

## EDITORIALS

**Gene Expression Profile Testing in Skin Cancer Prognosis: The Data is Clear – It's Time to Get on Board**

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Prognosis in skin cancer has traditionally been based on subjective clinical and histologic parameter-based systems, the most prominent of them being American Joint Committee on Cancer (AJCC) staging. “Early” melanomas have good outcomes and “advanced” cases have significant mortality and morbidity. However, clinical and pathological concordance and reproducibility remain low, suggesting that these subjective prognostic indicators fall below the limits of reliability in these staging schemata.<sup>1</sup> For that reason, there have been calls to augment these traditional approaches using objective molecular and genetic techniques to improve the accuracy for the staging of skin cancer patients.<sup>2</sup> A large number of independent, peer-reviewed studies evaluating gene expression profile tests have been published (see Table), yet transition of these molecular-based tests into clinical care has not been as rapid for cutaneous melanoma as might have been expected, based on the data. Here, we explore some of the non-scientific and political reasons why this may be the case.

Gene Expression Profile (GEP) prognostic testing was originally developed for uveal

melanomas where its use has become standard-of-care. There are several versions of the test under development but the currently approved, most widely used and broadly validated cutaneous version of the test stratifies risk of metastasis through the assessment of the degree of expression of 31 genes related to melanoma progression. Its utility has been widely recognized by clinicians. Over 16,000 melanomas in the US were 31-GEP assessed in 2019.

Validity and utility of the 31-GEP test has been proven in a number of ways. The test has been directly validated for 5-year recurrence risk in retrospective and prospective studies including over 1,500 patients. Those studies demonstrated that the test accurately predicts metastasis risk independent of clinical and pathologic factors, with strong sensitivity and negative predictive value (NPV). Additionally, a significantly poorer prognosis has been observed for identified high-risk patients across all studies to date. Multivariate regression analysis has consistently shown independent and generally superior prognostic accuracy of the 31-GEP test compared to sentinel lymph node biopsy

(SLNBx) and other clinicopathologic factors (Table).

31-GEP accuracy has also been positively reported in 2 recent systematic reviews/meta-analyses as meeting the highest standards for prognostic tools as described by the Strength of Recognition Taxonomy (SORT) system.<sup>3,4</sup> The test has consistently improved upon the critical accuracy metrics of sensitivity and NPV over those assessed by clinicopathologic staging alone, including patients who were diagnosed with thin tumors, in published validation studies that have included nearly 2,700 patients. Given that some AJCC criteria are somewhat subjective and some (such as Breslow thickness) may be underestimated from sampling error,<sup>5</sup> this may explain how the addition of the objective 31-GEP information to the AJCC system has been demonstrated to statistically significantly improve prognostic assessment beyond AJCC alone.<sup>6</sup> The 31-GEP test has also been shown to assess the probability of SLN positivity in T1-T2 lesions.<sup>7</sup> In addition, studies have demonstrated that the integration of 31-GEP data into management evaluation influences management intensity appropriately.<sup>8</sup>

More importantly, because there are so many more SLNBX- than + patients and thin than thicker lesions, the absolute number of people who die in these aggregate “low-risk” groups are greater than in the high-risk groups identified through AJCC criteria alone.<sup>9</sup> Studies have demonstrated that the 31-GEP test identifies high-risk melanoma patient subsets that are more likely to experience metastasis/death within low-risk patient groups who have SLNBx- disease, stage I to IIA tumors, and thin tumors.<sup>10</sup>

These findings have led to modification of the National Comprehensive Cancer

Network (NCCN) guidelines to recommend that GEP for melanoma can provide useful information on individual risk of recurrence as an adjunct to standard AJCC staging<sup>11</sup> and been validated by the standards required for CMS for insurance coverage of the test in the Medicare population for evaluation of candidates for SLNBx.

Despite this overwhelming evidence, some have still raised objections to integrating this approach into melanoma management.<sup>12</sup> Critics suggest that this test has not been FDA approved and therefore its validity has been questioned. However, as this test is not a drug or device, FDA approval is not required but the appropriate federal approval for this type of test (CLIA) was obtained. Their suggestion that all identified higher-risk thin melanoma patients will automatically have more intense follow-up regimens is also not supported by impact studies. Rather, these studies demonstrated that, like any clinical data, the additional information provided by 31-GEP testing was not blindly followed but was appropriately integrated as part of the overall management decision process.<sup>8</sup> They derive “consensus” statements using only a 50% agreement threshold when this process typically requires a supermajority. They support a prognostic test (SLNBx) with significant morbidity but criticize the 31-GEP test which has been shown in some studies to be prognostically superior with no morbidity. They ignore multiple prospective trials that have demonstrated efficacy and wrongly suggest that prospective randomized controlled trials are needed for validation when these are not required (or even possible to perform for prognostic tests as there is no way to interpret a control [non-tested] group) for purely evaluating prognostic tests.<sup>13</sup>

**Table.** Representative clinical validity, utility and impact studies for the 31-GEP test for melanoma prognosis

Clinical validity studies	Study design; objective	N	Multivariate Comparators	GEP risk (recurrence)
<b>Greenhaw, <i>J Am Acad Dermatol</i> 2020</b>	SR/MA	1,479	BT, U, SLNB, age	Class 2B HR=2.9**
<b>Litchman, <i>SKIN J Cut Medicine</i>, 2020</b>	SR/MA	1,407	BT, U, SLNB	Class 2B HR=7.2**
<b>Gastman, <i>Head Neck</i> 2019</b>	Archival; CV	157	BT, U, SLNB, MR	Class 2 HR=3.0
<b>Gastman, <i>J Am Acad Dermatol</i> 2019</b>	Archival; CV	690	BT, U, SLNB, MR	Class 2B HR=2.92**
<b>Keller, <i>Cancer Med</i> 2019</b>	Prospective; CV	159	BT, U, SLNB, age	Class 2 HR=9.2**
<b>Podlipnik, <i>J Eur Acad Dermatol Veneorol</i> 2019</b>	Prospective; CV	86	AJCC, age	Class 2 HR=18.8*
<b>Vetto, <i>Future Oncol</i> 2019</b>	Retrospective; CV, CU	1,421	N/A	N/A
<b>Greenhaw, <i>Dermatol Surg</i> 2018</b>	Prospective; CV	256	N/A	Class 2 OR=22 <sup>‡</sup>
<b>Zager, <i>BMC Cancer</i> 2018</b>	Retrospective; CV	523	BT, U, SLNB, MR	Class 2 HR=5.40**
<b>Hsueh, <i>J Hematol Oncol</i> 2017</b>	Prospective; CV, CU	322	BT, U, SLNB, MR	Class 2 HR=7.15*
Clinical utility studies	Study design; objective	N	Modified Surveillance	Management change rates
<b>Dillon, <i>SKIN: J Cutan Med</i> 2018</b>	Prospective; CU	247	FU, I, L	49%
<b>Schuitevoerder, <i>JDD</i> 2018</b>	Retrospective, CU	91	FU, R, AT	52%
<b>Berger, <i>Curr Med Res Opin</i> 2015</b>	Retrospective; CU	156	FU, I, L, R	53%
Clinical impact studies	Study design	N	Target groups	Risk-appropriate management impact
<b>Mirsky, <i>J Drugs in Dermatol</i> 2018</b>	Patient vignette; adjunctive testing	164	Dermatology NPs/PAs	Yes
<b>Svoboda, <i>J Drugs in Dermatol</i> 2018</b>	Patient vignette; GEP recommendations	181	Dermatologists	Yes
<b>Farberg, <i>J Drugs in Dermatol</i> 2017</b>	Patient vignette; BT inflection points; adjunctive testing	169	Dermatology residents	Yes

Abbreviations: AT – Adjuvant therapy; BT – Breslow thickness; CMRO – Current Medical Research and Opinion; CU – clinical utility; CV – clinical validity; FU – followup; HR – hazard ratio; I – imaging; JAAD – Journal of the American Academy of Dermatology; JEAVD – Journal of the European Academy of Dermatology and Venereology; L – laboratory workup; MR – mitotic rate; OR – odds ratio; R – referral; SLNB – sentinel lymph node biopsy; U – ulceration; \* p≤0.01; \*\*p≤0.0001; <sup>‡</sup>multivariate analysis was not performed in this study

Consensus-based appropriate usage criteria for 31-GEP testing have been developed and published.<sup>14</sup> Equally important to recognize is that 31-GEP testing is not for use in all lesions. Usage has not been validated with in-situ and stage IV melanomas nor for predicting patient response to therapies. In addition, melanomas with Breslow thickness <0.3mm may not benefit.<sup>15</sup>

Finally, the usage of GEP testing for skin cancer prognosis has now extended beyond melanoma. A 40-GEP test has shown early promise for assessing prognosis in patients with advanced cutaneous squamous cell carcinoma.<sup>16</sup>

There have now been over 20 independent peer-reviewed data-driven studies demonstrating consistent clinical validity, efficacy, and positive impact of the 31-GEP test. Given this strong existing supportive published evidence, discounting the value of GEP testing based on hypothetical models, inter-specialty competition with concerns regarding personal adverse economics or personal biases/conflicts for those that may be developing competitive methodologies leading to the subjective/hypothetical defining of “harm” for patients is not data justified.

An objective review of published data clearly demonstrates that we have now reached the point where, given the evidence, GEP testing for melanoma prognosis is long beyond the suggestion that it is just for “experimental” usage. It’s time for this debate to be concluded so that our patients can benefit. The train has left the station. It’s time to get on board.

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