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Authors

Levin, Albert M
Lindquist, Karla J
Avila, Andrew
et al.

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Performance of the Genomic Evaluators of Metastatic Prostate Cancer (GEMCaP) Tumor Biomarker for Identifying Recurrent Disease in African American Patients

Albert M. Levin[1,*], **Karla J. Lindquist**[2], **Andrew Avila**[3], **John S. Witte**[2], **Pamela L. Paris**[3,*], and **Benjamin A. Rybicki**[1,*]

[1]Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, 48202, USA

[2]Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, CA 94158, USA

[3]Department of Urology, Helen Diller Family Comprehensive Cancer, University of California at San Francisco, San Francisco, CA 94143, USA

Abstract

Evaluation of prostate cancer prognosis after surgery is increasingly relying upon genomic analyses of tumor DNA. We assessed the ability of the biomarker panel Genomic Evaluators of Metastatic Prostate Cancer (GEMCaP) to predict biochemical recurrence in 33 European American and 28 African American prostate cancer cases using genome-wide copy number data from a previous study. “Biomarker positive” was defined as ≥20% of the 38 constituent copy number gain/loss GEMCaP loci affected in a given tumor; based on this threshold, the frequency of a positive biomarker was significantly lower in African Americans (n=2; 7%) than European Americans (n=11; 33%; p=0.013). GEMCaP positivity was associated with risk of recurrence (HR=5.92; 95%CI=2.32–15.11; $p=3*10^{-4}$) in the full sample and among European Americans (HR=3.45; 95%CI=1.13–10.51; p=0.032) but was not estimable in African Americans due to the low rate of GEMCaP positivity. Overall, the GEMCaP recurrence positive predictive value (PPV) was 85%; in African Americans, PPV was 100%. When we expanded the definition of loss to include copy-neutral loss of heterozygosity (i.e. loss of one allele with concomitant duplication of the other), recurrence PPV was 83% for European American subjects. Under this definition, five African American subjects had a positive GEMCaP test value; four went on to develop biochemical recurrence (PPV=80%). Our results suggest that the GEMCaP biomarker set could be an effective predictor for both European American and African American men diagnosed with localized prostate cancer who may benefit from immediate aggressive therapy after radical prostatectomy.

Co-corresponding Authors: Benjamin A. Rybicki, PhD, Department of Public Health Sciences, 3E One Ford Place, Henry Ford Health System, Detroit, MI 48202, brybick1@hfhs.org, Telephone: 313.874.6399, Fax: 313.874.6730, Pamela L. Paris, PhD, Department of Urology, Helen Diller Family Comprehensive Cancer, University of California at San Francisco, San Francisco, CA 94143, pparis@cc.ucsf.edu, Telephone: 415.514.2559, Fax: 415.514.4927.
*These authors contributed equally to this work.

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Keywords

prostate cancer; biomarker; African American; DNA copy number alterations; biochemical recurrence

Introduction

Accurate risk assessment of prostate cancer recurrence and outcome is vital for men who receive treatment with curative intent, such as radical prostatectomy. Many risk models use clinical disease-associated variables to categorize recurrence risk. Two of the most widely used tools are a three-level categorization published by D'Amico et al. (1) and a continuous nomogram devised by Kattan et al. (2) However, concordance rates for nomograms and actual pathologic stage or recurrence are only about 70%; (3) this suggests that clinical and pathological data alone are insufficient in predicting the biological course of a tumor.

Histologically similar prostate may follow drastically different disease courses—better tools are needed to identify which patients have more aggressive tumors and should receive adjuvant therapy. We discovered a suite of DNA-based biomarkers that predict prostate cancer recurrence and metastasis (4) called the Genomic Evaluators of Metastatic Prostate Cancer (GEMCaP). Evaluation of prostate tumors from an independent cohort of 27 patients found that GEMCaP classified recurrent cases slightly better than the Kattan nomogram (78% versus 75%). (5) In a more recent high-risk cohort of 54 patients who received only radical prostatectomy for initial treatment for localized disease, GEMCaP's risk prediction accuracy was slightly higher than that of the Kattan postoperative nomogram (67% versus 65%). (6) More importantly, GEMCaP accurately predicted unfavorable outcomes in lymph node-negative patients that the nomogram had classified as being at low risk of recurrence.

African Americans have a higher incidence of prostate cancer and higher mortality rates than age-matched European Americans. (7) While studies comparing racial differences in prostate tumor DNA copy number alterations (CNAs) have not found notable differences, African Americans tend to have a higher frequency of CNAs—often in regions associated with aggressive disease. (8, 9) GEMCaP has not been previously evaluated in an African American sample. Using existing data from a multi-ethnic sample of prostate cancer patients, (10) we compared the predictive value of GEMCaP in African American and European American patients.

Materials and Methods

See Supplementary Materials for detailed Methods.

Study Subjects and GEMCaP Loci CNA assessment

Approval for the study was obtained from the Institutional Review Board of the Henry Ford Health System (Detroit, MI); informed consent was acquired from all participants. We identified 62 radical prostatectomy patients (33 European American, 29 African American) from a previously completed hospital-based case-control study of prostate cancer (11) with available whole genome copy number data. (10) The clinical/pathological characteristics of

the patients are presented in Supplementary Table 1. We used available clinical data to compute the Kattan (2) and CAPRA-S (12) post-operative nomograms to estimate five-year recurrence risk for each patient to compare with GEMCaP predictions.

Two Illumina (San Diego, CA) 1M-Duo single nucleotide polymorphism (SNP) arrays were genotyped for each patient (one tumor, one germline DNA specimen from blood). (10) B-allele frequency (BAF) segmentation (13) (version 1.1.0) was used to identify CNA regions (gain, loss, and copy neutral loss-of-heterozygosity (14, 15)).

Of the 39 GEMCaP CNA loci, 38 (15 gain, 23 loss) that mapped to human genome build 19 (hg19) were used to assess GEMCaP biomarker positivity. For each tumor, a locus was given a score of "1" if at least one SNP within the GEMCaP locus boundaries had a CNA that was consistent in direction with the GEMCaP prediction; otherwise it was scored as "0." The GEMCaP score is the sum of the locus-specific scores; GEMCaP biomarker positivity is defined as a score ≥8 (≥20% positive loci), a threshold established in the original GEMCaP study. (4) Whole genome sequencing was available for four of the African American tumor-normal specimen pairs using the Complete Genomics (Mountain View, CA) next generation cancer sequencing platform. Sequence-based estimates of copy-number for the GEMCaP loci were compared with those from the SNP-array using the Bland-Altman method. (16)

Statistical Analyses

Fisher's exact test was used to assess differences in CNA frequencies between African American and European American subjects for each of the GEMCaP loci and for overall biomarker positivity. Biochemical recurrence (BCR) was defined as two consecutive detectable (>0.2 ng/ml) and rising prostate specific antigen (PSA) levels post-surgery. (17, 18) This definition includes individuals without undetectable post-surgery PSA levels (i.e. not cured). To assess the ability of GEMCaP to predict BCR, the positive predictive value (PPV; probability of developing recurrence given a positive GEMCaP test) and negative predictive value (NPV; probability of not developing recurrence given a negative GEMCaP test) were calculated. Time-to-event analyses were performed with time-to-BCR defined as duration between surgery date and recurrence-defining PSA or censored due to end of study, loss to follow-up, or death. Hazard Ratios (HR) for BCR were estimated using Cox proportional hazards models overall and stratified by self-identified ethnicity, adjusting for age, tumor stage, and the first genome-wide principal component based on SNP genotypes (assessed in blood samples from each subject). (19) Heterogeneity in the ethnicity-specific hazard ratios was evaluated using a one-degree-of-freedom likelihood ratio test.

Results

Table 1 details the frequency distribution of CNAs within the GEMCaP genomic loci by ethnicity. The base-pair mapping of these loci in hg19 are presented in Supplementary Table 2. Frequency differences for copy-neutral loss and gross copy number loss events were observed between African American and European American tumors. For 20 of the 23 GEMCaP copy loss loci (91%), there was a higher frequency of loss in European American versus African American tumors. Differences in four of these were statistically significant ($p<0.05$). In comparison, for 8 of the 15 GEMCaP copy gain loci, there was a higher

frequency of gain in European American versus African American tumors, with none reaching statistical significance. Copy-neutral loss was proportionally more prevalent in African American than European American tumors, with the largest difference (21% higher) shown for locus 31 on chromosome 8 (Table 1). The largest difference for a non-chromosome 8p locus was found at locus 35 on chromosome 13, with 14.2% more copy-neutral loss in African American tumors. For the GEMCaP copy loss loci, no significant differences in frequency were observed between ethnicities when copy-neutral loss was included in the definition of loss (Table 1).

The distributions of GEMCaP scores for individual tumors by ethnicity and inclusion of copy-neutral loss events in the definition are displayed in Supplementary Figure 1. Based on the original definition, GEMCaP biomarker positivity was higher in European Americans (n=11; 33.3%) than African Americans (n=2; 6.9%; p=0.013). When copy-neutral events were included in the GEMCaP definition, biomarker positivity remained over twice as high in European Americans (n=12; 36.4%) than African Americans (n=5; 17.2%), although no longer statistically significant (p=0.153).

BCR data was available for 61 individuals (28 African American, 33 European American); results of these analyses are displayed in Table 2. Median follow-up was 3.6 years; maximum follow-up was 8.8 years. GEMCaP positivity was associated with an increased risk of recurrence in the full sample (HR=5.92; 95%CI=2.32–15.11; $p=3.0*10^{-4}$) and among European Americans (HR=3.45; 95% CI=1.13–10.51; p=0.032); recurrence was not estimated in African Americans due to the low rate of GEMCaP positivity. GEMCaP's overall PPV was 84.6%; in African Americans, PPV was 100%. When copy-neutral loss events were included in the GEMCaP definition, positivity was also associated with an increased risk of recurrence overall (HR=3.42; 95%CI=1.58–7.38; p=0.002). When stratified by ethnicity, hazard ratios were similar to the overall estimate but not statistically significant for African Americans (Table 2). A formal test of heterogeneity of the ethnicity-specific hazard ratios did not indicate a significant difference (p=0.435). Under this definition, ethnicity-specific PPVs were 80.0% for African Americans and 83.3% for European Americans; corresponding NPVs were 65.2% and 42.9%.

In Figure 1, GEMCaP positivity (including copy-neutral losses) is compared to five-year recurrence risk predictions based on the Kattan and CAPRA-S pre-operative nomograms. GEMCaP predicted disease recurrence despite low Kattan and CAPRA-S prediction scores, demonstrating the added value of somatic genetic predictors of recurrence in conjunction with clinical/pathological predictors.

Supplementary Table 3 compares sequence- and SNP-based GEMCaP loci copy number estimates for four African American tumor specimens. Estimates were 53% identical across the four specimens; 9% of sequence-based calls were higher (median difference: 0.1; range: 0.1–0.6) and 38% SNP-based calls were higher (median difference: 0.1; range 0.1–0.8). A Bland-Altman plot (16) was used to assess quantitative agreement between the two measurements (Supplementary Figure 2). The 95% confidence limits were established at a copy number difference of ±0.33 (±1.96*standard deviation). At these thresholds, 5.3%

(n=8) of values were in quantitative disagreement. However, for all of these loci, the direction of the CNA (7 loss, 1 gain) was identical between methods.

Discussion

Use of somatic CNAs in DNA from prostate and other solid tumors to inform disease prognosis has proliferated in recent years; however, biomarker development in this area has largely been limited to populations of primarily European ancestry. Prostate cancer is known to have striking differences by race-ethnicity in both disease incidence and mortality. (7, 20) While societal and cultural factors may partially explain this disparity, inherent differences in disease biology may also play a role. (20, 21)

In a genome-wide study of prostate cancer CNAs, (10) we found combined loss and copy-neutral events were associated with increasing disease grade, stage, and diagnostic PSA. In the present study, we reanalyzed this data to assess GEMCaP biomarker status (5) and its predictive ability by ethnicity. While our numbers are modest, with only four recurrent/GEMCaP positive African American cases among the 28 analyzed, our results suggest that the GEMCaP biomarker has a PPV similar to that previously reported in European Americans. (5, 6) These promising results are consistent with the few studies that have examined racial differences of CNAs in prostate tumors. (8, 9) This is also the first time copy-neutral loss events have been used in the definition of the GEMCaP biomarker—our results suggest that the addition of copy-neutral loss calls is informative, although our sample size is too small to detect the observed modest differences in GEMCaP PPV, NPV, sensitivity, and specificity.

In another African American study of somatic CNAs using high-density SNP-arrays, Castro et al. (9) analyzed 20 prostate cancer tumors and identified 17 regions with significant loss and four regions with significant gains. Most of the regions identified had previously been linked to prostate cancer by studies in predominantly European American patients; however, they identified a novel region of loss at 4p16.3. When loss frequency in African American tumors was compared to data from a previously-published cohort of European American patients with similar pathological characteristics, the African American sample showed higher frequency of loss at loci including 6q13–22, 8p21, 13q13–14, and 16q11–24, and gains at 7p21 and 8q24; all of these were more frequent in metastatic lesions. (22) They concluded that the clinically-localized cancers from African American men resembled metastatic cancers from White men. More recently, Rose et al. used a BAC-based array to identify 27 chromosomal regions with significantly different copy number changes between African American and European American tumors. (8)

The CNA regions identified in the Rose and Castro studies overlapped with some GEMCaP loci (Supplementary Table 4). Twenty-two GEMCaP loci had significant CNAs in the Castro et al. sample, 19 of which (16 loss, 3 gain) were consistent with GEMCaP. Nine GEMCaP loci had significant CNAs in the Rose et al. sample, all of which (3 loss, 6 gain) were in the expected direction. In both of these studies, the only GEMCaP loci that displayed significant CNAs were in the 6q21 loss region. These studies demonstrate the relevance of GEMCaP loci in other samples of African Americans.

In summary, our results suggest that GEMCaP, a CNA biomarker developed in European American patients, has potential utility in African Americans. We are planning a meta-analysis of GEMCaP in existing prostate cancer CNA datasets with biochemical recurrence data to confirm GEMCaP as a cross-ethnic clinical indicator of more aggressive therapy following radical prostatectomy. Studies to identify biomarker sets specifically optimized for African American men will require larger cohorts with adequate follow-up for recurrence and metastatic disease—however, the identification of such biomarkers holds the promise to reduce ethnic disparities in prostate cancer outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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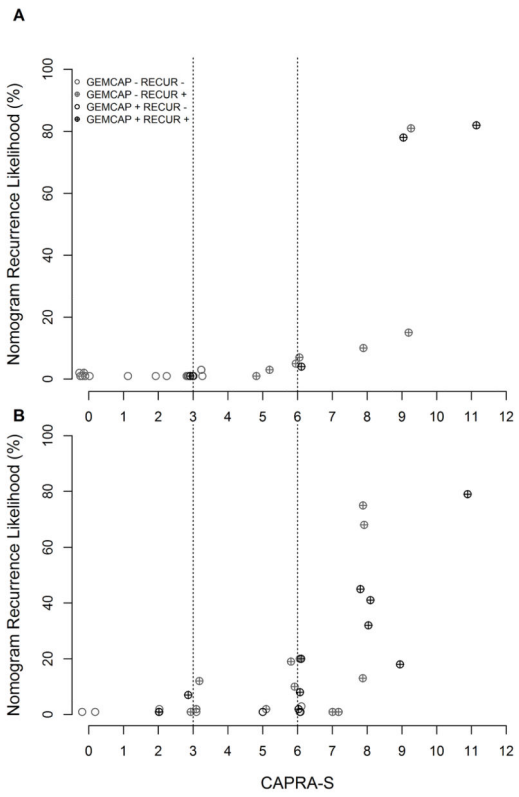

Figure 1.

Comparison of GEMCaP with established pathological predictors of biochemical recurrence following radical prostatectomy (CAPRA-S and a post-operative nomogram) in (A) African American and (B) European American men.

Note: Vertical lines on each of the figure panels delineate low (left), medium (center), and high (right) risk categories as defined by CAPRA-S score. A small amount of random noise was added to each CAPRA-S integer value to “jitter” the points to aid in distinguishing those that overlap.

Table 1

Frequency distribution of observed copy number alterations at the GEMCaP loci by ethnicity.

			African American (N=29)			European American (N=33)			P-value**	
			Gain	Loss	Neutral Loss	Gain	Loss	Neutral Loss		
Locus	Expected CNA Type	Cytoband	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	Expected CNA	+ Neutral Loss
1*	GAIN	2qtel	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	-	-
2	GAIN	3q26.2	4 (13.8)	0 (0.0)	2 (6.9)	4 (12.1)	0 (0.0)	0 (0.0)	1.00	-
3	GAIN	3q26.32	0 (0.0)	0 (0.0)	2 (6.9)	4 (12.1)	0 (0.0)	0 (0.0)	0.12	-
4	GAIN	3q26.3	0 (0.0)	0 (0.0)	2 (6.9)	2 (6.1)	0 (0.0)	0 (0.0)	0.49	-
5	GAIN	5p15.1	1 (3.5)	0 (0.0)	1 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.47	-
6	GAIN	7p22.3	0 (0.0)	0 (0.0)	1 (3.5)	1 (3.0)	1 (3.0)	0 (0.0)	1.00	-
7	GAIN	7p22.3	0 (0.0)	0 (0.0)	1 (3.5)	1 (3.0)	0 (0.0)	1 (3.0)	1.00	-
8	GAIN	7q11.22	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	1.00	-
9	GAIN	7q11.23	0 (0.0)	1 (3.5)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	1.00	-
10	GAIN	7q22.1	0 (0.0)	0 (0.0)	1 (3.45)	1 (3.0)	0 (0.0)	0 (0.0)	1.00	-
11	GAIN	7q31.31	0 (0.0)	0 (0.0)	2 (6.9)	1 (3.0)	1 (3.0)	0 (0.0)	1.00	-
12	GAIN	9q34.1	1 (3.5)	0 (0.0)	1 (3.45)	0 (0.0)	0 (0.0)	1 (3.0)	0.47	-
13	GAIN	11p15.4	1 (3.5)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.47	-
14	GAIN	17q21.33	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00	-
15	GAIN	17q25.3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00	-
16	GAIN	22q13.1	0 (0.0)	1 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00	-
17	LOSS	4p13	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)	1 (3.0)	0 (0.0)	1.00	0.60
18	LOSS	5q13.1	0 (0.0)	4 (13.8)	1 (3.5)	0 (0.0)	4 (12.1)	2 (6.1)	1.00	1.00
19	LOSS	5q14.3	0 (0.0)	3 (10.3)	3 (10.3)	1 (3.0)	2 (6.1)	1 (3.0)	0.66	0.28
20	LOSS	5q21.1	0 (0.0)	1 (3.5)	3 (10.3)	0 (0.0)	5 (15.2)	0 (0.0)	0.20	1.00
21	LOSS	5q21.2	0 (0.0)	1 (3.5)	3 (10.3)	0 (0.0)	5 (15.2)	0 (0.0)	0.20	1.00
22	LOSS	5q21.3	0 (0.0)	1 (3.5)	3 (10.3)	0 (0.0)	5 (15.2)	1 (3.0)	0.20	0.74
23	LOSS	5q23.1	0 (0.0)	1 (3.5)	3 (10.3)	0 (0.0)	3 (9.1)	1 (3.0)	0.62	1.00
24	LOSS	6q14.1	0 (0.0)	3 (10.3)	2 (6.9)	0 (0.0)	7 (21.2)	0 (0.0)	0.31	0.76
25	LOSS	6q21	0 (0.0)	2 (6.9)	3 (10.3)	1 (3.0)	9 (27.3)	0 (0.0)	0.05	0.28
26	LOSS	6q21	0 (0.0)	3 (10.3)	2 (6.9)	0 (0.0)	9 (27.3)	1 (3.0)	0.12	0.25

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			African American (N=29)			European American (N=33)			P-value**	
			Gain	Loss	Neutral Loss	Gain	Loss	Neutral Loss		
Locus	Expected CNA Type	Cytoband	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	Expected CNA	+ Neutral Loss
27	LOSS	8p22	0 (0.0)	8 (27.6)	4 (13.8)	0 (0.0)	13 (39.4)	1 (3.0)	0.42	1.00
28	LOSS	8p21.2	0 (0.0)	8 (27.6)	5 (17.2)	0 (0.0)	15 (45.5)	1 (3.0)	0.19	0.80
29	LOSS	8p21.2	0 (0.0)	8 (27.6)	5 (17.2)	0 (0.0)	15 (45.5)	1 (3.0)	0.19	0.80
30	LOSS	8p21.2	0 (0.0)	8 (27.6)	5 (17.2)	0 (0.0)	14 (42.4)	1 (3.0)	0.29	1.00
31	LOSS	8p12	1 (3.5)	6 (20.7)	6 (20.7)	0 (0.0)	14 (42.4)	0 (0.0)	0.10	1.00
32	LOSS	10q23.31	0 (0.0)	0 (0.0)	3 (10.3)	0 (0.0)	4 (12.1)	1 (3.03)	0.12	0.71
33	LOSS	13q14.11	0 (0.0)	2 (6.9)	2 (6.9)	0 (0.0)	7 (21.2)	1 (3.03)	0.16	0.35
34	LOSS	13q14.11	0 (0.0)	2 (6.9)	2 (6.9)	0 (0.0)	7 (21.2)	1 (3.03)	0.16	0.35
35	LOSS	13q14.11	0 (0.0)	2 (6.9)	5 (17.2)	0 (0.0)	9 (27.3)	1 (3.03)	0.05	0.78
36	LOSS	13q14.13	0 (0.0)	2 (6.9)	3 (10.3)	0 (0.0)	8 (24.2)	1 (3.03)	0.09	0.38
37	LOSS	13q14.2	0 (0.0)	2 (6.9)	3 (10.3)	0 (0.0)	8 (24.2)	1 (3.03)	0.09	0.38
38	LOSS	13q14.3	0 (0.0)	1 (3.5)	3 (10.3)	0 (0.0)	8 (24.2)	1 (3.03)	0.03	0.23
39	LOSS	16q23.1	0 (0.0)	3 (10.3)	1 (3.5)	0 (0.0)	6 (18.2)	0 (0.0)	0.48	0.74

Abbreviations: CNA, copy number alteration; CHR, chromosome; N, count; %, percentage; SPC, specificity (% of subjects without recurrence who also had a negative GEMCaP biomarker); HR, hazard ratio; 95%CI, 95% confidence interval; P, p-value.

*This "qtel" region of chromosome 2 was removed from consideration as it did not map to a region in hg19.

**P-value from Fishers exact tests of expected CNA frequency differences between African American and European American tumors. "Expected CNA" indicates that only gain and loss are included in the test. For GEMCaP loss loci, "+ Neutral Loss" indicates that both loss and copy neutral loss are included in the definition of expected loss.

Table 2

Hazard ratios for PSA recurrence based on the GEMCaP biomarker overall and by ethnicity.

Ethnicity	GEMCaP	Recurrence No	Recurrence Yes	HR†	95%CI	P	ACC	PPV	NPV	SEN	SPC
All	Positive	2	11	5.92	2.32–15.11	$3.9^{*}10^{-4}$	59.0	84.6	52.1	32.4	92.6
	Negative	25	23								
	Positive *	3	14	3.42	1.58–7.38	0.002	62.3	82.4	54.5	41.2	88.9
	Negative*	24	20								
AA	Positive	0	2	-‡	-‡	-‡	64.3	100.0	61.5	16.7	100.0
	Negative	16	10								
	Positive *	1	4	2.22	0.45–5.84	0.254	64.3	80.0	65.2	33.3	93.8
	Negative*	15	8								
EA	Positive	2	9	3.45	1.13–10.51	0.032	54.5	81.8	40.9	40.9	81.8
	Negative	9	13								
	Positive*	2	10	3.40	1.17–9.89	0.026	57.6	83.3	42.9	45.5	81.8
	Negative*	9	12								

Abbreviations: HR, hazard ratio; 95%CI, 95% confidence interval; P, p-value; ACC, overall recurrence classification accuracy of GEMCaP; PPV, the positive predictive value (%positive for recurrence among those with the biomarker) for “positive” GEMCaP subjects; NPV, negative predictive value (% negative for recurrence among those without the biomarker) for “negative” GEMCaP subjects; SEN, sensitivity (% of subjects with recurrence who also had a positive GEMCaP biomarker); SPC, specificity (% of subjects without recurrence who also had a negative GEMCaP biomarker).

* Including neutral loss events in GEMCaP copy loss regions in determining GEMCaP positivity.

† Estimated from a Cox proportional hazards model adjusted for age, the first genome-wide principal component, and tumor stage.

‡ Model parameter estimate did not converge.