REPORT

Improving Risk Stratification Among Veterans Diagnosed With Prostate Cancer: Impact of the 17-Gene Genomic Prostate Score Assay

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Prostate cancer (PCa) represents a significant management challenge for the Department of Veterans Affairs (VA). Between 12,000 and 14,000 veterans are diagnosed with PCa within the VA every year.[1] The majority of these patients have low-risk PCa, a clinically indolent form of cancer that is of questionable clinical relevance.[2] Clinical practice guidelines recommend active surveillance (AS) as the management strategy of choice for men diagnosed with very low- and low-risk PCa.[3] Despite a growing consensus on the appropriateness of AS for very low- and low-risk PCa, there is wide variation in AS utilization nationally and within VA medical centers (VAMCs).[4-6] Aggregate AS increased sharply between 2010 and 2013 but still accounted for management in just 40% of patients with PCa.[7]

Lack of confidence in conventional risk assessment tools may contribute to the limited use of AS. Traditional PCa metrics, such as prostate specific antigen (PSA) levels, biopsy Gleason score, tumor stage, burden of disease (the percentage of positive biopsy cores), and nomograms that integrate these factors are of great value but subject to significant limitations.[8-10] A substantial number of men diagnosed with PCa following biopsy experience upgrading or downgrading of their Gleason score based on surgical pathology.[11] Disparity between biopsy and surgical Gleason grading poses a major challenge because some patients with apparently indolent disease may harbor occult aggressive cancer that poses a small but finite risk of metastasis.[12] Conversely, some patients with apparently aggressive cancer may have an indolent disease that is not likely to pose a threat to their quality and length of life, but they proceed with invasive treatment for cancer that has little benefit.[11] Integrated classification systems, such as the National Comprehensive Cancer Network's (NCCN) risk grouping, perform better than solitary clinical metrics but remain limited in scope (ie, risk and ability to predict outcomes).[13]

Approximately 7% of veterans in VAMCs may have been exposed to Agent Orange (AO).[14] A total of 26% of veterans with PCa are black men.[14] Black race has been clearly linked to worse outcomes in PCa.[15-17] However, an observational cohort analysis of 1270 patients with PCa within the VA demonstrated that in this equal-access healthcare system, PCa mortality in black and white patients was similar.[18]

ABSTRACT

BACKGROUND: Active surveillance (AS) has been widely implemented within Veterans Affairs' medical centers (VAMCs) as a standard of care for low-risk prostate cancer (PCa). Patient characteristics such as age, race, and Agent Orange (AO) exposure may influence advisability of AS in veterans. The 17-gene assay may improve risk stratification and management selection.

OBJECTIVES: To compare management strategies for PCa at 6 VAMCs before and after introduction of the Oncotype DX Genomic Prostate Score (GPS) assay.

STUDY DESIGN: We reviewed records of patients diagnosed with PCa between 2013 and 2014 to identify management patterns in an untested cohort. From 2015 to 2016, these patients received GPS testing in a prospective study. Charts from 6 months post biopsy were reviewed for both cohorts to compare management received in the untested and tested cohorts.

SUBJECTS: Men who just received their diagnosis and have National Comprehensive Cancer Network (NCCN) very low-, low-, and select cases of intermediate-risk PCa.

RESULTS: Patient characteristics were generally similar in the untested and tested cohorts. AS utilization was 12% higher in the tested cohort compared with the untested cohort. In men younger than 60 years, utilization of AS in tested men was 33% higher than in untested men. AS in tested men was higher across all NCCN risk groups and races, particular in low-risk men (72% vs 90% for untested vs tested, respectively). Tested veterans exposed to AO received less AS than untested veterans. Tested nonexposed veterans received 19% more AS than untested veterans. Median GPS results did not significantly differ as a factor of race or AO exposure.

CONCLUSIONS: Men who receive GPS testing are more likely to utilize AS within the year post diagnosis, regardless of age, race, and NCCN risk group. Median GPS was similar across racial groups and AO exposure groups, suggesting similar biology across these groups. The GPS assay may be a useful tool to refine risk assessment of PCa and increase rates of AS among clinically and biologically low-risk patients, which is in line with guideline-based care.

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For author information and disclosures, see end of text.

An association between AO exposure and PCa is controversial but a topic of ongoing research.[19,20]

The development and clinical implementation of molecular testing is one means by which physicians may provide additional risk assessment based on an individual's tumor biology.[21] The NCCN guidelines on PCa have cited molecular diagnostics as an option to aid in management decisions.[10] One such molecular marker for use in the PCa biopsy space is the Oncotype DX Genomic Prostate Score Assay (Genomic Health; Redwood City, CA).[22,23] This assay uses a proprietary algorithm that measures the expression of 12 cancer-specific genes and 5 reference genes to yield a Genomic Prostate Score (GPS) result, which ranges from 0 to 100, with higher scores implying a more aggressive tumor phenotype. The GPS result is integrated with the patient's NCCN clinical risk group to provide a refined estimate for the likelihood of favorable pathology, defined as a pathological Gleason score less than 3+4 and pT2 disease (tumor confined to the prostate).[24] The GPS assay has been validated as an independent predictor of adverse pathology (AP) in clinical studies, one of which was conducted at 2 military hospitals and included 81 black patients, representing 20% of the total cohort.[22,23] Subgroup analyses demonstrated that the GPS assay was an independent predictor of AP and biochemical recurrence in both Caucasian and African American men.[22]

Given the racial diversity, potential for exposure to AO, and the high prevalence of competing comorbidities among veterans with PCa, it is important to study genomic testing specifically within VAMCs before considering widespread adoption of this technology. To our knowledge, studies of molecular diagnostics in veterans with PCa have been limited.

In this supplement, we analyze treatment patterns across 6 VAMCs before and after introduction of the GPS assay. We hypothesized that incorporation of the GPS assay would lead to a significant increase in aggregate utilization of AS in veterans who received the test compared with a historical cohort that did not have molecular profiling of their tumors.

Methods

Study Design

This was a 2-part study with retrospective and prospective components. Through retrospective chart review, we studied management patterns for men with NCCN very low-, low-, and intermediate-risk PCa who did not receive molecular profiling and were managed at 1 of 6 VAMCs. In a prospective clinical trial at these same VAMCs, veterans with clinically similar PCa were offered GPS testing. Those who agreed to participate reviewed the test results with their urologists and incorporated the information into their management decision making.

Facility Selection

We identified 6 VAMCs from a geographically diverse sampling of the country. We conducted a historical review of data from VA Central Cancer Registry (VACCR) and VA Corporate Data Warehouse (CDW) to ensure that these sites had a high volume of veterans diagnosed with low-risk PCa and that they offered all standard-of-care management options for PCa.[14]

Patient Selection

Patients with newly diagnosed NCCN very low-, low-, or select intermediate-risk PCa were included in the study. To be eligible, men with intermediate-risk PCa were required to have a biopsy Gleason score of 3+3, with a PSA level between 10 and 20 ng/mL or a biopsy Gleason score of 3+4 with 3 or fewer positive biopsy cores and 33% or less positive cores for tumor and a PSA level less than 20 ng/mL.

Men who had yet to make a management decision and for whom biopsy tissue was available for analysis were eligible to participate in the prospective cohort. Physicians at each site offered enrollment to all eligible patients. Patients in the prospective cohort were enrolled between March 2015 and February 2016.

The retrospective cohort was identified by screening patients with PCa managed at 1 of the 6 VAMCs between January 2014 and March 2015. All clinically eligible patients (using the same criteria as the prospective study) were included in the untested cohort. Approximately 200 patients were expected to be included in each cohort (tested and untested), with no single physician providing more than 35 patients to each cohort.

Regulatory Approvals

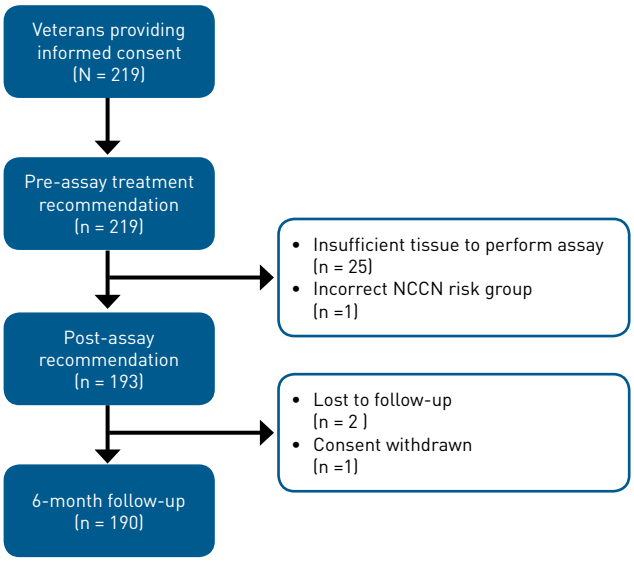
The Institutional Review Board and the VA Research and Development Committee at each VAMC approved the conduct of the study. We obtained informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization from veterans in the tested cohort. For the untested cohort, we obtained HIPAA authorization and a waiver of informed consent.

Data Collection

The primary sources of data were the VA's electronic health records (EHRs): the VACCR[14]; and the VA CDW. Demographic information (eg, age, race) and exposure to AO were obtained from patient registration in the CDW. Clinical characteristics, such as clinical stage, NCCN risk group, and management decisions were obtained from review of the EHRs. Pathology reports were accessed to determine the presence of cancer and the biopsy Gleason score.

Management decisions for both cohorts were determined by reviewing the record from 6 months after the initial diagnostic biopsy. AS was recorded as the management strategy if a chart note indicated that this was the treatment decision or if no other treatment for PCa was recorded. Urologists also completed questionnaires capturing their treatment recommendations before and after reviewing the assay results with patients.

FIGURE 1. Consort Diagram Illustrating Patient Population Enrolled in Prospective Study



NCCN indicates National Comprehensive Cancer Network.

All chart abstractions were conducted centrally at the Bedford VA. Prior to conducting the chart review for this study, the 2 nurse abstractors independently reviewed identical records in groups of 5 until they achieved greater than 90% observed agreement across all questions. The pair of nurse-abstractors then proceeded to review charts independently for the study.

Data Analysis

We conducted univariate descriptive analyses to describe the demographic and clinical characteristics, distribution of GPS results, and the management decisions in the retrospective and prospective cohorts. We conducted bivariate analyses to compare the untested and tested populations. Independent variables included age, race, AO exposure, Gleason score, cancer stage, NCCN risk group, and GPS result. Outcome variables were genomic testing and management choice. For statistical comparisons, we used the χ^2 test for categorical variables, paired *t* test for means of continuous variables, and 1-way analysis of variance when there were more than 2 levels for the independent variable. All statistical analyses were conducted using SAS 9.4 (SAS, Cary, NC).

Results

Two hundred male veterans were included in the untested cohort and 219 were enrolled in the prospective study (**Figure 1**). Of the prospectively enrolled veterans, 29 were ineligible for the final analysis. Reasons for exclusion included insufficient tissue for genomic analysis (25 patients), lost to follow-up (2 patients), incorrect assignment of NCCN risk group (1 patient), and withdrawal of patient consent (1 patient). All results presented included 200 untested patients and 190 tested patients.

Clinical characteristics, including age, race, and AO exposure, were similar between the untested and tested patients (**Table 1**). The untested cohort included more NCCN intermediate-risk patients than the tested cohort (46% vs 35%); this was driven by the greater number of patients with a Gleason score of 3+4 in the untested cohort (37% vs 26%).

The median GPS result in the prospective cohort was 26.5, with a range of 0 to 61. A wide range of GPS results existed within each racial group and among those exposed to AO and those who were unexposed (**Figure 2**). There was also a wide range of GPS results within each participating VAMC (data not shown). The distribution of GPS results within individual NCCN risk groups is illustrated in the **Appendix**. The median GPS result was lowest (25) in NCCN low-risk patients and highest (28) in NCCN intermediate-risk patients (Table 1 and Appendix). The median likelihood of favorable pathology (determined by integration of GPS and NCCN risk group) ranged from 84% in the NCCN very low-risk group to 58% in the NCCN intermediate-risk group.

Black veterans accounted for 15% of the untested patients and 21% of the tested patients (Table 1). Among untested black veterans, the use of AS was 66% compared with 61% in untested white veterans. In the tested cohort, the use of AS among black veterans was 80%, a 14% absolute difference between untested and tested veterans, while AS use was 72% in tested white veterans, with an 11% absolute difference. The median GPS result was lower among black veterans compared with white veterans (24 vs 27). The range of likelihood of favorable pathology, as predicted by GPS results, was wide in both groups and had substantial overlap (48%-89% in black veterans vs 32%-91% in white veterans).

Table 2 illustrates the frequencies of risk refinement in various NCCN risk groups following GPS testing. Biological risk (derived by synthesis of GPS result and NCCN risk group) was lower than expected, based on NCCN risk group alone, in 24 (12%) of tested patients and higher than expected in 13 (7%) of patients. The highest frequency of risk refinement (30%) occurred in NCCN low-risk patients. In this group, 20% of patients had a biological risk that was lower than expected based on NCCN risk alone, and 10% had a higher than expected risk. Risk refinement occurred in 12% of NCCN very low-risk patients and in 12% of intermediate-risk patients.

A wide variety of management strategies were documented in the untested and tested cohorts, including AS, radical prostatectomy, radiation therapy (external beam radiation therapy and brachytherapy), and multimodal therapy. AS was the most common initial management strategy in both cohorts, although there was substantial variability in use of AS across VAMCs in both

the untested (range: 31%- 84%) and tested (range: 43%-93%) cohorts (data not shown). Sixty-two percent of the untested patients and 74% of tested patients (Table 1) were managed with AS at 6 months post diagnosis. This represents a 12% absolute and 19% relative difference in AS between untested and tested patients. The largest observed difference in AS between tested and untested men was among veterans under the age of 60; the rate of AS was 33% higher in the tested patients compared with the untested cohort (**Figure 3**). Across the NCCN risk groups, greater use of AS was most pronounced in the NCCN low-risk group; the rates of AS in untested versus tested men were 72% (n = 50) and 90% (n = 73), respectively. AS use also increased in tested veterans not exposed to AO (a 19% absolute increase) (Table 1). The overall impact of GPS testing on treatment decisions in each NCCN risk group is illustrated in Table 2.

Urologists were asked to record their treatment recommendations before and after receiving the GPS results. Across all groups, a change in treatment recommendations was observed for 16% of patients, with 12% changing to higher-intensity treatment (either AS to any treatment or any single treatment to multimodal therapy) and 4% changing to lower-intensity treatment (either any single treatment to AS or multimodal therapy to a single treatment or AS). These changes were most common in the intermediate NCCN risk group, with 22% of patients changing to higher-intensity treatment and 5% changing to lower-intensity treatment.

Discussion

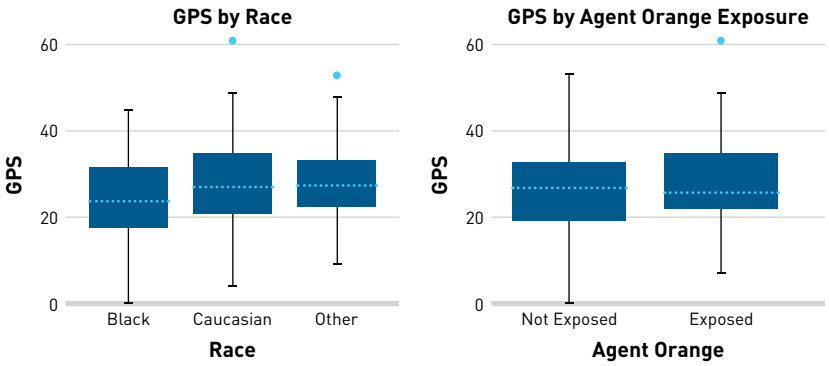
AS is increasingly favored as the initial management strategy of choice for newly diagnosed, low-risk PCa.[3] However, its implementation varies across practice settings.[4-6] In this analysis, we report on the use of AS in 6 VAMCs before and after the introduction of a genomic test, the Oncotype DX GPS. By providing molecular information to supplement clinical characteristics, genomic testing may improve identification of patients who can be safely managed on AS and those who are likely to benefit from

TABLE 1. Characteristics of Veterans in Each Cohort

	Untested (n = 200)		Tested (n = 190)		
	Number	%	Number	%	*P*
Age, years, median (range)	66 (43-83)		66 (50-85)		
Race					.10
White	164	82%	131	69%	
Black	29	15%	39	21%	
Other	7	4%	20	11%	
Agent Orange exposure					.50
Exposed	46	23%	49	26%	
Not exposed	154	77%	141	74%	
Gleason Score					.02
3+3	127	64%	141	74%	
3+4	73	37%	49	26%	
NCCN risk group					.10
Very low	36	18%	42	22%	
Low	73	37%	81	43%	
Intermediate	91	46%	67	35%	
AS (all patients)	124	62%	139	74%	
AS by NCCN risk group					.20
Very low	32	89%	37	90%	
Low	54	74%	72	90%	
Intermediate	38	42%	30	45%	
AS by race					<.01
White	102	61%	93	72%	
Black	19	66%	31	80%	
Other	3	60%	15	80%	
AS by Agent Orange exposure					.60
Exposed	31	68%	31	63%	
Not Exposed	93	59%	108	78%	
GPS, all patients, median (range)	Not assessed		26.5 (0-61)		
Median GPS by NCCN risk group	Not assessed				
Very low			26.5		
Low			25		
Intermediate			28		
Median GPS by race	Not assessed				
White			27		
Black			24		
Other			27.5		
Median GPS by Agent Orange exposure	Not assessed				
Exposed			26		
Not exposed			27		

AS indicates active surveillance; GPS, Genomic Prostate Score; NCCN, National Comprehensive Cancer Network.

FIGURE 2. Median GPS Results Similar Across All Racial Groups and in Patients Exposed Versus Not Exposed to Agent Orange



GPS indicates Genomic Prostate Score; NCCN, National Comprehensive Cancer Network.

TABLE 2. Change in Risk Classification After GPS Testing

	Change in GPS Risk Classification		
Pre-Assay NCCN Risk Group	Lower Risk, Number (%)	No Change, Number (%)	Higher Risk, Number (%)
Very low	-	37 (88%)	5 (12%)
Low	16 (20%)	57 (70%)	8 (10%)
Intermediate	8 (12%)	59 (88%)	-

GPS indicates Genomic Prostate Score; NCCN, National Comprehensive Cancer Network.

immediate treatment. These molecular markers may be particularly helpful in patient subgroups where there is controversy about appropriate management (eg, black patients, men exposed to AO, intermediate-risk disease).

The GPS assay produced a wide range of results among all patients, within each NCCN risk group, and across all VAMCs. These result support previous work demonstrating considerable biological heterogeneity within the low-risk PCa population; clinical risk factors alone do not capture this level of nuance for individuals.[25] The GPS assay provided refined risk-group estimates in approximately 20% of patients across all NCCN risk groups. This number is substantially lower than what was observed in a previous analysis of the clinical utility of the GPS assay, which has shown refinement in 39% of patients.[26] These differences could reflect differences in the patient populations, as the previous study was conducted at 2 large community practices and 1 academic center, or may simply reflect the diverse biology in PCa.

The rate of AS in this study was higher in both untested and tested patients compared with other contemporary PCa cohorts, such as CaPSURE, a contemporary prospective registry of 15,000 men with PCa, in which the AS rate for low-risk patients was approximately 40%.[7] Our findings are, however, consistent with previous reports of AS rates within the VA.[4,27] Despite a high baseline rate of AS in the VA (as evidenced by our untested cohort), the rate of AS increased with the use of GPS testing; this higher utilization was driven primarily by more AS in younger veterans and those with NCCN low-risk disease. Younger patients may have more to lose from immediate therapy and may benefit from the greater confidence in at least a period of AS before definitive treatment. Low-risk patients are generally regarded as highly suitable candidates for AS.[3] These findings give confidence that the GPS result is useful in helping these 2 groups make decisions that favor nonintervention. An increase in AS may be attributed to greater physician and/or patient confidence in treatment planning in these groups after receiving individualized biological information from the GPS assay. Study results in other cohorts have confirmed that patient decisional conflict declines[28] and that physician confidence increases with incorporation of GPS testing.[26,28]

This prospective study included a large cohort of black men with PCa who received genomic testing to aid in their treatment decision process. Interestingly, the rate of AS was higher in black veterans than white veterans in both the untested and tested cohorts. VA physicians are clearly willing to offer AS to all veterans, regardless of race. Similar to previous studies, the median and range of GPS results were similar between black and white patients,[22] supporting the idea that the GPS assay measures PCa genes that are expressed similarly in both black and white patients. AS rates were higher in black and white veterans with incorporation of GPS results, although the difference was greater in black veterans. Collectively, these data suggest that the GPS assay can be a very useful tool in guiding management decisions in black men with low-risk PCa who are considering treatment versus surveillance. Additional studies in larger patient cohorts are needed to confirm these findings.

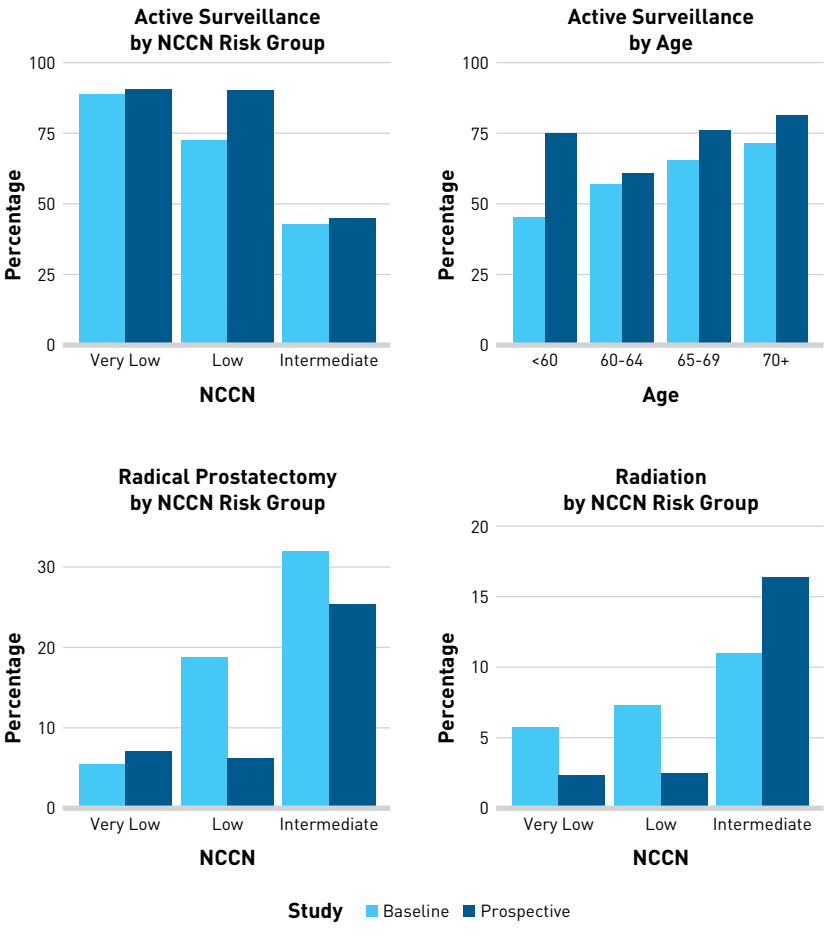
This study has several limitations. The untested cohort included a significantly larger proportion of intermediate-risk patients. Although this may be construed to imply that the greater utilization of AS in the tested cohort was driven by lower baseline risk, within group changes indicate that there was higher AS utilization in tested patients regardless of baseline risk group; this change was most pronounced for the NCCN low-risk category but was present in NCCN very-low and intermediate-risk patients. We considered any patients who did not receive a definitive treatment within

6 months of biopsy as undergoing AS. Hence, some patients classified as receiving AS may have been simply delaying planned definitive management. The untested patients were seen in the VA in the 2 years prior to enrollment of the tested patients. Practice patterns are evolving in the direction of higher AS rates across all practice settings,[6] and some of this shift may be related to temporal tends. However, we believe it unlikely that the differences between groups in this study would have been achieved in a 1- to 2-year period, particularly since the institutions and providers were the same and the baseline rate of AS was already very high.

Conclusions

To our knowledge, this study represents the first report of biopsy-based genomic testing for PCa within VAMCs. This cohort was also enriched for black patients, an important group in which there is ongoing controversy about the appropriateness of AS for initial management. We confirm prior studies' findings demonstrating that the refinement of risk provided by the GPS assay can support increased adoption of AS for an initial management approach. This increased adoption was seen across age, race, and NCCN risk groups, with the largest increases observed in men younger than 60 years, black veterans, and NCCN low-risk patients, which is also in line with guideline-based care. Future studies showing the persistence on AS and longer-term outcomes should be considered to further support the utility of the GPS assay. ■

FIGURE 3. Proportion of Patients in the Baseline (Untested) and Prospective (Tested) Cohort Receiving Active Surveillance as a Function of NCCN Risk Group and Age and Radical Prostatectomy and Radiation by NCCN Risk Group



NCCN indicates National Comprehensive Cancer Network.

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APPENDIX

Improving Risk Stratification Among Veterans Diagnosed With Prostate Cancer: Impact of the 17-Gene Genomic Prostate Score Assay

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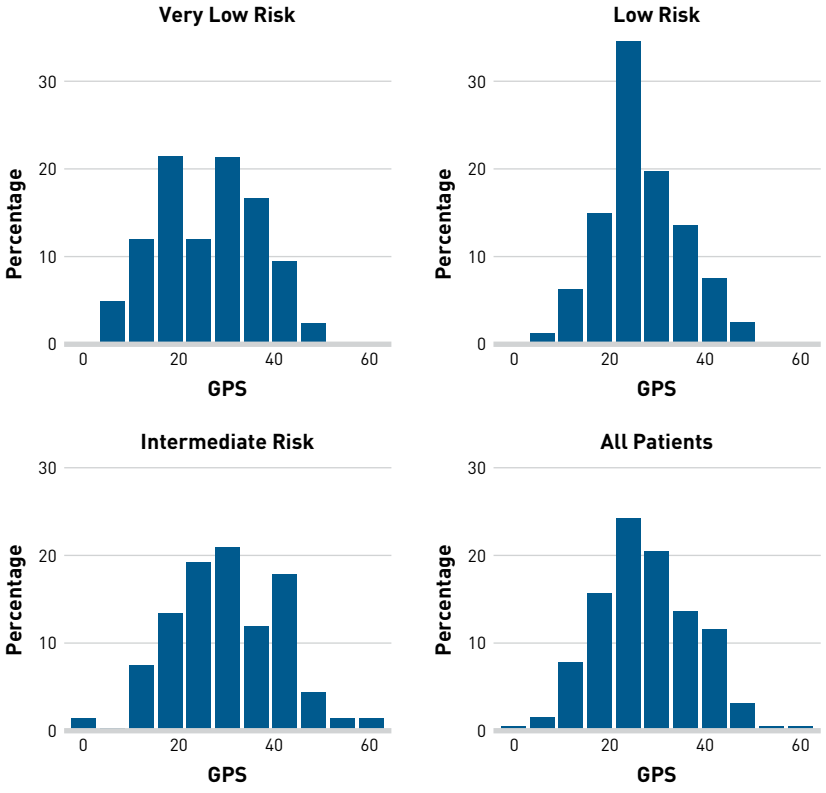
APPENDIX. Distribution of GPS Results by NCCN Risk Group and in All Patients



GPS indicates Genomic Prostate Score; NCCN, National Comprehensive Cancer Network.