Evidence review of the prognostic 40-gene expression profile test for cutaneous squamous cell carcinoma

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Synopsis

- High-risk cutaneous squamous cell carcinoma (cSCC) is a subset of cSCC commonly requiring a more aggressive treatment regimen, due to an increased probability of recurrence, nodal/distant metastasis, or disease specific death.
- Guidelines and staging criteria for cSCC are overall vague, creating a burden for clinicians when establishing an appropriate treatment plan. [1]
- In many cancer types, molecular prognostics have had a significant and appropriate impact in patient care.[2,3,4]
- The purpose for the development of the prognostic 40-GEP test was to identify high-risk cSCC early in the disease state, such that its result could complement current risk assessment methods for development of more personalized management plans to reduce the risk of poor outcomes for cSCC patients.

Objective

- To describe the performance of the 40-GEP test as a method of accurate assessment of a patient's risk for metastasis after diagnosis of cSCC with one or more risk factors.

Methods

- Previously published and unpublished clinical utility data addressing the impact of the 40-GEP on patient management plans were summarized.[5-7]
- Previously published clinical validation data from independent cases with verified clinicopathologic information and known outcomes were assessed by Kaplan-Meier survival analysis and Cox regression analysis.[8,9]
- Analytical validation of the performance of the 40-GEP test included precision experiments to assess inter-assay and intra-assay reliability and the assessment of its technical success rate.[10]

Results

- Three separate clinical impact surveys were distributed to dermatologic clinicians (n=598).[5-7] **Table 1** presents the results of physician responses to "no 40-GEP" and post-40-GEP test results regarding management changes. Responses for all surveys demonstrated that the prognostic information garnered through the 40-GEP could aid in cSCC patient management in a risk appropriate manner. A representative patient vignette highlights that 97.5% of clinicians would change patient management intensity recommendations based on the 40-GEP with reduced intensity for Class 1 and increased intensity for Class 2B post-test management decisions (**Figure 1**).
- **Figure 2** demonstrates the ability of the 40-GEP test to classify patients based on risk of metastasis.[8,9]
- Regardless of the specific risk factor or clinicopathologic risk assessment method included in the multivariable regression analysis, the 40-GEP demonstrated independent and statistically significant prognostic value with hazard ratios (HR) for Class 2A and 2B similar to or beyond that of clinicopathologic factor-based systems. (**Table 2**).
- Reliability of the 40-GEP test for class call assignments was verified by inter- and intra-assay concordance of 93% (n=27/29) and 98% (n=45/46), respectively.[10] Over the duration of one year, 98% of all clinically tested samples with sufficient tumor content gave actionable Class call outcomes, highlighting the low multi-gene failure rate of the test. (**Table 3**).[10]

Clinical Utility[5-7]

Table 1. 40-GEP testing consistently changes management recommendations across 3 clinical impact studies

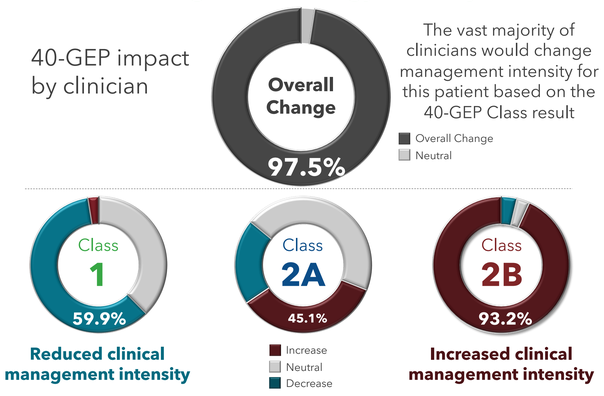
Clinical Impact Studies of 40-GEP[5-7]			
Clinicians	**Patients**	**Specific clinical recommendation changed with 40-GEP**	**Overall change in management plan recommended with 40-GEP**
34 real-world test users	6 real-world cases	F/U, SLNB, baseline nodal imaging, adjuvant radiation, adjuvant chemotherapy, surveillance imaging	Integration of the 40-GEP Class call significantly impacted recommended patient management plans in a risk-appropriate manner while staying within guidelines.
162 dermatologists*	2 patient vignettes	F/U, SLNB, nodal imaging, adjuvant radiation, adjuvant chemotherapy	
402 dermatologists	3 patient vignettes	F/U, SLNB referral, radiation, chemotherapy, immunotherapy	

F/U = follow up schedule; SLNB = sentinel lymph node biology; *Majority dermatologists with 8.6% dermatology NP/PA, 1.2% dermatopathologist, 1.9% other

Publications on proposed incorporation of 40-GEP testing:

- Cross-specialty expert panel reports decision-making points where 40-GEP testing could inform clinical management[12]
- Proposed risk-aligned incorporation of 40-GEP testing into management strategies within NCCN guidelines[11]

Figure 1. Example of 40-GEP impact on overall management strategy intensity[6]



67-year-old male
1.2 cm scalp lesion with poor differentiation, 1.2 mm depth
(2 high-risk clinicopathologic factors)
NCCN High-Risk cSCC • AJCC T1 • BWH T2a

(Adapted from Litchman et al.)

Clinical Validity[9]

Figure 2. The 40-GEP accurately classifies patients by metastatic risk

40-GEP Risk Class	Overall Cohort 3-year MFS (95% CI)	Overall Event Rate
Class 1	93.9% (90.7-97.2%)	6.6%
Class 2A	80.5% (75.0-86.5%)	20.0%
Class 2B	47.8% (31.2-73.3%)	52.2%
Without 40-GEP	85.5% (82.2-88.9%)	15.0%

All cases were high-risk by NCCN guidelines for localized cSCC or met Mohs micrographic surgery appropriate use criteria.

Table 2. The 40-GEP provides independent prognostic value to existing risk assessment methods

Multivariate Cox Regression			
Risk Factor	n	Hazard Ratio	p value
40-GEP Result			
Class 1	212	1.00	---
Class 2A	185	**2.33**	0.013
Class 2B	23	**6.86**	<0.001
Clinicopathologic Risk Factors			
Poor Differentiation	58	2.29	0.011
Perineural Invasion	53	1.22	ns
Deep Invasion	72	2.05	0.039
Tumor Diameter	N/A	1.07	ns

Multivariate Cox Regression			
Risk Factor	n	Hazard Ratio	p value
40-GEP Result			
Class 1	212	1.00	---
Class 2A	185	**2.97**	<0.001
Class 2B	23	**11.4**	<0.001
AJCC8 T Stage			
T1/T2	340	1.00	---
T3/T4	80	2.69	<0.001

40-GEP Result			
Class 1	212	1.00	---
Class 2A	185	**2.92**	<0.001
Class 2B	23	**9.50**	<0.001
NCCN Risk Group			
High	255	1.00	---
Very High	165	1.99	0.009

40-GEP Result			
Class 1	212	1.00	---
Class 2A	185	**2.98**	<0.001
Class 2B	23	**9.42**	<0.001
BWH T Stage			
T1/T2a	364	1.00	---
T2b/T3	56	2.38	0.002

Cases were comprehensively staged based on medical records, pathology reports, and definitive surgical reports.

(Adapted from Ibrahim et al.)

Analytic Validity[10]

Table 3. The 40-GEP shows robust repeatability and reproducibility[10]

Intra-assay concordance	98%
Inter-assay concordance	93%
Sample longevity and stability	96%
Overall technical success	98%

Conclusions

- The data across the three critical pillars of molecular testing demonstrate the robustness, accuracy and utility of the 40-GEP test.
- Clinical utility data illustrates that physicians understand 40-GEP test results and how to appropriately integrate these results into their clinical considerations for treatment of cSCC patients with one or more risk factors, ideally leading to a more personalized treatment pathway.
- Clinical validity data supports the use of the test as an adjunct to current risk assessment to better evaluate a patient's metastatic risk.
- Analytical validity data exhibited robust technical reliability of the 40-GEP on clinical samples along with high concordance rates across multiple performance experiments.

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Disclosures

- This study was sponsored by Castle Biosciences, Inc.
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