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Prognostic Gene Expression Profiling in Cutaneous Melanoma:

Identifying the Knowledge Gaps and Assessing the Clinical Benefit

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Abstract

IMPORTANCE—Use of prognostic gene expression profile (GEP) testing in cutaneous melanoma (CM) is rising despite a lack of endorsement as standard of care.

OBJECTIVE—To develop guidelines within the national Melanoma Prevention Working Group (MPWG) on integration of GEP testing into the management of patients with CM, including (1) review of published data using GEP tests, (2) definition of acceptable performance criteria, (3) current recommendations for use of GEP testing in clinical practice, and (4) considerations for future studies.

EVIDENCE REVIEW—The MPWG members and other international melanoma specialists participated in 2 online surveys and then convened a summit meeting. Published data and meeting abstracts from 2015 to 2019 were reviewed.

FINDINGS—The MPWG members are optimistic about the future use of prognostic GEP testing to improve risk stratification and enhance clinical decision-making but acknowledge that current utility is limited by test performance in patients with stage I disease. Published studies of GEP testing have not evaluated results in the context of all relevant clinicopathologic factors or as predictors of regional nodal metastasis to replace sentinel lymph node biopsy (SLNB). The performance of GEP tests has generally been reported for small groups of patients representing particular tumor stages or in aggregate form, such that stage-specific performance cannot be ascertained, and without survival outcomes compared with data from the American Joint Committee on Cancer 8th edition melanoma staging system international database. There are significant challenges to performing clinical trials incorporating GEP testing with SLNB and adjuvant therapy. The MPWG members favor conducting retrospective studies that evaluate multiple GEP testing platforms on fully annotated archived samples before embarking on costly prospective studies and recommend avoiding routine use of GEP testing to direct patient management until prospective studies support their clinical utility.

CONCLUSIONS AND RELEVANCE—More evidence is needed to support using GEP testing to inform recommendations regarding SLNB, intensity of follow-up or imaging surveillance, and postoperative adjuvant therapy. The MPWG recommends further research to assess the validity and clinical applicability of existing and emerging GEP tests. Decisions on performing GEP testing and patient management based on these results should only be made in the context of discussion of testing limitations with the patient or within a multidisciplinary group.

Prognostic gene expression profile (GEP) testing for cutaneous melanoma (CM) is designed to predict recurrence or metastatic risk based on expression patterns of a selected panel of genes from the primary tumor. Although routine GEP testing is not endorsed by the

American Academy of Dermatology (AAD)[1] or National Comprehensive Cancer Network (NCCN)[2] CM guidelines outside of a clinical trial or study, its use is becoming more prevalent. For example, the DecisionDx-Melanoma test (31-GEP, Castle Biosciences) is covered by Centers for Medicare & Medicaid Services ($7193)[3] for sentinel lymph node (SLN) biopsy (SLNB)–eligible patients. Approximately 1000 31-GEP tests are processed every month.[4] Based on reported incidence in the US,[5] up to 5% to 10% of cases are being tested. MelaGenix (NeraCare) is available in Europe, and a test from SkylineDx has been developed. A recent survey of pigmented lesion specialists revealed that 29% had ordered a prognostic GEP test, yet only half of these physicians reported that the test results influenced patient management.[6] Although GEP testing has the potential to improve staging and guide interventions such as SLNB, surveillance imaging intensity, and adjuvant therapy, it is not clear which patients should be tested or how to act on the results.[7] Additionally, there may be hazard for some patients forgoing SLNB based on results from GEP testing,[8] including failure to qualify for adjuvant therapeutic options or a clinical trial. In November 2019, following 2 online surveys, the national Melanoma Prevention Working Group (MPWG) and other international melanoma specialists convened to review 3 different GEP test platforms in various stages of clinical development and outline recommendations for evaluating prognostic GEP tests based on current evidence and consensus. These results are discussed herein, along with challenges regarding future prospective clinical trials that aim to incorporate GEP testing into clinical decision-making.

Methods

Participants

The MPWG is an interdisciplinary group of dermatologists, medical oncologists, surgical oncologists, dermatopathologists, epidemiologists/statisticians, basic scientists, and patient advocates dedicated to evidence review for best practices in melanoma prevention and early detection. An MPWG Pigmented Lesion Subcommittee previously published consensus statements on melanoma screening[9] and management of dysplastic nevi.[10] The MPWG members and additional international melanoma specialists participated in 2 rounds of an online survey.

Review of the Literature

We reviewed journal articles published from 2015 to 2019 related to GEP testing in CM that were indexed in PubMed. Additionally, relevant abstracts presented at the American Society of Clinical Oncology from 2017 to 2019 were reviewed.

Online Survey Process

An MPWG GEP subcommittee (D.G., E.G.B., R.I.H., C.C.-L., C.C.K., S.A.L., K.C.N., and S.M.S.) held 2 conference calls to develop initial questions, review anonymous survey data, and refine subsequent questions. Participants were sent links by email to Qualtrics-based surveys, and 2 of us (D.G. and N.O.) collated the data. The University of Utah Institutional Review Board (No. 125960) approved this survey activity.

Summit Meeting

The GEP subcommittee convened a 2-hour meeting (November 20, 2019) during the Society for Melanoma Research Congress in Salt Lake City, Utah. Predesignated speakers conducted a literature review and discussions of CM guidelines regarding GEP testing, online survey results, use of GEP results as a biomarker, statistical considerations for clinical trials incorporating GEP testing, SLNB, and adjuvant therapy, and the merits of analyzing banked-tumor specimens from completed clinical trials.

Results

Why Routine Prognostic GEP Testing Is Not Endorsed by AAD/NCCN Guidelines

Current AAD[1] and NCCN[2] melanoma clinical practice guidelines do not specify particular interventions based on GEP test results, although they recognize that prognostic GEP testing may classify CMs according to low vs high risk for metastatic recurrence. Concerns persist regarding minimal overlap among gene panels across studies[11–16] and whether GEP testing provides additional independent prognostic information compared with known clinicopathologic factors (ie, Breslow thickness, quantitative mitotic rate, ulceration, lymphovascular invasion, tumor-infiltrating lymphocytes, melanoma subtype, primary tumor site, regression, SLN status, American Joint Committee on Cancer [AJCC] stage, and patient age/sex). The eighth edition of the AJCC *Cancer Staging Manual* (AJCC8)[17] international database has validated melanoma-specific survival (MSS) based on nearly 50 000 patients with stage I to III melanoma observed since 1998 from the US, Australia, and Europe, most of whom were pathologically staged with SLNB.[18,19]

Without clinical trial assessment, the available evidence is insufficient to determine whether currently available GEP tests are simply a surrogate for a combination of known clinicopathologic factors associated with risk of recurrence/mortality. None of the published studies have evaluated all available clinicopathologic features of prognostic significance per international pathology reporting guidelines.[20] Contemporary assessment is further limited by lack of comparison in most studies to AJCC8,[17] which incorporates additional microscopic positive nodes for staging; however, the utility of this prognostic factor may be less valuable because many patients no longer undergo complete nodal dissection following a positive SLNB result given the Multicenter Selective Lymphadenectomy Trial II (MSLT-II)[21] and German Dermatologic Cooperative Oncology Group study (DeCOG-SLT)[22] outcomes. There is also limited evidence that GEP testing informs the need for imaging surveillance, SLNB, or adjuvant treatment. Current data do not sufficiently address issues related to false-positive and false-negative GEP test results (ie, high-risk test patients who fare well, and low-risk test patients who do not). While the latest NCCN guidelines[2] note that prognostic GEP testing may have value as an adjunct to AJCC staging, further investigation of large, contemporary data sets of unselected patients (as has been performed in patients with breast cancer)[23,24] was deemed necessary to define whether such testing can provide clinically actionable information.

Perceived Role of GEP Testing Among Melanoma Experts

In the current first-round online survey, the perceived clinical effect of GEP testing for early-stage (T1a/T1b) CM ranged from low to high, with more than 70% of respondents recognizing the potential value of accurately predicting patients with SLN positivity and those likely to relapse (eTable 1 in the Supplement). Because T1 tumors represent up to one-third of CM deaths,[25] GEP-based selection of those at highest risk for metastasis could potentially decrease melanoma mortality if adjuvant therapy were effectively used, although it has not yet been studied in this manner. There was also skepticism about the current ability of GEP testing to improve prognostication for T1 tumors, which are associated with greater than 95% 10-year MSS, according to AJCC8 staging from the worldwide collaborative data set.[17] Most (61%-77%) respondents agreed that GEP testing could have high clinical effect for patients with stage II and III A disease by identifying those who might be spared from routine imaging surveillance and/or benefit from systemic adjuvant therapy. Although fewer than 50% of respondents agreed that clinical utility of GEP testing should be determined from highly annotated retrospective studies (eg, National Cancer Trials Network) rather than prospective clinical trials, most agreed that future studies should use multiple testing platforms.

In the second-round online survey and at the summit meeting, there was consensus regarding the value of representative cohorts and the need for prospective randomized clinical trials (similar to those performed for breast cancer[23,24]) as all GEP platforms continue to evolve worldwide. While fewer than 50% of respondents agreed on the minimum acceptable prognostic accuracy for GEP testing, the majority (61%-80%) believed that worthwhile trials would address whether GEP testing could predict SLN positivity, compare favorably to SLNB in predicting risk of relapse, and identify patients who could be spared surveillance imaging and/or benefit from adjuvant therapy. Most (68%) respondents agreed that GEP testing had the greatest potential to influence the clinical management of patients with stage II disease.

Review of Currently Available GEP Testing Platforms

The 31-GEP Test—Two retrospective[26,27] and 3 prospective[28–31] external validation studies have been published following the initial publication of 31-GEP test data in 2015.[16] These studies demonstrated the prognostic ability of the 31-GEP test to identify low-risk (class 1) and high-risk (class 2) CM (Table 1). Despite differing study designs and variable follow-up, the performance of the 31-GEP test appeared consistent across studies and in a recent meta-analysis published following the summit meeting.[32] When evaluated as an independent covariate in multivariate analyses of patients with mixed-stage disease, results have been independently associated with relapse; however, no studies reported multivariate analyses accounting for all known clinicopathologic variables associated with MSS (noted previously). Additionally, most patients were not staged according to AJCC8[17] or compared with MSS from the AJCC8 data set, and follow-up times were insufficient to detect delayed recurrences for thin CM.[33–35] Thus, the incremental value of the 31-GEP test beyond established clinicopathologic prognostic factors and AJCC8 staging remains uncertain. In evaluation of the limited data reported in a stage-specific manner, the 31-GEP test misclassified the majority of patients with stage I disease with melanoma

recurrence[26,27,30,36]; in contrast, most patients with stage II and III disease with recurrence were correctly classified as class 2. The 31-GEP test was also evaluated as prognostic for SLN metastasis, although only unadjusted analyses were used.[8]

The Combined Clinicopathologic and GEP Platform—Statistical modeling merged clinicopathologic and GEP factors associated with nodal metastasis[13] into a combined model (CP-GEP; Table 2). In a validation cohort, the CP-GEP model improved predictive capacity for SLN positivity.[13] In partnership with SkylineDx, an external validation was performed.[14] A revised CP-GEP model that included age, Breslow thickness, and expression of 8 target genes (including only 2 from the original GEP group[13]) yielded a negative predictive value of approximately 90%, and estimated that for T1/T2 tumors, an SLNB reduction rate of 40% could be achieved. Limitations of the published data include key differences between this external validation and the original CP-GEP model: age of the cohorts, inclusion of T4 tumors, use of only age and Breslow thickness as clinicopathologic factors, and use of a different gene set. Performance outcomes, such as area under the curve, sensitivity, specificity, false-positive and false-negative rates, and stage-specific breakdown, were not reported.[14] This test recently became commercially available,[39] and further validation testing was published following the summit meeting.[40]

The MelaGenix Platform—MelaGenix, which is commercially available in Europe, was developed from a panel[12] that was narrowed to 7 protective genes and 1 high-risk gene using a training cohort of 125 CMs.[37] This 8-GEP test was examined in a validation cohort (Table 2). Combining a dichotomized gene expression risk score (GRS) with SLN status improved prognostic performance, and when the GRS was examined as a continuous variable it complemented AJCC7 staging in predicting MSS. Recently, in patients with stage II disease, high GRS was associated with decreased recurrence-free survival, distant metastasis-free survival, and MSS.[38] Patients with low and high GRS had a 10-year MSS of 92%and 67%, respectively; 10-year MSS for AJCC substages was 88% (IIA), 82% (IIB), and 75% (IIC), suggesting that the GRS may add value to AJCC classification in defining both low-risk and high-risk patients.

Essential Elements for Incorporation of a GEP Test Into Melanoma Staging and Clinical Care Guidelines

New prognostic tests (including GEP) must improve the accuracy of the best, currently available risk prediction models by a clinically (and not solely statistically) significant amount and should thereby alter the treatment plan (eg, whether or not to increase surveillance, perform SLNB, or recommend adjuvant therapy). The test should add to the positive predictive value of current models (eg, by identifying more patients at high risk of relapse) while minimizing false-positive predictions (eg, by identifying patients who otherwise would have been predicted to relapse but who do not). Ideally, it should add to the negative predictive value of current models while minimizing false-negative predictions (eg, patients otherwise considered low risk but who will ultimately relapse).

A GEP test should preferably be developed from the primary tumors of patients with a relatively high incidence of events (a development/discovery set) and then evaluated with a

much larger test cohort that is more representative of the entire clinical spectrum of disease. If the GEP test performs well across the major parameters outlined previously and against the best risk prediction models currently available, it should then be evaluated in an unselected, large, independent validation set of patients (and preferably in more than 1 validation set) to ensure reproducibility and durability. The end points of these analyses must be well defined (eg, SLNB positivity, locoregional or distant recurrence, and disease-specific death) and analyzed separately.

There was consensus at the summit on the following concepts: (1) GEP test scores should be analyzed as continuous variables to avoid misleading interpretation of dichotomous low-risk and high-risk values that may not reflect true biologic significance; (2) GEP scores for a given end point should be evaluated against standard clinicopathologic variables and upcoming AJCC8 risk stratification models to ensure that they are additive; (3) GEP tests should be evaluated across the entire disease spectrum of intended use, to add value in high-risk patients and avoid harm in low-risk patients; (4) GEP test results should be reproducible, widely available, and cost-effective (not simply cost-additive) to be incorporated in national/international clinical practice guidelines; and (5) test validation must be performed while minimizing investigator or commercial bias.

Clinical Trial Considerations

Clinical research questions are best addressed by prospective randomized clinical trials, particularly if interventions based on GEP testing represent a change in standard care (such as surveillance, SLNB, and/or adjuvant therapy). Potential biomarkers such as GEPs, whether integral or integrated into trial design,[41] should be analytically and clinically validated before they can be used in clinical trials to determine eligibility and assign or stratify patients for treatment. Analytic validation provides confirmation that the performance characteristics of the assay are reliable and suitable for the intended clinical trial.[42] Clinical validation reflects the ability of the assay to predict the outcome of interest. Potential randomized clinical trial designs incorporating GEP testing in the context of SLNB or adjuvant therapy decision-making are shown in eTable 2 in the Supplement. Results from GEP testing also have the potential to inform decisions regarding use of imaging surveillance for higher-risk patients with stage IB to II disease and could be the subject of a clinical trial.

Although prospective clinical trials are desirable, given the anticipated cost and number of patients required (eTable 2 in the Supplement), summit participants believed it is important to first perform retrospective studies using representative clinically annotated banked specimens (with long-term outcomes data) to support evaluation of particular GEPs prospectively in future trials. For example, retrospective studies of large, contemporary data sets may be sufficient to determine if GEP testing could adequately predict SLN positivity. Unfortunately, GEP testing is not incorporated into ongoing adjuvant trials in patients with stage IIB/C disease (eg, KEYNOTE-716 [placebo vs pembrolizumab, NCT03553836] and Check Mate 76K [placebo vs nivolumab, NCT04099251]). However, several completed cooperative group trials (eg, S1404, E1609, E1697, EORTC1325) and industry-sponsored studies (CheckMate 238, CheckMate 915) containing well-annotated specimens might

provide opportunities to assess GEP test performance. We recognize that industry may be reluctant to sponsor a study that might identify patients who would not benefit from their GEP test or therapeutic product. Beyond the potential for tissue degradation with use of older biospecimens, there are also limitations to using completed trial data sets that include use of prior AJCC staging classifications that lack contemporary clinicopathologic factors, lack of uniform pathologic staging with SLNB, and outdated systemic/adjuvant therapies (eg, high-dose interferon or ipilimumab).

Discussion

A multidisciplinary group of melanoma specialists reviewed the current evidence and discussed recommendations for use of GEP testing in CM. The consensus of the MPWG is that there are insufficient data to support routine use of currently available prognostic GEP tests to inform management for patients with CM. The MPWG recommends further research to assess the validity and clinical applicability of existing and emerging GEP tests. Although current GEP platforms require significant amounts of tissue, it is likely that future technologies will enable testing from smaller specimens, potentially facilitating multiple parallel platform assessments. While spatial transcriptomics[43] is an exciting research technique, it requires extensive analytical validation and evidence of association with clinical outcomes before being evaluated as a clinical test. Cell-free circulating tumor DNA shows promise as a biomarker for the management of patients with stages III and IV melanoma, although the sensitivity of circulating tumor DNA assays is related to patient tumor burden.[44] Current data have not yet suggested a role for monitoring minimal residual disease in patients with resected stage I/II disease.[44]

An international consortium for testing and comparing prognostic accuracy of multiple GEP platforms should be established in a standardized fashion. Such an initiative would also permit uniform reporting of prognostic testing data[45] in accordance with the REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) recommendations.[46] Additionally, net-benefit analysis may determine whether basing clinical decisions on a test would do more good than harm and would ideally include patient-reported outcomes and quality-of-life metrics, in contrast to traditional indices, such as sensitivity, specificity, or area under the curve, which are statistical abstractions and not necessarily informative about clinical value.[47] We acknowledge that funding for any trial initiative will be challenging.

Importantly, we must recognize that there may be non scientific elements involved in the adoption of new technologies into clinical practice that involve bias and other factors related to financial gain.[48,49] Physicians who were collaborators invalid at ion studies may favorably influence their colleagues and perceive that the use of a new test could alter their reputation or revenue (either positively or negatively). Dermatologists may be biased in favor of a test that would allow them to perform more excisions and send fewer patients for SLNB, while surgical oncologists may be biased against a test that limits the use of SLNB. Medical oncologists and pharmaceutical companies may be biased against a test that limits the use of adjuvant therapy or in favor of one that expands its use. Finally, a prognostic test company will have financial motivation to maximize its utilization in as many clinical scenarios as possible. Rigorous peer review is essential to ensure that the validation data supporting use

of the technology are sufficient. The remedy to these different biases is transparency, regulatory oversight, and a shared intent to balance the necessity to protect patients from potentially inaccurate testing that may provide a false sense of security or perceived increased risk with the desire to develop and implement new, promising technologies.

Limitations

The limitations of our study include inability to review all relevant data, including proprietary industry data and other data published after the manuscript was submitted. Additionally, there was a relatively low combined response rate to both surveys.

Conclusions

The MPWG consensus is that there are insufficient data to support routine use of currently available prognostic GEP tests to inform management for patients with CM. The MPWG recommends further research to assess the validity and clinical applicability of existing and emerging GEP tests. Decisions on performing GEP testing and patient management based on these results should only be made in the context of discussion of testing limitations with the patient or within a multidisciplinary group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

What evidence is needed for incorporation of prognostic gene expression profile (GEP) testing into clinical practice for patients with melanoma?

Findings

Findings of GEP testing are needed from large, representative patient cohorts with adequate clinical follow-up to enable statistical modeling and validation, and these findings must be compared with known relevant melanoma clinicopathologic factors. The currently published evidence is insufficient to establish that routine use of GEP testing provides additional clinical value for melanoma staging and prognostication beyond available clinicopathologic variables.

Meaning

Before GEP testing is routinely used, the clinical benefit to the management of patients with melanoma must be established through further clinical investigation.

Table 1.

Summary of External Validation Studies of the 31-GEP Test

Source	Type	Patients	Findings	Recurrences correctly classified[a]
Zager et al[26]	Retrospective	• 523 Patients; 16 centers • 50% Stage I • 18% Stage II • 32% Stage III • Metastatic event or >5 y event-free f/u	• Class 1: 5-y 88% RFS, 93% DMFS • Class 2: 5-y 52% RFS (HR, 2.1; 95% CI, 1.3-3.4, $P = .003$)[b] • 60% DMFS (HR, 2.7; 95% CI, 1.5-4.8; $P = .002$)[b]	• Stage I[c]: 35% (6/17) • Stage II: 77% (30/39) • Stage III: 76% (63/83)
Greenhaw et al[27]	Retrospective	• 256 Patients; single center • 86% Stage I • 14% Stage II • Mean f/u, 1.9 y	• Class 1: 5-y 93% MFS • Class 2: 5-y 69% MFS • Breslow thickness and ulceration independently associated with class 2	• Stage I[d]: 0% (0/1) • Stage II: 83% (10/12)
Hsueh et al[28,29]	Prospective	• 342 Patients; 11 centers • 67% Stage I • 22% Stage II • 11% Stage III • Metastatic event or median event-free f/u, 3.2 y	• Class 1A: 3-y 96% RFS; 97% DMFS • Class 1B: 3-y 91% RFS; 93% DMFS • Class 2A: 3-y 80% RFS; 84% DMFS • Class 2B: 3-y 62% RFS (class 2B HR, 4.24; 95% CI, 1.80-10.01; $P = .001$)[e]; 80% DMFS (class 2B HR, 3.21; 95% CI, 1.06-9.69; $P = .04$)[e]	• Stages I-III[f]: 60% (26/43) • Stage-specific performance not reported
Keller et al[30]	Prospective	• 159 Patients; single center (partial overlap with Hsueh et al[28]) • 60% Stage I • 25% Stage II • 14% Stage III • Median f/u, 3.5 y	• Class 1: 3-y 97% RFS; 99% DMFS • Class 2: 3-y 47% RFS (HR, 9.2; 95% CI, 3.0-28.5; $P = .0001$)[g] • 64% DMFS (HR, 19.0; 95% CI, 2.1-170.5; $P = .009$)[h]	• Stage I[f]: 0% (0/3) • Stage II: 86% (12/14) • Stage III: 92% (11/12)
Podlipnik et al[31]	Prospective	• 86 Patients; 5 centers • 72% Stages IB-IIA • 28% Stages IIB-IIC • Median f/u, 26 mo	• Class 1: 100% no recurrence • Class 2: 79% no recurrence (HR, 18.9; 95% CI, 1.8-2549.8; $P = .01$)[i]	• Stages IB-IIC[f]: 100% (7/7) • Stage-specific performance not reported
Vetto et al[8]	Prospective	• 838 Patients[j]; multicenter • T1/T2 patients with SLNB (or eligible) • Cohort 1: 326 T1/T2 patients with SLNB (or eligible) • Cohort 2: 512 T1/T2 patients with SLNB (or eligible)	• Cohort 1 • Class 1A: 6.2% SLNB positive • Class 2B: 8.3% SLNB positive • Cohort 2 • Class 1A: 6.3% SLNB positive • Class 2B: 24.5% SLNB positive	NA

Abbreviations: DMFS, distant metastasis–free survival; f/u, follow-up; GEP, gene expression profile; HR, hazard ratio; MFS, metastasis-free survival; NA, not applicable; RFS, recurrence-free survival; SLNB, sentinel lymph node biopsy.

[a] For class 2 result identifying patients who developed disease recurrence.

[b] Multivariate Cox regression analysis based on 244 cases with complete data for Breslow thickness, mitotic rate, ulceration, SLNB, and GEP result.

[c] Patients diagnosed from 2000 to 2014; American Joint Committee on Cancer (AJCC) edition used for staging not reported.

[d] Patients diagnosed from 2013 to 2018; AJCC edition used for staging not reported.

[e] Multivariate Cox regression analysis based on 49 cases with complete data for Breslow thickness, mitotic rate, ulceration, SLNB, and GEP result.

[f] AJCC 7th edition used for staging.

[g] Multivariate Cox regression analysis based on 159 cases with complete data for age, Breslow thickness, ulceration, SLNB, and GEP result.

[h] Multivariate Cox regression analysis based on 159 cases with complete data for Breslow thickness, ulceration, SLNB, and GEP result.

[i] Multivariate Cox regression analysis based on 86 cases with complete data for age, AJCC stage, and GEP result.

[j] Not all patients in the cohort underwent SLNB, and percentage who underwent SLNB was not reported.

Table 2.

Summary of Published Studies Using Other GEP Platforms

Source	GEP test	Patients	Findings	Test performance
Meves et al[13]	CP-GEP	• Development cohort: 360 patients	• CP model: AUC, 0.78 (95% CI, 0.73-0.83) • CP-GEP model: AUC, 0.89 (95% CI, 0.85-0.93; $P < .001$); HR, 17.32 (95% CI, 8.02-37.41)[a]	• Sensitivity: 89%[b] • Specificity: 76% (cutoff point 0.1)
		• Validation cohort: 146 patients • 4 Centers • 50% Stage I • 18% Stage II • 32% Stage III	• CP model: AUC, 0.68 (95% CI, not reported) • CP-GEP model: AUC, 0.93 (95% CI, 0.87-0.97)[c]	• Sensitivity: 100% • Specificity: 80% • Stage-specific breakdown not reported[d]
Mulder et al[14,e]	CP-GEP	• 211 Patients; single center • 24% T1 • 43% T2 • 33% T3 • 27.5% SLNB positive	• SLNB reduction rate: 40%	• T1-T3: NPV, 89%[b] • T1-T2: NPV, 91% • Complete stage-specific breakdown not reported[f]
Gambichler et al[37,e]	8-GEP	• 203 Patients; 2 centers • Stages IA-IIIC	• High GRS: 5-y 70% RFS (HR, 2.40; 95% CI, 1.18-4.89; $P = .015$)[g] • SLNB positive: 5-y 65% RFS (HR, 2.11; 95% CI, 1.02-4.37; $P = .046$)	• GRS plus SLNB: sensitivity of relapse detection increased from 38.7% (SLNB alone) to 67.7% • Stage-specific breakdown not reported[h]
Amaral et al[38]	8-GEP	• 245 Patients • 48% Stage IIA • 32% Stage IIB • 20% Stage IIC • >2-y f/u	• High GRS: 5-y 82% MSS (HR, 1.55; 95% CI, 1.13-2.13; $P = .006$)[g]	• GRS found to add value to AJCC[i] classification in defining both low-risk and high-risk patients

Abbreviations: AJCC, American Joint Committee on Cancer; AUC, area under the curve; CP, clinicopathologic, f/u, follow-up; GEP, gene expression profile; GRS, gene expression risk score; HR, hazard ratio; MSS, melanoma-specific survival; NPV, negative predictive value; RFS, recurrence-free survival; SLNB, sentinel lymph node biopsy.

[a] Multivariate Cox regression analysis based on 360 cases with complete data for age, tumor ulceration, Breslow thickness, SLNB result, and molecular factors (4 genes in original GEP group).

[b] For predicting SLNB positivity.

[c] Multivariate Cox regression analysis based on 146 cases with complete data for age, Breslow thickness, SLNB result, and molecular factors (8 genes, including 2 from original GEP group).

[d] Patients diagnosed from 2000 to 2014; AJCC edition used for staging not reported.

[e] Only the abstract was available for review.

[f] Patients diagnosed from 2007 to 2017; AJCC edition used for staging not reported.

[g] Multivariate analysis that included tumor thickness, age, and GRS.

[h] Years of diagnosis and AJCC edition used for staging were not reported.

[i] Patients diagnosed from 2000 to 2016; AJCC edition used for staging not reported.