Improvement of risk assessment in cutaneous melanoma (CM) by a prognostic 31-gene expression profile (31-GEP) test over AJCC-based staging alone

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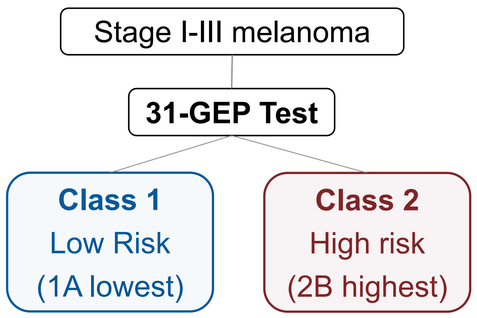
BACKGROUND

- A substantial number of melanoma-related deaths occur in patients originally diagnosed with early American Joint Committee on Cancer (AJCC) stage disease, suggesting aggressive tumor biology despite having clinicopathologic features associated with low-risk disease.
- A 31-gene expression profile (31-GEP) test has been developed and validated in retrospective and prospective studies[1-8] to predict 5-year metastatic risk from primary cutaneous melanoma (CM) tumor tissue with a high degree of technical reliability.[9]
- The 31-GEP test classifies melanoma as Class 1A (lowest risk), Class 1B (low risk), Class 2A (increased risk), or Class 2B (highest risk).
- This prognostic information is used to inform patient management decisions, including frequency of follow-up and surveillance imaging, referrals, sentinel lymph node biopsy guidance, and consideration of adjuvant therapy.[10-15]



OBJECTIVE

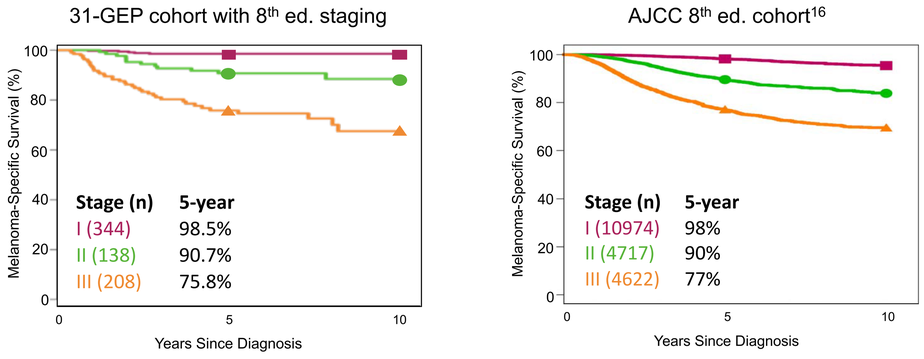
To determine the impact on risk prediction when results from the 31-GEP test are used with AJCC 8th edition staging.

METHODS

- Archival formalin-fixed paraffin-embedded CM tumor samples from 18 U.S. centers (n=690, Stage I-III) along with clinical, pathological, and outcomes data for each case were collected under an IRB-approved protocol[1-4]. Stage I-II cases were restaged according to AJCC 8th edition criteria.
- The 31-GEP test was performed in a CAP-accredited/CLIA-certified laboratory using high-throughput RT-PCR assays as previously described[1-5].
- The Kaplan-Meier method was used to estimate 5-year recurrence-free (RFS; time to either a regional or distant metastatic event), distant metastasis-free (DMFS; time to any metastatic event beyond the regional nodal basin), and melanoma-specific survival (MSS; time from diagnosis to death documented as from melanoma) rates with significance determined by log-rank test. All non-recurrent cases had at least 5 years of follow-up.
- Class 1A- and 2B-predicted MSS outcomes for each stage were compared to rates associated with AJCC 8th edition stage[16].
- Based on National Comprehensive Cancer Network (NCCN) guidelines for surveillance and follow-up, AJCC binary low and high-risk groups are defined as Stage I-IIA and Stage IIB-IV, respectively. Cox multivariate regression analysis for MSS was performed comparing AJCC binary risk and 31-GEP test results.

RESULTS

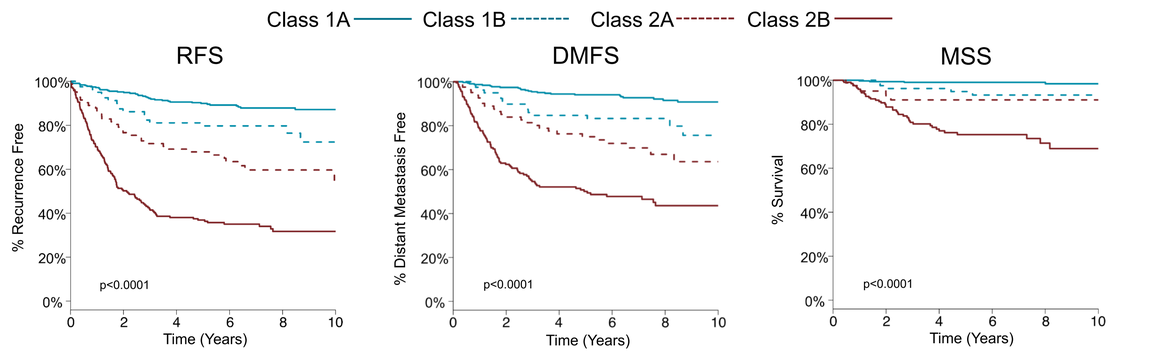
Figure 1. Stage-specific survival rates for the 31-GEP cohort align with the AJCC 8th edition database survival rates



	31-GEP cohort	AJCC 8th edition[16]
Earliest diagnosis year	1998	1998
Number of collaborating centers	18	10
Percent of cases from U.S. centers	100%	34%

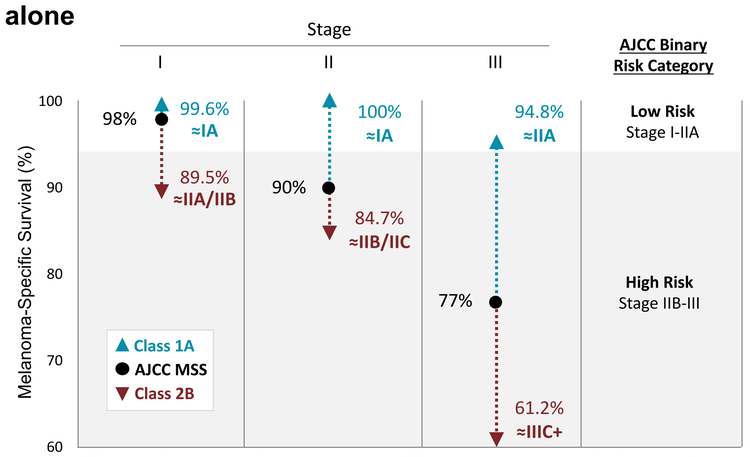
RESULTS

Figure 2. 31-GEP results identify significantly different risk groups[4]



Class (n)	5-year RFS (95% CI)	5-year DMFS (95% CI)	5-year MSS (95% CI)
1A (312)	90% (87-93%)	94% (91-97%)	99% (98-100%)
1B (80)	81% (73-90%)	85% (77-93%)	95% (90-100%)
2A (84)	68% (58-79%)	75% (66-85%)	91% (85-98%)
2B (214)	37% (31-44%)	50% (43-58%)	75% (69-83%)

Figure 3. Addition of 31-GEP test results improves risk obtained by AJCC 8th edition staging alone



*For surveillance and follow-up purposes, NCCN guidelines propose dividing patients into binary risk groups based on AJCC Stage: low (Stage I-IIA) and high risk (Stage IIB-IV).

Cox multivariate regression analysis

n=690 58 events	MSS HR (95% CI)	MSS p value
AJCC high risk	4.84 (2.3-10.1)	<0.0001
GEP Class 1B	3.38 (0.9-12.8)	0.073
GEP Class 2A	4.67 (1.3-16.4)	0.02
GEP Class 2B	10.1 (3.4-16.4)	<0.0001

Stage I			Stage II			Stage III		
Class (n)	5-year MSS (95% CI)	Event Rate	Class (n)	5-year MSS (95% CI)	Event Rate	Class (n)	5-year MSS (95% CI)	Event Rate
1A (249)	99.6% (98.8-100%)	0.4%	1A (21)	100% (100-100%)	0%	1A (42)	94.8% (88.0-100%)	7%
2B (19)	89.5% (76.7-100%)	11%	2B (83)	84.7% (76.3-94.1%)	13%	2B (112)	61.2% (50.1-74.7%)	28%

CONCLUSIONS

- In the study cohort of Stage I-III melanoma cases[1-4] with similar survival outcomes to the 8th edition AJCC cohort, the 31-GEP test result was able to add information to further stratify patients with lower and higher risks than predicted by clinicopathologic staging alone. Multivariate analysis demonstrated that a 31-GEP Class 2B result was an independent predictor of MSS with a greater hazard ratio than AJCC binary risk.
- As accurate risk assessment is important for patient management decisions, use of the 31-GEP test can help guide these choices, including follow-up, sentinel lymph node biopsy guidance, surveillance and possible adjuvant therapy, as has been previously published[10-15].

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