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Regional Adoption of Commercial Gene Expression Testing for Prostate Cancer

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IMPORTANCE Although tissue-based genomic tests can aid in treatment decision-making for patients with prostate cancer, little is known about their clinical adoption.

OBJECTIVE To evaluate regional adoption of genomic testing for prostate cancer and understand common trajectories of uptake shared by regions.

DESIGN, SETTING, AND PARTICIPANTS This dynamic cohort study of patients diagnosed with prostate cancer used administrative claims from Blue Cross Blue Shield Axis, the largest source of commercial health insurance in the US, to characterize temporal trends in the use of commercial, tissue-based genomic testing and calculate the proportion of tested patients at the hospital referral region (HRR) level. Eligible patients from July 1, 2012, through June 30, 2018, were those aged 40 to 89 years with prostate cancer diagnosed from July 1, 2012, through June 30, 2018.

MAIN OUTCOMES AND MEASURES Group-based trajectory modeling was used to classify regions according to discrete trajectories of adoption of commercial, tissue-based genomic testing for prostate cancer. Across regions with distinct trajectories, HRR-level sociodemographic and health care contextual characteristics were compared, using data previously calculated among Medicare beneficiaries.

RESULTS A total of 92 418 men with prostate cancer who met inclusion criteria were identified; the median (interquartile range) age at diagnosis was 60 (56-63) years. Overall, the proportion of patients who received genomic testing increased from 0.8% in July 2012 to June 2013 to 11.3% in July 2017 to June 2018. Trajectory modeling identified 5 distinct regional trajectories of genomic testing adoption. Although less than 1% of patients in each group were tested at baseline, group 1 (lowest adoption) increased to 4.0%. Groups 2 (7.8%), 3 (14.6%), and 4 (17.3%) experienced more modest growth, while in group 5 (highest adoption), use increased to 33.8% of patients tested from June 2017 to July 2018. Compared with regions that more slowly adopted testing, HRRs with the highest rate of adoption (group 5) had higher HRR-level education measures (percentage [SD] with college education: group 1, 25.6% [4.8%]; vs group 2, 27.5% [7.3%]; vs group 3, 30.3% [9.1%]; vs group 4, 29.8% [8.2%]; vs group 5, 30.4% [11.4%]; *P* for trend = .03), median (SD) household income (group 1, $50 412.8 [$6907.4]; vs group 2, $54 419.6 [$11 324.5]; vs group 3, $61 424.0 [$17 723.8]; vs group 4, $58 508.3 [$15 174.6]; vs group 5, $58 367.0 [$13 180.5]; *P* for trend = .005), and prostate cancer resources, including clinician density (No. [SD] of clinicians per 100 000: group 1, 2.5 [0.3]; vs group 2, 2.5 [0.5]; vs group 3, 2.6 [0.5]; vs group 4, 2.7 [0.7]; vs group 5, 2.6 [0.5]; *P* for trend = .04) and prostate cancer screening (percentage [SD] of prostate-specific antigen testing among patients aged 68-74 y: group 1, 29.4% [11.8%]; vs group 2, 32.4% [11.2%]; vs group 3, 33.1% [12.7%]; vs group 4, 36.1% [9.7%]; vs group 5, 28.8% [11.8%]; *P* for trend = .05).

CONCLUSIONS AND RELEVANCE In this cohort study of patients with prostate cancer, the adoption of commercial tissue-based genomic testing for prostate cancer was highly variable in the US at the regional level and may be associated with contextual measures related to socioeconomic status and patterns of prostate cancer care. These findings highlight factors underlying differential adoption of prognostic technologies for patients with cancer.

Invited Commentary

Supplemental content

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Tissue-based multigene panel (genomic) tests have been developed and are commercially available for patients with several forms of cancer, including breast, melanoma, and prostate.[1-4] Although a range of prognostic tests assess distinct cancer types and underlying pathways, they share a common goal of personalizing decision-making, often modifying the necessity or intensity of treatment based on an individual's risk. These tests have been particularly promising for the management of prostate cancer, where the aggressiveness of the disease varies considerably among men with localized cancers.[5] In retrospective studies, several multigene panels for prostate cancer have been shown to add independent prognostic information beyond standard clinical variables, such as prostate-specific antigen (PSA) level, Gleason score, or clinical stage.[6] Although it has been assumed that genomic tests will enhance the precision with which the disease is managed (ie, increased active surveillance for nonaggressive cancers and timely treatment for those with aggressive disease), the effectiveness of testing has not been independently established.[7-9] Nevertheless, genomic tests have recently become incorporated into major clinical practice guidelines, such as those from the National Comprehensive Cancer Network, and are covered by most major insurance carriers, including Medicare.

Despite mounting clinical evidence and guideline integration, little is known about the real-world use of genomic testing for prostate cancer. Although variation has been demonstrated among practices within a particular state, no published studies have examined national trends in the utilization of genomic testing or regional variation associated with their use.[10] More broadly, understanding the regional-level adoption of genomic testing can reveal insights about new diagnostic technologies in cancer care. The adoption of new therapeutic technologies has historically been shown to vary substantially across regions, often superseding patient-level factors.[11] It is not known whether similar patterns apply to diagnostic tests that are performed by a remote laboratory and therefore may be less sensitive to resource differences at the local level. Although genomic tests are not reimbursable to the physician, other forces may differ at the regional level; such as treatment patterns, use of other technologies, such as magnetic resonance imaging (MRI); and the contribution of peer influence.[12,13] Lastly, as testing may be associated with less treatment of low-risk prostate cancer, understanding variation in its use can inform strategies to standardize and improve care.

We aimed to characterize national trends in the use of genomic testing following the initial diagnosis of prostate cancer. To understand variation in adoption of genomic testing across regions, we examined use across distinct health care marketplaces at the hospital referral region (HRR) level. Beyond assessing the presence of variation alone, we used a method for evaluating developmental trajectories shared by regions, with the aim of uncovering a taxonomy of regional adoption. Furthermore, we sought to determine whether health care contextual factors assessed at the regional level were associated with the trajectory of genomic testing adoption. We hypothesized that uptake of genomic testing would vary substantially across regions, but that regions with similar trajectories of growth would also share conditions relating to education, resources, and contextual measures of prostate cancer care. As a result, this analysis seeks to establish whether regional conditions are associated with the pace with which new prognostic technologies for cancer care are adopted.

Key Points

Question How have new prognostic gene expression (genomic) tests for prostate cancer been adopted in the US?

Findings This dynamic cohort study of commercially insured patients with prostate cancer found that although adoption of genomic testing was highly variable, there were distinct regional trajectories of adoption. Rapid regional adoption of genomic testing was associated with higher contextual measures of income, education, and prostate cancer services.

Meaning Among a cohort of patients with prostate cancer, regional variation in the use of new prognostic genomic tests for prostate cancer was associated with underlying differences in resources and prostate cancer services.

Methods

Study Design and Data Source

We performed a dynamic cohort study to assess the use of commercially available genomic tests for prostate cancer from July 1, 2012, through June 30, 2018, and included claims through December 31, 2018. The primary data source was administrative claims from Blue Cross Blue Shield Axis, the largest source of commercial insurance claims in the US. Blue Cross Blue Shield Association (BCBSA) is a federation of 36 individual health insurance organizations and companies across the US, providing care to 1 in 3 people in the US. Using a secure data portal, we accessed a limited data set of deidentified claims. The primary study outcome was claims for commercially available tissue-based gene expression testing in the 6-month period following the new diagnosis of prostate cancer based on timing thresholds for initial clinical decision-making.[14] This study was deemed non-human subjects research by the Yale University Institutional Review Board. Informed consent was not needed for this study of deidentified secondary data.

Cohort Selection and Study Variables

We included patients aged 40 to 89 years who were diagnosed with prostate cancer, identified by diagnosis code. We further identified claims for genomic testing using Current Procedural Terminology and National Provider Identifier codes to reflect common commercially available genomic tests for prostate cancer performed at centralized laboratories (eTable in the Supplement).[15] Biopsy-based genomic tests are intended to aid decision-making in the time period following initial diagnosis. To ensure that we identified new, incident cases of prostate cancer, we excluded patients without claims for a prostate biopsy within 90 days of a first prostate cancer diagnosis.

We included tests performed within 6 months of initial diagnosis and preceding the date of definitive treatment if it was undertaken. Lastly, we restricted inclusion to HRRs with at least 10 patients diagnosed with prostate cancer in a 12-month period to allow for adequate sampling within regions at each time period. Through the use of deidentified administrative claims, we did not assess cancer grade, stage, or other clinical variables.

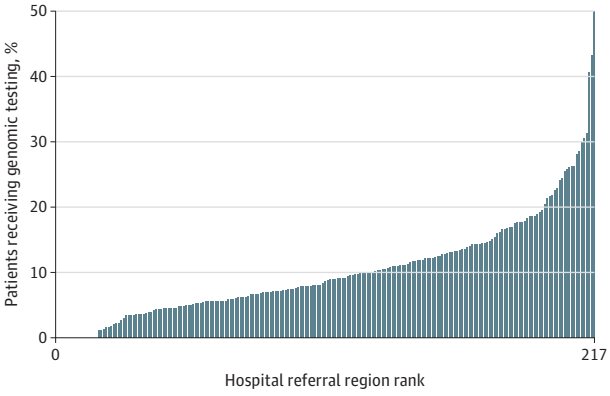
To understand how adoption of genomic testing varied across regions, we evaluated testing at the HRR level using the boundaries described in the Dartmouth Atlas of Health Care. The HRRs reflect regional health care markets for tertiary medical care that have been calculated based on referral practices for major cardiac care and neurosurgery and also have been used to evaluate variation in prostate cancer care.[16,17] We assigned patients to HRRs based on their zip code of residence.[18] We also compiled ecological indicators assessed at the HRR level as previously defined by the Dartmouth Atlas using data from the Medicare population in 2014: percentage of use of PSA testing among Medicare beneficiaries aged 68 to 74 years, prostate cancer incidence, use of prostatectomy by age, use of radiation treatment, use of hormonal therapy for prostate cancer, and proportion of patients receiving no treatment or delayed treatment for prostate cancer.[19] These measures were not directly assessed within the BCBSA cohort.

Statistical Analysis

We calculated the proportion of eligible patients who received claims for genomic testing within each HRR at each 12-month period. In each interval, we described the distribution of HRR-level adoption of genomic testing using summary statistics and plots.

We used group-based trajectory modeling (GBTM) to identify clusters of HRRs with similar trajectories of genomic testing adoption. In GBTM, a form of finite mixture modeling, maximum likelihood estimation is applied to longitudinal data to identify groups sharing a common trajectory.[20] Unlike other techniques used to estimate growth trajectories, such as latent growth modeling, GBTM does not assume a single functional form of all trajectories and is therefore not constrained by a single pattern (ie, some groups may rise, fall, or remain flat). In addition to identifying the presence of variation among HRRs, GBTM also allows us to specify a distinct number of groups and uncover regions with similar trajectories of genomic testing adoption. We performed GBTM using zero-inflated Poisson models using the 12-month HRR-level count of patients receiving genomic testing, offset for the number of patients diagnosed with prostate cancer during that time interval. We explored varying numbers of latent classes and polynomial functions and used Akaike information criteria to select the model with best fit. We used descriptive statistics and nonparametric Kruskal-Wallis tests of association to compare contextual measures across the 5 trajectories of genomic testing adoption.[21] In addition, we used nonparametric Mann-Kendall tests to identify monotonic trends across latent strata of genomic testing adoption. We conducted GBTM using the crimCV package in R, version 3.6.0 (R Project for Statistical Computing). All other analyses were performed using SAS, version 9.4 (SAS Institute).

Figure 1. Vertical Line Plot Demonstrating Variation in the Proportion of Patients Receiving Commercial Tissue-Based Genomic Testing for Prostate Cancer by Hospital Referral Region, June 2017 to July 2018, Ranked Lowest to Highest



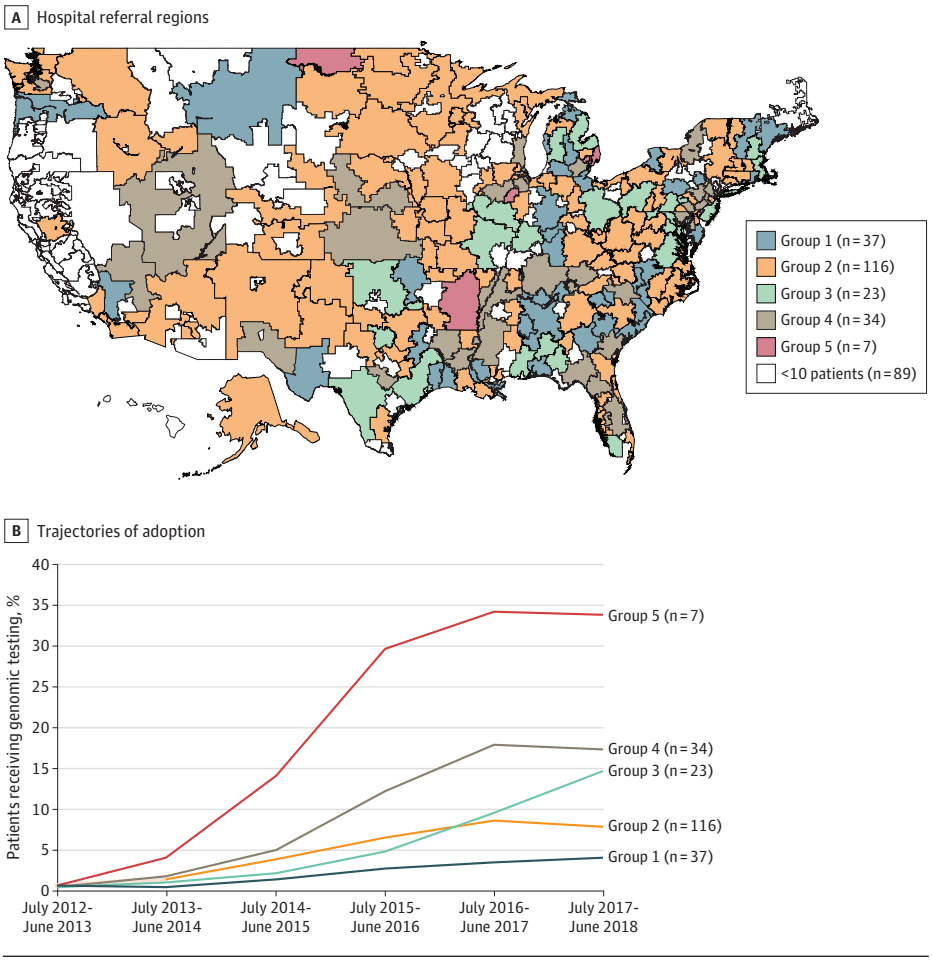
Results

The study cohort consisted of 92 418 patients with prostate cancer diagnosed from July 1, 2012, through June 30, 2018, who met criteria for enrollment. The median (interquartile range) age at prostate cancer diagnosis was 60 (56-63) years. There were 217 evaluable HRRs after exclusion of regions with fewer than 10 patients who were diagnosed with prostate cancer in any 12-month period. Overall, there was minimal baseline use of genomic testing (0.8% among those diagnosed from July 2012 through June 2013), which increased to 11.3% among those diagnosed from July 2017 through June 2018. There was substantial variation at the HRR level in the use of genomic testing (**Figure 1**). For example, the highest rate of utilization was in Minot, North Dakota, which increased from less than 1.0% at baseline to 50.0% of patients with prostate cancer diagnosed from July 2017 through June 2018. In contrast, there were 17 regions in which no testing was performed in the latter study period.

Trajectory modeling indicated best model fit with 5 distinct patterns of genomic testing adoption at the HRR level (**Figure 2**). Although all regions had minimal utilization at baseline, group 1 (lowest trajectory of adoption) increased to 4.0%. In group 5 (highest trajectory of adoption), use increased to 33.8%. Three distinct groups (2-4) exhibited increased but modest adoption, reaching 7.8%, 14.6%, and 17.3%, respectively. Geographic analysis revealed that 4 of 7 HRRs in group 5 (highest adoption) were in Michigan, but were otherwise geographically unrelated, and included regions in Arkansas, Illinois, and North Dakota. Similarly, HRRs in the lowest cluster of adoption revealed no clear geographic relationship and were spatially unrelated.

We compared HRR-level prostate cancer–specific indicators previously assessed in the Medicare population by the Dartmouth Atlas across the 5 strata of genomic testing adoption. There were similar distributions of race as well as treatment patterns, including use of surgery, radiotherapy, hormonal therapy, and no treatment for prostate cancer (**Table**).

Figure 2. Trajectories of Tissue-Based Genomic Testing Adoption Among Commercially Insured Patients With Prostate Cancer



A, Geographic representation of hospital referral regions based on the probability of group membership; B, Trajectories of adoption from baseline (July 2012) through June 2018.

Regions with greater use of genomic testing had a higher percentage (SD) of individuals with college education (group 1, 25.6% [4.8%]; vs group 2, 27.5% [7.3%]; vs group 3, 30.3% [9.1%]; vs group 4, 29.8% [8.2%]; vs group 5, 30.4% [11.4%]; *P* for trend = .03), higher median (SD) household income (group 1, $50 412.8 [$6907.4]; vs group 2, $54 419.6 [$11 324.5]; vs group 3, $61 424.0 [$17 723.8]; vs group 4, $58 508.3 [$15 174.6]; vs group 5, $58 367.0 [$13 180.5]; *P* for trend = .005), higher urologist clinician density (No. [SD] of clinicians per 100 000: group 1, 2.5 [0.3]; vs group 2, 2.5 [0.5]; vs group 3, 2.6 [0.5]; vs group 4, 2.7 [0.7]; vs group 5, 2.6 [0.5]; *P* for trend = .04), and higher percentage (SD) of PSA testing among patients aged 68 to 74 years (group 1, 29.4% [11.8%]; vs group 2, 32.4% [11.2%]; vs group 3, 33.1% [12.7%]; vs group 4, 36.1% [9.7%]; vs group 5, 28.8% [11.8%]; *P* for trend = .05).

Discussion

In this evaluation of commercially available genomic testing for prostate cancer, we found that there was increasing use of testing in the period following the promotion and availability of these tests. However, there was also substantial regional variation in the use of genomic testing, with many HRRs that showed absent or minimal adoption. We identified 5 clusters of geographic regions that shared similar trajectories of genomic testing adoption, noting a greater than 8-fold difference in use between high-adopting and low-adopting regions. Clusters of HRRs that more rapidly adopted genomic testing had higher median income, education levels, and measures of prostate cancer care, including clinician density and rates of PSA screening. These findings suggest that similar regional conditions may underlie shared developmental trajectories in the use of new risk assessment technologies used in decision-making for cancer care. Given ongoing efforts and expenditures related to prognostic biomarkers across cancer care, our findings offer timely insights about how these tools have been applied in the real-world setting.

This work can provide a context for understanding how prognostic tests for cancer enter clinical care. Although a small number of HRRs rapidly adopted genomic testing for prostate cancer, most regions exhibited a variable but slower pace of growth. These findings are in line with other aspects of prostate cancer care that are highly regionalized, including PSA

Table. Comparison of Patient Age and Hospital Referral Region–Level Characteristics Among Trajectories of Genomic Testing Adoption for Prostate Cancer

Characteristic	Patients, % (SD)					*P* value	*P* value for trend[a]
	Group 1: low	Group 2: low-moderate	Group 3: moderate	Group 4: high-moderate	Group 5: high		
Race/ethnicity							
White	78.2 (13.0)	81.6 (11.8)	78.6 (12.1)	75.3 (12.7)	79.5 (11.1)	.07	.19
Black	17.5 (13.1)	11.9 (10.1)	15.1 (10.5)	17.1 (13.0)	15.7 (11.9)	.02	.44
Other	4.4 (4.7)	6.5 (6.8)	6.2 (5.9)	7.6 (5.9)	4.8 (2.4)	.07	.01
College and above	25.6 (4.8)	27.5 (7.3)	30.3 (9.1)	29.8 (8.2)	30.4 (11.4)	.21	.03
Median (SD) income, $	50 412.8 (6907.4)	54 419.6 (11 324.5)	61 424.0 (17 723.8)	58 508.3 (15 174.6)	58 367.0 (13 180.5)	.06	.005
Urologist density (clinicians per 100 000), No. (SD)	2.5 (0.3)	2.5 (0.5)	2.6 (0.5)	2.7 (0.7)	2.6 (0.5)	.20	.04
PSA testing among patients aged 68-74 y	29.4 (11.8)	32.4 (11.2)	33.1 (12.7)	36.1 (9.7)	28.8 (11.8)	.15	.05
Prostate cancer incidence per 1000, No. (SD)	7.4 (2.9)	7.5 (3.6)	7.2 (2.3)	7.2 (2.9)	12.8 (6.7)	.10	.51
Use of androgen deprivation therapy among men >75 y (per 1000), No. (SD)	375.7 (96.6)	382.6 (97.2)	357.4 (78.1)	361.9 (67.8)	318.2 (37.5)	.37	.29
No treatment of prostate cancer in men >75 y (per 1000), No. (SD)	356.1 (79.2)	350.3 (93.8)	350.0 (74.0)	342.7 (81.8)	359.5 (69.3)	.97	.68
Use of radiotherapy in patients >75 y (per 1000), No. (SD)	263.9 (78.6)	263.7 (66.1)	256.2 (45.3)	264.4 (81.5)	258.3 (49.5)	.97	.62
Use of prostatectomy in patients <75 y (per 1000), No. (SD)	196.5 (78.2)	206.8 (84.2)	182.8 (65.2)	183.6 (71.0)	208.5 (73.2)	.64	.43

Abbreviation: PSA, prostate-specific antigen.

[a] Mann-Kendall test of monotonic trends.

screening,[22] use of staging imaging,[23] mode of definitive treatment,[24,25] and use of active surveillance.[26,27] As a tool performed in remote laboratories, genomic testing differs from other aspects of care that depend on local factors, such as access to experienced clinicians, or capital investment in imaging, surgical, or radiation platforms.[28-30] Therefore, variation appears to be associated with discretionary practices that differ between regions. These findings are in line with data from the state of Michigan, in which use of genomic testing at the urology practice level ranged from 0% to 93%, suggesting a high degree of variation even within regions.[10] We observed a trend between regional use of PSA testing and greater adoption of genomic testing. These findings may reflect stronger regional preferences for prostate cancer detection that could contribute the use of technologies associated with decision-making. Therefore, variation in the use of genomic testing for prostate cancer appears to be associated with the discretionary nature of the tests, regional differences in prostate cancer diagnostic services, and familiarity with the technology.[31]

The use of GBTM to study the adoption of genomic testing is a novel application that yielded insights about patterns of growth. This approach, initially developed in the field of criminology, provides a tool for understanding and conveying developmental trajectories that has been applied across many other disciplines.[21,32] In this study, GBTM allowed us to uncover latent clusters of adoption of a new prostate cancer prognostic technology. For example, although HRR-level adoption of genomic testing was highly variable, there were trajectories shared by otherwise unrelated geographic regions. This suggests that similar sets of conditions at the local level might promote the adoption of new technologies, such as access to research-oriented medical centers, relationships with industry, or potentially patient-driven interest. Future work may further explore the shared factors associated with the adoption of prognostic cancer tests, particularly in the period before their effectiveness is established.

Our findings highlight potential sources of disparity that may be emerging in the use of genomic testing for prostate cancer. We found that groups of HRRs with higher income and education levels adopted genomic testing more rapidly. Importantly, we did not find monotonic trends in regional distributions of race between trajectories of genomic testing adoption. These results could reflect the study sample, which was derived from younger, commercially insured patients, which may mitigate racial disparities in access to cancer care.[33] However, these findings could also be attributable to the absence of individual-level data on a patient's race, and we cannot exclude the possibility that differences existed within HRRs. Furthermore, these results must be reconciled against prior work that has found significant racial disparities in the use of prostate MRI among Medicare beneficiaries.[34] Future patient-level analysis is therefore needed to clarify whether racial disparities have extended to the use of genomic testing. Nonetheless, our findings are consistent with other studies that have identified sociodemographic variation at the regional level in the adoption of diagnostic technologies for other cancers, including digital breast tomography.[21] Disparity in the use of new precision medicine technologies is an important but understudied question given the expansion of new forms of testing and treatment, such as next-generation sequencing.[35] As a result, this work can catalyze greater interest in studying not only the effectiveness of these tests, but the equity of their dissemination.

As national practice patterns converge on active surveillance for low-risk prostate cancer, variation in the use of genomic testing raises questions about their optimal clinical positioning and accessibility. As a tool that seeks to augment decision-making in localized prostate cancer, the utility of gene expression tests is related to the baseline management preferences of both patients and physicians.[36,37] A recent American Society of Clinical Oncology guideline indicated that commercially available biomarkers should be selected in situations when management would affect clinical management, and that routine ordering is not recommended.[38] The degree of variation observed in this study indicates that genomic testing remains highly discretionary, with some regions existing as outliers in both high and low use. Furthermore, our findings indicate that testing is likely applied less selectively to patients within a minority of HRRs, raising questions about cost-effectiveness.[39] Therefore, to improve consistency, guidelines could go further to define clinical factors, such as extremes of age, preference, or comorbidity, that may modify the utility of genomic testing.[40]

Limitations

Despite the strengths of this work, there are notable limitations that require discussion. Using an exclusively claims-based approach, we are unable to assess patient-level clinical or sociodemographic characteristics. As a result, the study population includes all patients with prostate cancer and is not restricted to those recommended to undergo testing (ie, low-risk and intermediate-risk disease). Therefore, the proportions reported were calculated using all incident prostate cancer cases, which underestimates the use of testing in low-risk and intermediate-risk patients. In addition, we compared sociodemographic characteristics at the HRR level using observations previously derived from the Medicare population, which may not mirror privately commercially insured patients who are younger, more frequently employed, and in better health. Although recent work has demonstrated that patterns in the BCBSA population can be generalized to the Medicare population in breast cancer, our findings may not be applicable to other payers or age demographics.[21] Furthermore, based on the coverage pattern of BCBSA, there are several regions that are underrepresented, including the western US. Although we took several steps to ensure that we identified patients newly diagnosed with the disease, we cannot rule out the possibility that individuals with an existing diagnosis of prostate cancer subsequently entered care within BCBSA or that genomic testing was self-paid by the patient. We assessed genomic testing based on claims for testing linked to a small number of national laboratories that perform these services; however, the clinical and pathologic characteristics of patients were not evaluable using this approach, limiting our ability to understand the utility or outcome of testing. Lastly, we did not account for the use of other risk assessment technologies, such as prostate MRI, which occupy a similar and often complementary role as genomic testing.[41,42]

Conclusions

Evaluating a large sample of commercially insured patients with prostate cancer, we found that there was substantial variation in the use of tissue-based gene expression tests aimed at risk stratification of localized disease. Although use varied at the HRR level, distinct patterns of adoption were shared by otherwise geographically unrelated regions. Clusters of regions that more rapidly adopted genomic testing had higher measures of income, education attainment level, and intensity of prostate cancer screening practices. These findings suggest that similar conditions relating to resources and clinical care may be associated with the adoption of new forms of prognostic risk assessment technologies. Further research appears to be warranted to clarify the contribution of patient-level factors to testing as well as the effectiveness of these tests in improving clinical decision-making.

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Concept and design: Leapman, Gross, X. Ma.
Acquisition, analysis, or interpretation of data: Leapman, Wang, S. Ma, X. Ma.
Drafting of the manuscript: Leapman, Wang.
Critical revision of the manuscript for important intellectual content: All authors.
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Administrative, technical, or material support: Leapman.
Supervision: Leapman, Gross, X. Ma.

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