urologists are hesitant to place men with multiple biopsy cores of GrdGrp 1 or those with >50% of an individual core on surveillance.<sup>5</sup> In this study we sought to determine if this hesitance is rationally based, by using OncotypeDx Prostate to measure biologic potential (as measured by GPS and the estimation of LFP) of GrdGrp 1 tumors as a function of tumor volume. We found that OncotypeDx Prostate performed similarly in our cohort as in other reported series, with reclassification rates of 6.3% for NCCN VLR to LR, 7.2% of LR to IR, and 43% LR to VLR in our study compared to published rates of 6-9% 10-11%, and 33-51%, respectively.<sup>20,21</sup> Also as expected, we found that higher tumor volume was associated with a lower LFP. However, the absolute differences were small across all measures of tumor volume and these differences did not correlate with a clinically meaningful difference in predicting reclassification to a higher NCCN risk group. In addition, we found no relationship between GPS score and tumor volume. A recent study demonstrated that NCCN very low and low risk men with GPS scores below 30 had a 0% 10-year risk of metastasis.<sup>27</sup> In our cohort, 62/297 (20.8%) men were above this threshold, and this was irrespective of tumor volume. Furthermore, Whalen demonstrated that an estimated LFP > 76% was associated with favorable pathology at radical prostatectomy,<sup>28</sup>; in this study, estimated LFPs ranged from 76.1 – 82.4%, with only men in the highest quartile of tumor volume as estimated by percent maximal core involvement approaching this threshold. In summary, our findings suggest that in men with GrdGrp 1 disease, high tumor volumes often considered unsafe for active surveillance in current clinical practice are usually associated with a high likelihood of favorable pathology, suggesting that eligibility for active surveillance should be based on the biologic potential of the tumor rather than tumor volume on biopsy. Recent data, has demonstrated that genomic testing has an impact in helping providers and patients make the decision to pursue active surveillance.<sup>29,30</sup> And although current genomic testing is costly, it is difficult to quantify economic benefits of providing patients with reassurance with regards to

their cancer diagnosis based on their own tumor biology, of decreasing the rates of prostate cancer overtreatment, and of the value of personalized care in our current health system.

There are several limitations of our study that warrant discussion. First, the retrospective nature of this study is inherently subject to selection bias. Specifically, genomic testing is not routinely offered to all patients at our institution as a result of cost and provider preference. Consequently, this patient population and these results may not be generalizable, although as noted OncotypeDx Prostate performed similarly in this cohort as in published reports from other institutions. Secondly, this study is not designed to answer many clinically relevant questions regarding the utility of genomic testing. For example, what is the long-term durability of a favorable genomic test for men being managed with active surveillance? Can genomic testing be used as surrogate for a confirmatory biopsy in surveillance protocols? And is genomic testing cost effective for patients, providers, and/or payors? Thirdly, this study utilize reclassification based on a genomic testing as an outcome, which is not the standard for measuring oncologic outcomes in prostate cancer. However, studies have demonstrated that genomic tests strongly correlate with oncologic outcomes such as adverse biologic features at prostatectomy, biochemical failure and the development of metastatic disease.<sup>14,27</sup> With the accrual of time, studies evaluating genomic testing must look at hard oncologic outcomes such as prostate specific mortality, metastasis, and biochemical failure in patients who progress to treatment. Unfortunately, this was not possible in this cohort with a median follow-up of 17.9 months and the relatively low number of men progressing to radical prostatectomy from surveillance. Nonetheless, this study does provide some insight into the relationship between prostate cancer volume at biopsy and genomic testing in a large cohort of men with prostate cancer.

## CONCLUSIONS

Increasing volume of prostate cancer is not associated with adverse genomic scores as measured by GPS. Although disease volume is associated with decreasing LFP, this relationship does not appear to be clinically significant with likelihood of favorable pathology only varying 5% between highest and lowest volume quartiles. Moreover, disease reclassification by genomics demonstrated no correlation with disease volume in this cohort of men with GrdGp 1 prostate cancer. This suggests that for NCCN VLR and LR patients, the biologic potential of

disease as measured by genomics, rather than volume on biopsy, should inform decisions on active surveillance candidacy.

ACCEPTED MANUSCRIPT

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Table 1: Baseline demographic and clinical characteristics at diagnosis of men with favorable risk prostate cancer undergoing OncotypeDx testing at our institution (n = 296)

**Characteristic****Continuous, median (IQR)**

Age at diagnosis, years	62.5 (58.0-66.6)
Body-mass-index, kg/m <sup>2</sup>	27.8 (25.6-30.3)
Year of testing	2014 (2013-2015)
Follow-up, months	17.9 (8.3-28.2)
PSA at diagnosis, ng/ml	4.8 (3.8-6.1)
PSA density, ng/ml/cm <sup>3</sup> (n = 245)	0.11 (0.08-0.16)
Prostate volume, cm <sup>3</sup> (n = 245)	40.0 (31.0-52.6)
Total no. of cores at biopsy, initial	12.0 (12.0-15.0)
Total no. of positive cores, initial	2.0 (1.0-3.0)
Positive cores, initial, % of total cores	17.0 (8.0-25.0)
No. of cores with ≥ 50% involvement	0 (0.0-0.0)
Largest percent core involvement	15.0 (10.0-30.0)
GPS score	20.5 (15.0-28.0)
Percent likelihood of favorable pathology	81.0 (76.0-84.0)

**Categorical, n (%)**

Age at diagnosis, years	
≤ 50.0	5 (1.7)
50.1- 60.0	106 (35.8)
60.1-70.0	156 (52.7)
> 70	29 (9.8)
Abnormal DRE	0 (0.0)
Race/Ethnicity	
African American	48 (13.5)
European American	288 (80.9)
Other/Declined	20 (5.6)
Gleason score at initial biopsy	
G3+3	296 (100.0)
Serum PSA Level (ng/ml)	
≤ 10.0	296 (100.0)
NCCN Risk Strata	
Very low	112 (37.8)
Low	184 (62.2)

Table 2: Univariate comparison of GPS score and Likelihood Favorable Pathology (LFP) by volume of disease (n = 296)

Characteristic	GPS, Median (IQR)	p-value*	LFP, Median (IQR)
<b>Percent of positive cores</b>			
Quartile 1 (n = 108, range: 3.0-8.0%)	21.0 (16.0-28.0)	p = 0.981	83.0 (79.0-86.0)
Quartile 2 (n = 88, range: 9.0-17.0%)	21.0 (14.3-29.0)		80.5 (75.0-85.0)
Quartile 3 (n = 53, range: 20.0-25.0%)	20.0 (14.5-28.0)		78.0 (73.0-81.0)
Quartile 4 (n = 47, range: 27.0-75.0%)	20.0 (15.0-28.0)		78.0 (73.0-81.0)
<b>No. of cores with <math>\geq</math> 50% involvement</b>			
0 cores (n = 224)	20.0 (15.0-29.0)	p = 0.506	81.0 (77.0-85.0)
$\geq$ 1 core (n = 44, range: 1.0-4.0)	21.5 (16.0-28.0)		77.0 (73.0-80.0)
<b>Maximum percent involved in any core</b>			
Quartile 1 (n = 115, range: 1.0-10.0%)	20.0 (13.0-29.0)	p = 0.417	82.0 (78.0-86.0)
Quartile 2 (n = 22, range: 12.0-15.0%)	20.0 (15.0-25.3)		80.5 (78.0-85.0)
Quartile 3 (n = 68, range: 20.0-30.0%)	20.0 (14.0-28.0)		81.0 (76.5-84.0)
Quartile 4 (n = 62, range: 35.0-100.0%)	22.5 (16.0-29.5)		77.0 (73.0-80.0)
<b>PSA Density</b>			
Quartile 1 (n= 61, range: 0.01 - 0.08 ng/ml/cm <sup>3</sup> )	20.0 (15.5-28.0)	p = 1.000	82.0 (77.5-86.0)
Quartile 2 (n= 62, range: 0.09 - 0.11 ng/ml/cm <sup>3</sup> )	21.5 (12.8-28.3)		82.0 (76.8-86.0)
Quartile 3 (n= 62, range: 0.12 - 0.16 ng/ml/cm <sup>3</sup> )	19.5 (14.0-29.3)		80.0 (75.5-82.0)
Quartile 4 (n= 60, range: 0.17 - 0.56 ng/ml/cm <sup>3</sup> )	20.0 (15.0-26.0)		79.0 (76.0-82.0)

\*Calculated using Kruskal-Wallis test

Table 3: Clinical characteristics of patients with NCCN risk strata reclassified by OncotypeDx™ (n=98)

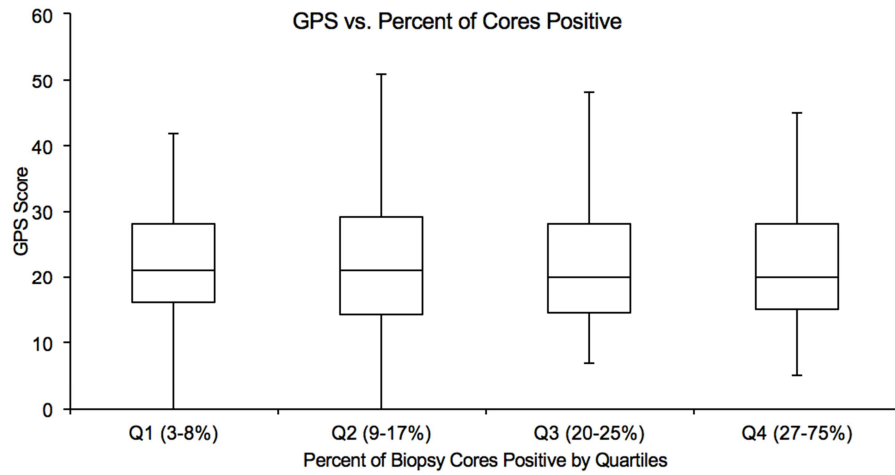
	VLR reclassified to LR (n=7)	LR reclassified to IR (n=13)	LR reclassified to VLR (n=78)
<b>Continuous, median (IQR)</b>			
Age at diagnosis, years	68.6 (61.5-72.5)	63.5 (59.3-72.2)	63.1 (56.6-66.4)
PSA at diagnosis, ng/ml	4.7 (3.3-6.0)	6.1 (4.1-8.0)	4.9 (3.8-6.1)
PSA density, ng/ml/cm <sup>3</sup> (n=80)	0.09 (0.06-0.20)	0.12 (0.10-0.15)	0.12 (0.08-0.17)
Prostate volume, cm <sup>3</sup> (n=80)	48.0 (37.5-57.5)	36.0 (30.5-48.8)	37.0 (29.0-49.3)
Total no. of cores at biopsy, initial	12.0 (12.0-14.0)	12.0 (11.0-13.0)	12.0 (12.0-18.0)
Total no. of positive cores, initial	2.0 (1.0-2.0)	3.0 (2.0-3.0)	3.0 (2.0-4.0)
Positive cores, initial, % of total cores	10.0 (8.0-17.0)	20.0 (12.0-35.5)	20.0 (9.8-30.0)
No. of cores with ≥ 50% involvement (n=88)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)
Largest percent core involvement (n=88)	10.0 (5.0-25.0)	20.0 (10.0-50.0)	20.0 (10.0-42.5)
GPS score	42.0 (40.0-51.0)	42.0 (41.5-44.5)	14.0 (11.0-16.0)
Percent likelihood of favorable pathology	76.0 (70.0-77.0)	63.0 (61.5-63.5)	81.0 (80.0-82.0)
<b>Categorical, n (%)</b>			
Age at diagnosis, years			
≤ 50.0	0 (0.0%)	0 (0.0%)	1 (1.3%)
50.1- 60.0	1 (14.3%)	3 (23.1%)	27 (34.6%)
60.1-70.0	4 (57.4%)	5 (38.5%)	46 (59.0%)
> 70	2 (28.6%)	5 (38.5%)	4 (5.1%)
Serum PSA Level (ng/ml)			
≤ 10.0	0 (0.0%)	1 (7.7%)	4 (5.1%)

VLR = NCCN very low risk, LR = NCCN low risk, IR = NCCN intermediate risk

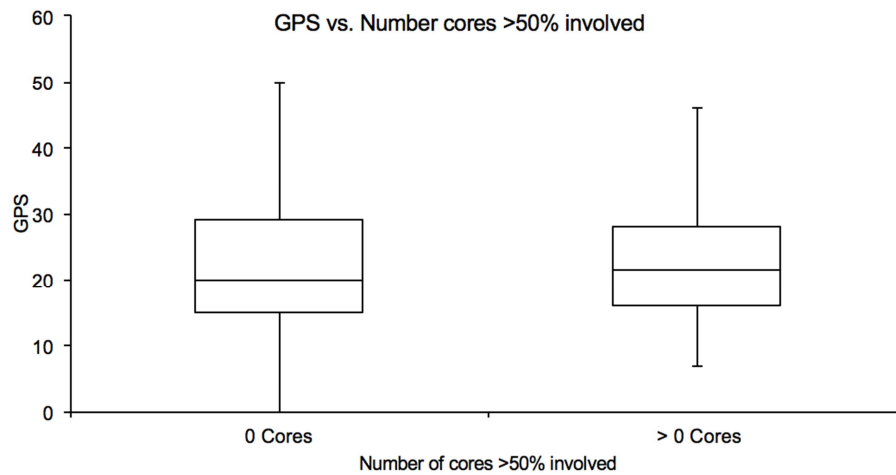
**Figure Legend**

Figure 1: Box plot of median GPS score by disease volume (a) percent positive cores, (b) number of cores >50% involved, (c) maximum core involvement, and (d) PSA density.

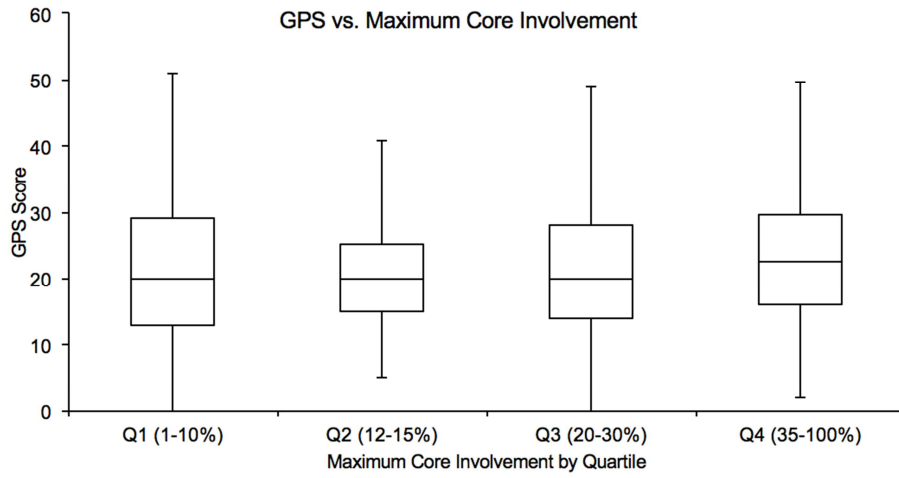
(a)



(b)



(c)



(d)

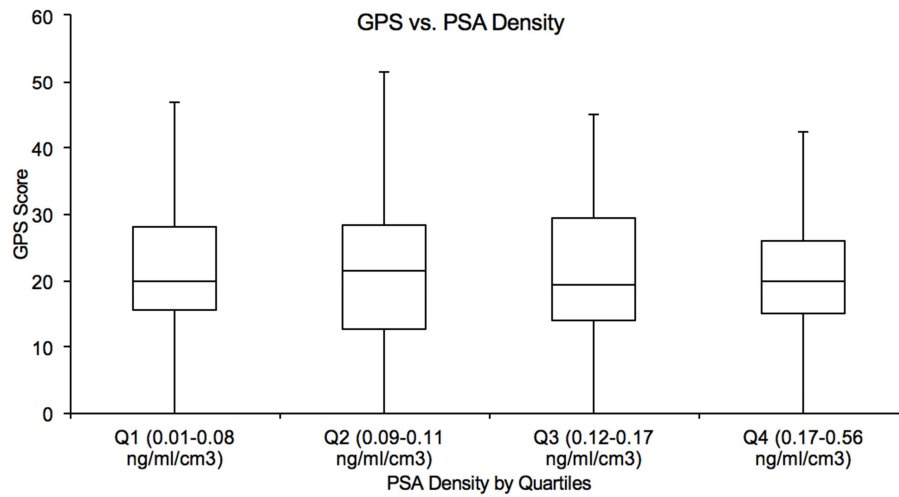
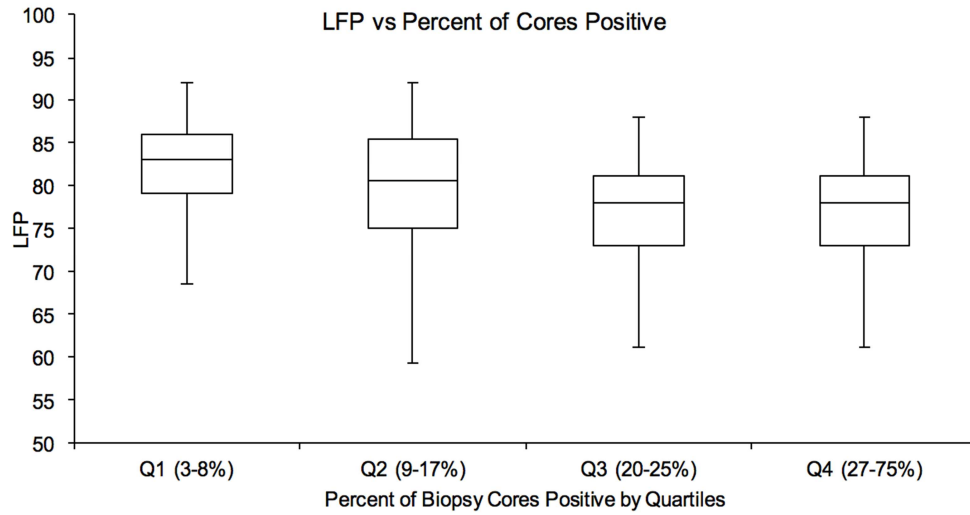
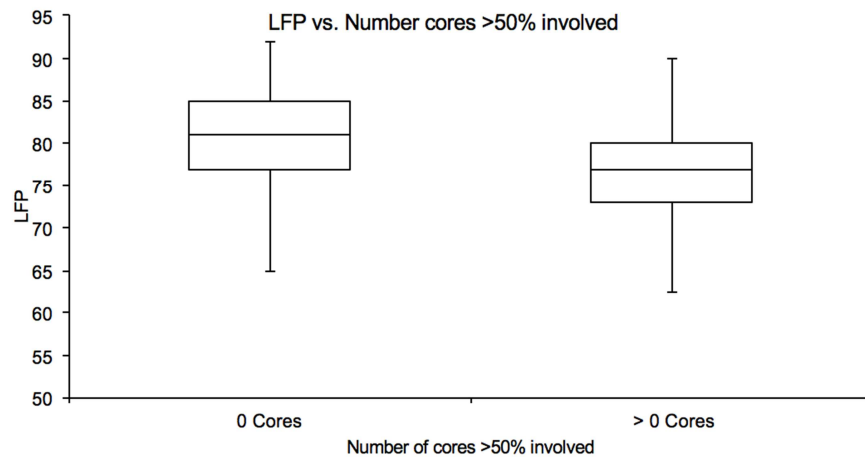


Figure 2: Box plot of median Likelihood Favorable Pathology (LFP) by disease volume (a) percent positive cores, (b) number of cores >50% involved, (c) maximum core involvement, and (d) PSA density.

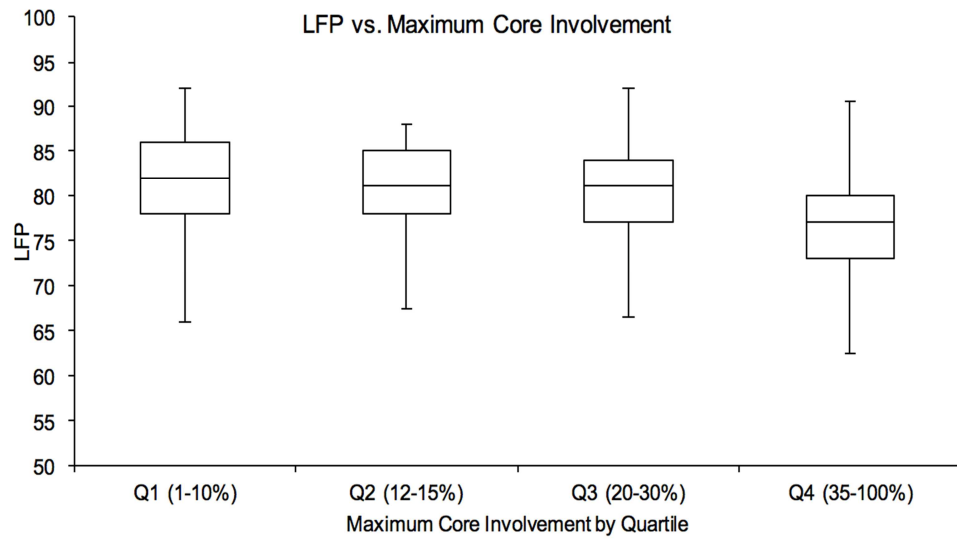
(a)



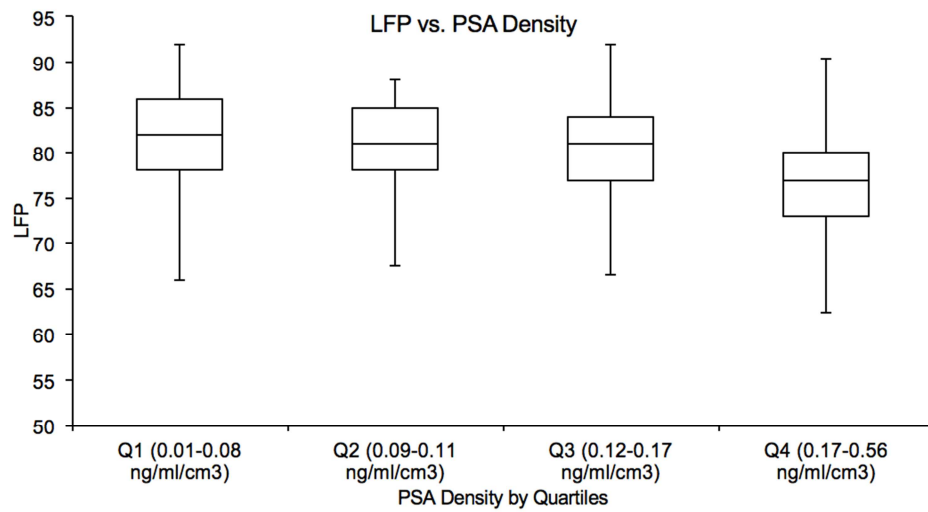
(b)



(c)



(d)



**Key of Definitions for Abbreviations**

GPS = Genomic Prostate Score

LFP = Likelihood of Favorable Pathology

NCCN VLR = National Comprehensive Cancer Network Very Low Risk

NCCN LR = National Comprehensive Cancer Network Low Risk

PSAD = Prostate Specific Antigen Density

GrdGrp = Gleason Grade Group