Continued evaluation of a 31-gene expression profile to predict metastasis in an expanded cohort of 782 cutaneous melanoma patients

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Background

- A 31-gene expression profile (GEP) test that predicts a cutaneous melanoma (CM) tumor's risk of metastasis independent of AJCC stage has been validated as an independent predictor of risk.[1-3]
- The test provides a binary outcome of low (Class 1) or high (Class 2) risk of metastasis within five years of diagnosis.
- The GEP has been shown to improve staging by identifying over 70% of patients, including clinically and pathologically node-negative patients, who develop distant metastasis or die from their disease.[1,2]
- We present a multi-center performance study analyzing the GEP in our cumulative cohort of CM patients, and in combination with sentinel lymph node (SLN) status.

Methods

- 261 previously unreported CM primary tumors from 9 centers were analyzed as part of an IRB-approved archival tissue study; data from this cohort were then combined with data from previous validation studies,[1-3] exclusive of the training set, for a combined cohort of 782 cases.
- The GEP test was performed in a CAP/CLIA-accredited laboratory using high-throughput RT-PCR assays. Expression data was analyzed using radial basis machine predictive modeling with new cases trained on a previously developed 164-patient cohort.
- Study endpoints included recurrence-free survival (RFS), defined as time to either a regional or distant metastatic event; distant metastasis-free survival (DMFS), defined as time to any metastatic event beyond the regional nodal basin; and melanoma-specific survival (MSS), defined as time from diagnosis to death documented as specifically resulting from melanoma.

Results

Table 1. Cohort demographics

Clinical characteristics	Overall (n = 782)	Class 1 (n=449)	Class 2 (n=333)
Median age (range), years	60 (18-94)	56 (18-94)	64 (19-94)
Development of regional/distant metastasis	224/170	56/40	168/130
Median time to metastasis/follow-up, years	1.3/6.9	2.1/7.4	1.1/5.9
AJCC stage			
I	382 (49%)	326 (85%)	56 (15%)
II	186 (24%)	59 (32%)	127 (68%)
III	207 (26%)	63 (30%)	144 (70%)
IV	7 (1%)	1 (14%)	6 (86%)
Breslow thickness			
Median (range), mm	1.3 (0.1-29.0)	0.7 (0.1-10.0)	2.6 (0.2-29.0)
≤1 mm	318 (40%)	286 (90%)	32 (10%)
>1 mm	458 (59%)	162 (35%)	296 (65%)
unreported	6 (1%)	1 (17%)	5 (83%)
Mitotic index			
<1 mm^2	141 (18%)	111 (79%)	30 (21%)
≥1 mm^2	395 (51%)	176 (45%)	219 (55%)
unreported	246 (31%)	162 (66%)	84 (34%)
Ulceration			
Absent	460 (59%)	332 (72%)	128 (28%)
Present	217 (28%)	44 (20%)	173 (60%)
unreported	105 (13%)	73 (70%)	32 (30%)
Nodal status			
Negative	305 (39%)	159 (52%)	146 (48%)
Positive	201 (26%)	63 (31%)	138 (69%)
unreported	276 (35%)	227 (82%)	49 (18%)

Figure 1. Kaplan-Meier analysis of RFS for GEP predicted outcomes comparing the 782-patient retrospective cohort (A) to three reported prospective studies[4-6] (B-D)

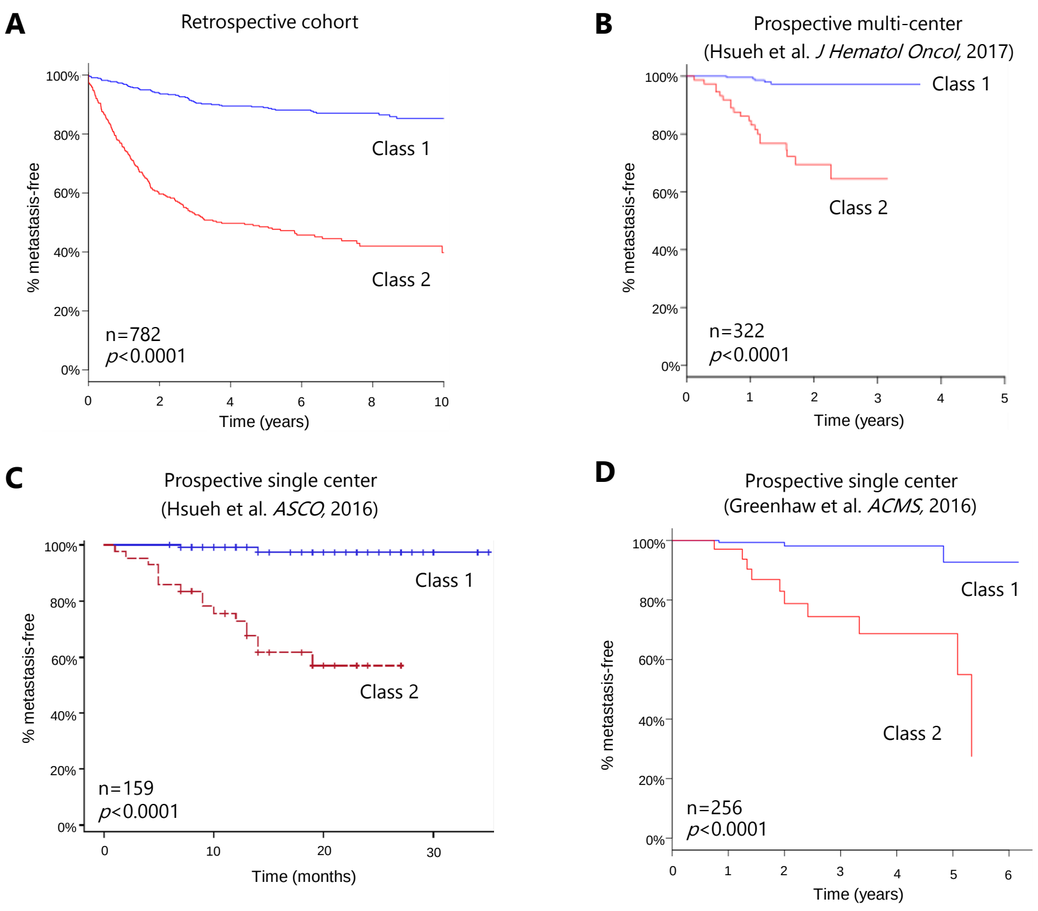


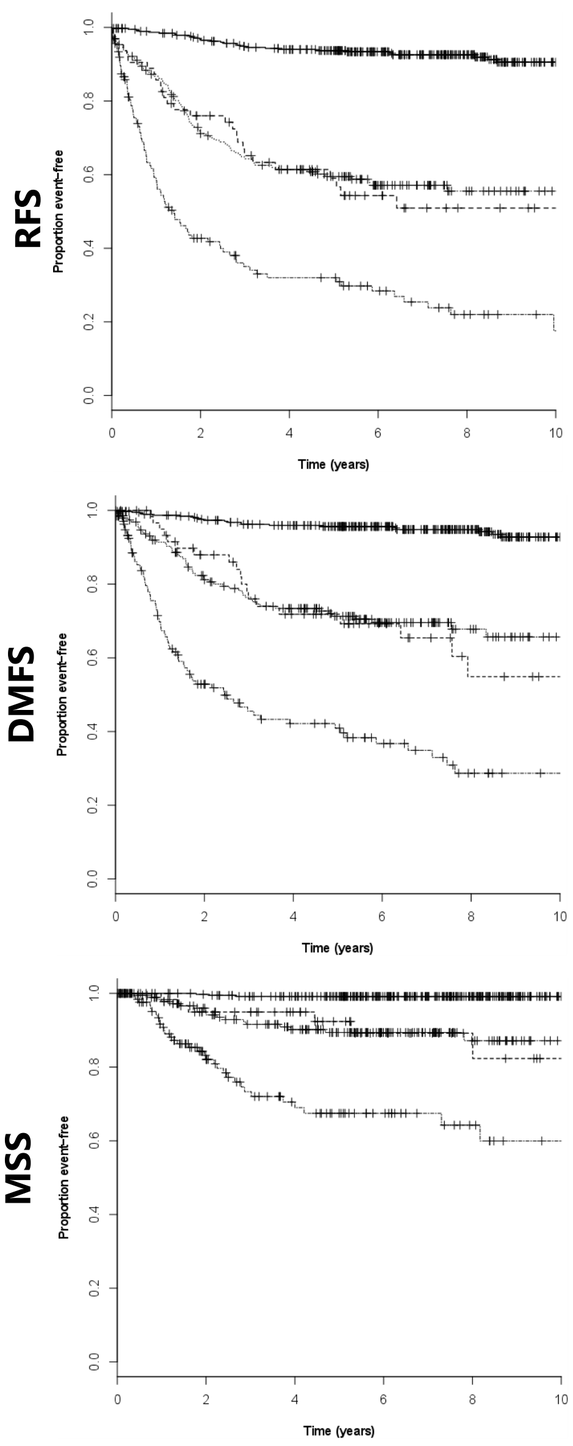
Table 2. Cox multivariate regression of survival outcomes in the 782-patient cohort

	RFS			DMFS			MSS		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Breslow depth	1.2	1.1-1.2	<0.001	1.2	1.1-1.3	<0.001	1.2	1.1-1.4	0.006
Mitotic rate	1.0	1.0-1.0	0.02	1.0	1.0-1.0	0.09	1.0	0.9-1.0	0.6
Ulceration	1.3	0.9-1.9	0.1	1.8	1.2-2.7	0.009	0.9	0.4-1.8	0.8
SLN positive	2.7	1.9-3.7	<0.001	3.1	2.1-4.6	<0.001	3.5	1.8-7.0	<0.001
GEP Class 2	2.7	1.8-4.1	<0.001	2.4	1.5-3.9	<0.001	4.3	1.7-11.0	0.003

Table 3. Kaplan-Meier analysis of survival rates for GEP and SLN predicted outcomes

	RFS		DMFS		MSS	
	5-year rate	# of events	5-year rate	# of events	5-year rate	# of events
Class 1 (n=449)	89%	56 (12%)	93%	40 (9%)	98%	9 (2%)
Class 2 (n=333)	49%	168 (50%)	59%	130 (39%)	81%	51 (15%)
Node negative (n=305)	74%	82 (27%)	83%	56 (18%)	95%	15 (5%)
SLN+ (n=201)	41%	118 (59%)	51%	95 (47%)	77%	39 (19%)

Figure 2 Kaplan-Meier analysis of RFS, DMFS and MSS for SLN and GEP predicted outcomes



	n	5-year RFS	# of events
Class 1/SLN- ——	159	87%	23 (14%)
Class 1/SLN+ ----	63	59%	27 (43%)
Class 2/SLN- ·····	146	60%	59 (40%)
Class 2/SLN+ –·–	138	32%	91 (66%)

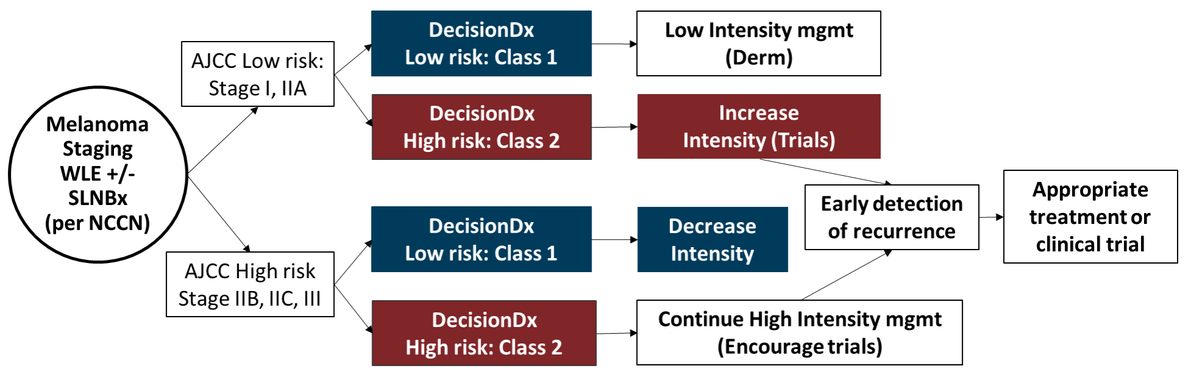
	n	5-year DMFS	# of events
Class 1/SLN- ——	159	92%	16 (10%)
Class 1/SLN+ ----	63	72%	19 (30%)
Class 2/SLN- ·····	146	73%	40 (27%)
Class 2/SLN+ –·–	138	41%	76 (55%)

	n	5-year MSS	# of events
Class 1/SLN- ——	159	98%	3 (2%)
Class 1/SLN+ ----	63	92%	6 (10%)
Class 2/SLN- ·····	146	91%	12 (8%)
Class 2/SLN+ –·–	138	67%	33 (24%)

Table 4. Net Reclassification Index comparing the addition of GEP to clinical or pathological nodal status

Endpoint	Sensitivity Change	Net Improvement
Recurrence	0.34 (p<0.0001)	0.13 (p<0.0001)
Distant Metastasis	0.32 (p<0.0001)	0.09 (p=0.027)

Figure 3. Schematic representation of risk stratification using AJCC stage with GEP test result to guide patients' clinical management



Conclusions

- Results achieved in this newly expanded cohort in a multi-center performance study delineate the prognostic accuracy of the 31-gene expression profile test.
- The GEP offers prognostic information that is independent from and adds to conventional staging methods.
- Outcomes in this retrospective cohort are consistent with results from prospective studies of the GEP test.
- GEP result can help guide clinical decision-making regarding risk-appropriate surveillance and follow-up.

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Disclosures

The proprietary GEP test is clinically available through Castle Biosciences as the DecisionDx®-Melanoma test (www.SkinMelanoma.com).