Literature review of a prognostic 31-gene expression profile (31-GEP) test for cutaneous melanoma (CM) risk prediction

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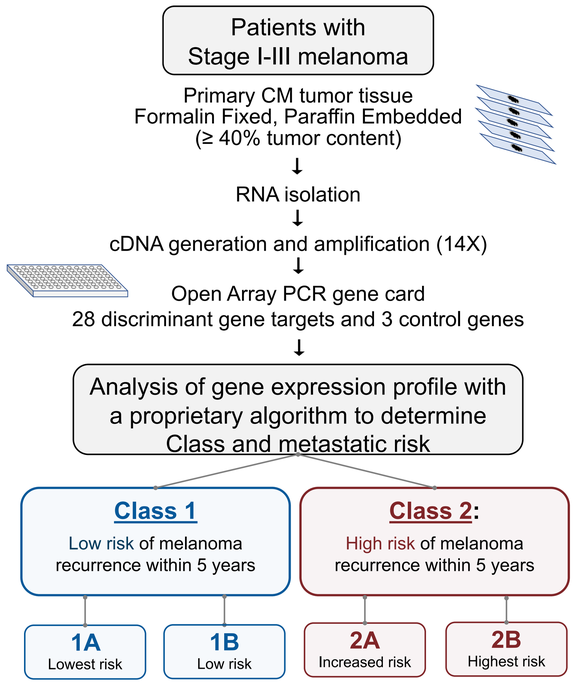
SYNOPSIS & OBJECTIVE

In several cancers, molecular testing has added prognostic value and utility in the clinical setting. A 31-gene expression profile (31-GEP) test has been developed and validated for determining metastatic risk in cutaneous melanoma, with Class 1 and 2 results indicating low and high risks, respectively. As melanoma staging and guideline recommendations continue to evolve, it is important to consider the evidence supporting the use of clinicopathologic and molecular factors in melanoma patient care. Herein, published evidence supporting the 31-GEP test, including clinical validity, analytical validity, and clinical utility, are reviewed. From clinical validity evidence spanning eight peer-reviewed articles (n=1268 total patients) including two prospective studies, the 31-GEP test consistently demonstrated accuracy to identify patients with CM at high risk for recurrence, metastasis, and melanoma-specific mortality. Published analytical validity data verified the reliability of 31-GEP testing with inter- and intra-assay concordance of 99% and 100%, respectively, and 98% technical success on specimens with sufficient tumor content. Clinical utility data from three studies (n=494 total patients) and two physician surveys indicate that the 31-GEP test results significantly impact management decisions for approximately 1 of 2 patients, consistent with the impact of genomic testing in other cancers. In contrast to other prognostic melanoma GEP tests that have been reported, the 31-GEP test has published evidence from multiple retrospective and prospective clinical validity studies beyond initial development, along with published analytical validity and clinical utility data, in support of its use for melanoma risk assessment and patient management decisions.

BACKGROUND & METHODS

- The 31-GEP test predicts a CM patient's risk of recurrence, metastasis, or melanoma-specific mortality at 5 years after diagnosis



- The 31-GEP test is performed in a CAP-accredited/CLIA-certified laboratory using high-throughput RT-PCR assays as previously described[1-4].
- Clinical validity, analytical validity, and clinical utility studies surrounding the 31-GEP are reviewed herein.

CLINICAL UTILITY

Data from 3 studies and 2 physician surveys indicate that the 31-GEP test results significantly impact management decisions for approximately 1 of 2 patients[10-14]

Table 1. Comparison of Clinical Utility Studies

Design (n)	GEP Impact
Prospectively tested patients, Retrospective chart review; (156 patients)[10]	53%
Prospective documentation of pre and post test plans; (247 patients)[11]	49%
Prospectively tested patients, Retrospective chart review; (90 patients)[12]	52%
Physician survey of clinical decisions with or without test results; (169 physicians)[13]	47-50%
Physician survey of clinical factors that affect use of 31-GEP test; (181 physicians)[14]	*

*overall GEP impact not assessed with study design

Figure 4. 31-GEP result drives surveillance changes in multicenter studies[10,11]

Change	Study: Berger et al.	Study: Dillon et al.
Class 1 Changed	37%	36%
Changed Class 1 w/ decrease	94%	67%
Class 2 Changed	77%	85%
Changed Class 2 w/ increase	94%	92%

Consistent specific modality changes across both studies:

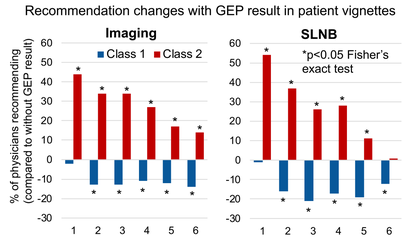
- Decreases in imaging, visits, and referrals with Class 1 result
- Increases in labs, imaging, visits and referrals with Class 2 result

Figure 5. Physician survey studies address key questions for 31-GEP use[13,14]

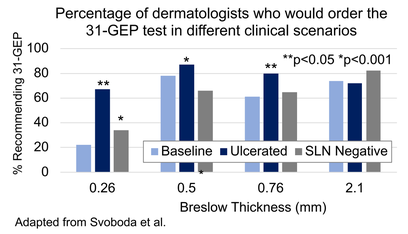
Does 31-GEP testing alter management decisions and if so, for what modality?[13]

Case	Clinical Features
1	0.6mm, 42y female, Stage IA
2	0.54 mm, 62y male, Stage IB, ulcerated, personal hx
3	0.76 mm, 69y male, Stage IB, ulcerated, personal hx
4	>0.5mm, 45y male, Stage IB/IIA
5	0.9 mm, 61y female, Stage IB, ulcerated, mitoses
6	1.2 mm, 38y female, Stage IIA, ulcerated

Adapted from Farberg et al.

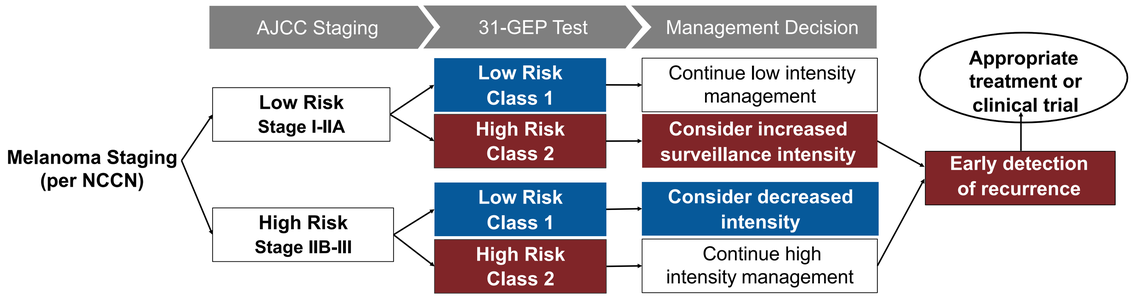


What features prompt physicians to recommend testing?[14]



Adapted from Svoboda et al.

Figure 6. Schematic representation of using AJCC staging with 31-GEP test result to guide clinical management



CLINICAL VALIDITY

Evidence supports consistent ability of the 31-GEP test to accurately identify recurrence, metastasis, and melanoma-specific mortality in CM patients[1-8]

Figure 1. Accuracy metrics of the 31-GEP test within a large retrospective cohort (n=690)

	31-GEP (n=690)	SLN (n=459)
RFS		
Sensitivity	75% (68-80%)	59% (52-66%)
Specificity	71% (67-75%)	68% (62-73%)
PPV	54% (49-60%)	58% (51-65%)
NPV	86% (82-89%)	69% (63-75%)
DMFS		
Sensitivity	76% (69-83%)	64% (55-71%)
Specificity	67% (63-71%)	66% (60-71%)
PPV	42% (36-48%)	47% (40-54%)
NPV	90% (87-93%)	79% (74-84%)
MSS		
Sensitivity	84% (73-93%)	74% (60-85%)
Specificity	61% (57-64%)	60% (55-65%)
PPV	16% (12-21%)	20% (14-26%)
NPV	98% (96-99%)	95% (91-97%)

SLN = sentinel lymph node

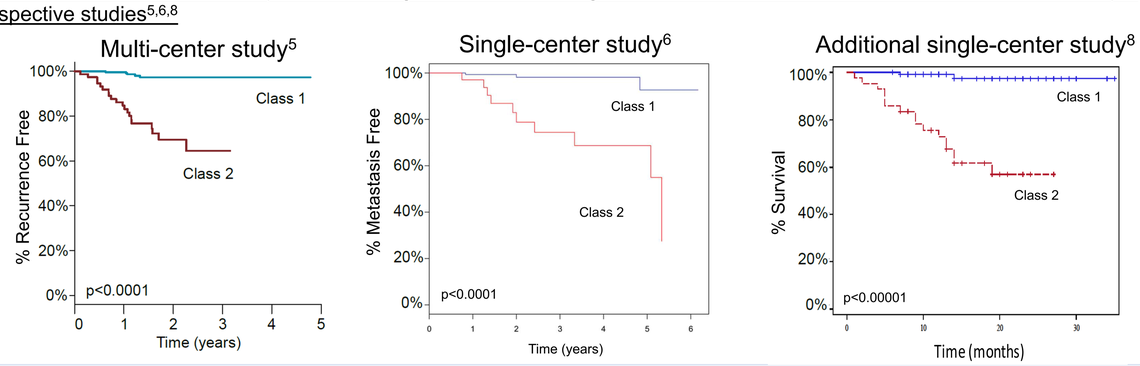
Figure 2. The 31-GEP test is an independent predictor of risk in a multivariate analysis across a large retrospective cohort of Stage I-III cases [4]

Cox Multivariate Analysis	RFS HR	RFS 95% CI	RFS P-value	DMFS HR	DMFS 95% CI	DMFS P-value	MSS HR	MSS 95% CI	MSS P-value
Breslow Depth	1.21	1.12-1.3	<0.0001	1.19	1.09-1.29	<0.0001	1.16	1.0-1.34	0.05
Mitotic rate	1.01	0.99-1.03	0.18	1.01	0.99-1.03	0.24	0.97	0.92-1.03	0.34
Ulceration	1.1	0.75-1.59	0.64	1.57	1.02-2.43	0.04	0.77	0.38-1.57	0.47
Positive node	2.45	1.74-3.46	<0.0001	3.02	2.0-4.57	<0.0001	3.83	1.85-7.95	0.0003
Class 1B	1.13	0.56-2.29	0.73	1.35	0.58-3.15	.48	4.37	0.84-22.72	0.08
Class 2A	1.48	0.77-2.84	0.24	1.53	0.68-3.43	.30	2.52	0.42-15.2	0.31
Class 2B	2.92	1.7-5.00	<0.0001	2.89	1.49-5.62	0.002	9.02	2.02-40.24	0.004

HR, hazard ratio; RFS, recurrence-free survival; DMFS, distant metastasis-free survival; MSS, melanoma-specific survival; GEP, gene expression profile; CI, confidence interval; 147 recurrences, 107 distant metastases, 36 melanoma-specific deaths

Subgroup analysis of this cohort also demonstrated independent ability of the 31-GEP test to detect patients at high risk for metastasis in low-risk populations of sentinel lymph node-negative, Stage I-IIA, and T1 tumors.

Figure 3. 31-GEP Class divides patients into high and low-risk categories for recurrence, metastasis and death across multiple prospective studies[5,6,8]



ANALYTICAL VALIDITY

Technical success studies demonstrate 99% inter- and 100% intra-assay concordance[9, 15]

Figure 7. 31-GEP results are highly concordant between assays (n=168 cases)[9]

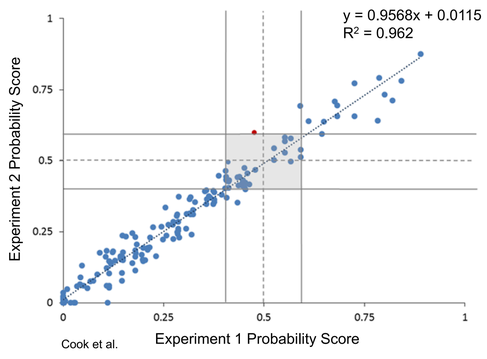
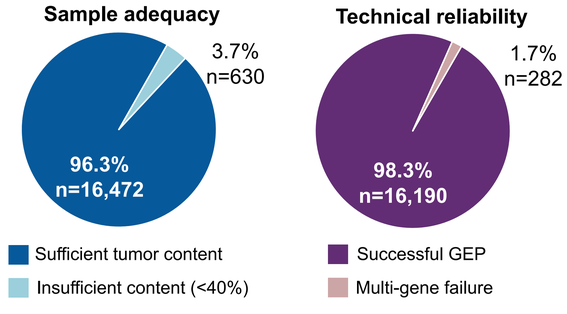


Figure 8. The 31-GEP test has high technical reliability on >17,000 clinical cases since July 2016[15]



CONCLUSION

In review of the literature, the value of the 31-GEP test for use in prognosis and clinical management decision making is supported by evidence from the 3 pillars of molecular tests: clinical validity, clinical utility, and analytical validity.

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