Incorporating the 40-gene expression profile (40-GEP) test within each clinicopathologic staging system improves metastatic risk-stratification in patients diagnosed with cutaneous squamous cell carcinoma (cSCC) and one or more high risk factors

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Background

- Available tumor and clinicopathologic risk-classification systems for cSCC include the American Joint Committee on Cancer, 8th Edition (AJCC8), Brigham and Women's Hospital (BWH) staging and the National Comprehensive Cancer Network (NCCN). Each system utilizes different risk factors to determine the T-stage or level of risk[6-8] and have limited and variable accuracy for determining metastasis risk[4,5].
- The 40-GEP test was developed and validated to statistically and independently stratify nodal/distant metastatic risk for cSCC patients with one or more risk factors into three risk categories: Class 1 (low), Class 2A (moderate) and Class 2B (high).[4,5]
- Clinical utility studies have demonstrated that physicians understand how to incorporate test results into risk assessments with staging or clinical factors,[9,10] and prospective utility studies demonstrate that the test is leading to changes in decision-making by clinicians.[11]
- 99% of orders for clinical testing are NCCN high-risk or very high-risk[10,12]

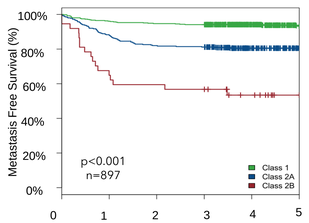
Methods

- The previous independent clinical validation cohort (n=420)[5] was combined with a novel, independent performance cohort (n=534) using the same inclusion criteria. The primary cohort for analysis (n=897) excluded patients in the combined cohort who were treated with adjuvant radiation therapy to remove the bias that would be introduced due to its impact on patient outcomes.
- Kaplan-Meier was used to determine metastasis-free survival (MFS). Univariate and multivariate Cox regression analyses were also performed. The likelihood ratio was calculated for each model and captures the relative amount of predictive power over a null model with no predictors. Positive (PPV) and negative (NPV) predictive values were calculated to assess the accuracy of metastasis-risk prediction for the 40-GEP in combination with clinical substages or NCCN risk category.

Results

Figure 1. 40-GEP accurately stratifies metastatic risk

40-GEP Risk Class	Overall Cohort: 3- year MFS (95% CI)	Overall Event Rate
Class 1	94.1% (92.1-96.2%)	6.5%
Class 2A	81.1% (77.1-85.3%)	19.4%
Class 2B	56.8% (42.8-72.2%)	45.9%
Overall	87.5% (85.4-89.7%)	13.2%



- Kaplan-Meier survival analysis of the combined cohort (n=897) demonstrated statistically significant 3-year metastasis-free survival between all classes.

Disclosures

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Clinical Issue and Objective

Each year, approximately 5% of the 1.8 million people in the U.S. diagnosed with cSCC will develop regional or distant metastasis.[1] Broad guidelines, along with lack of standardized and accurate risk assessment methods complicate treatment planning for these patients.[2,3]

The purpose of this study was to evaluate the performance of the 40-GEP test in the prognostication of metastasis and its ability to add independent prognostic value to current risk assessment systems in a large cohort of cSCC tumors with one or more high-risk factors.

Table 1. 40-GEP results independently improve metastatic risk prediction beyond staging and clinicopathologic risk classification systems

40-GEP vs Risk Assessment Methods					
Risk Factor		Cox Regression			
		Univariate		Multivariate	
		HR (*CI*)	p-value	HR (*CI*)	p-value
40-GEP	**n**				
Class 1	510	1.0	---	1.0	---
Class 2A	350	3.2 *(2.1-4.8)*	<0.001	2.8 *(1.8-4.2)*	<0.001
Class 2B	37	9.4 *(5.2-16.8)*	<0.001	6.2 *(3.4-11.4)*	<0.001
BWH	**n**				
T1/T2a	705	1.0	---	1.0	---
T2b/T3	74	4.8 *(3.3-7.0)*	<0.001	3.6 *(2.4-5.3)*	<0.001
40-GEP vs AJCC8					
40-GEP	**n**				
Class 1	510	1.0	---	1.0	---
Class 2A	350	3.2 *(2.1-4.8)*	<0.001	2.8 *(1.8-4.2)*	<0.001
Class 2B	37	9.4 *(5.2-16.8)*	<0.001	7.9 *(4.3-14.2)*	<0.001
AJCC8	**n**				
T1/T2	650	1.0	---	1.0	---
T3/T4	129	4.0 *(2.8-5.7)*	<0.001	3.4 *(2.3-4.8)*	<0.001
40-GEP vs NCCN					
40-GEP	**n**				
Class 1	498	1.0	---	1.0	---
Class 2A	347	3.2 *(2.0-4.8)*	<0.001	2.4*(1.6-3.8)*	<0.001
Class 2B	37	9.1 *(5.1-16.4)*	<0.001	6.0 *(3.3-10.9)*	<0.001
NCCN§	**n**				
High	570	1.0	---	1.0	---
Very High	312	4.6 *(3.1-6.7)*	<0.001	3.6 *(2.4-5.3)*	<0.001

- When interaction terms were added to the multivariate analysis, no significant interactions (p>0.05) were observed for all models (not shown). *n=897, 118 events of regional or distant metastasis HR = hazard ratio; CI = confidence interval; § =15 NCCN low-risk cases that did not have any events were dropped from the analysis.

Table 2. 40-GEP significantly improves metastatic risk prediction when used with staging systems

Model*	Likelihood ratio	ANOVA (p-value)
AJCC8 Staging	51.0	p < 0.0001
AJCC8 Staging + 40-GEP	98.0	
BWH Staging	55.8	p < 0.0001
BWH staging + 40-GEP	96.0	
NCCN very high	64.6	p < 0.0001
NCCN very high+ 40-GEP	100	

- When staging-alone models were compared to multivariate models that included the 40-GEP, a significant improvement in predictive accuracy was observed (ANOVA), as reflected in higher likelihood ratios when the 40-GEP is included with these staging systems.

Table 3. Improved prediction of positive and negative outcomes when including 40-GEP results with risk assessment systems

	Impact of 40-GEP on PPV			Impact of 40-GEP on NPV	
BWH Staging					
	Overall (without 40-GEP)	**40-GEP** Class 2 A&B	**40-GEP** Class 2B	**Overall** (without 40-GEP)	**40-GEP** Class 1
T1	--	13% ↑	33%	93%	97%
T2a	--	20% ↑	36%	87%	93%
T2b	35%	45%	67%	--	78% ↑
AJCC Staging					
T1	--	17% ↑	38%	91%	96%
T2	--	12% ↑	25%	92%	95%
T3	28%	37%	67%	--	84% ↑
NCCN Risk Groups					
High Risk	--	6% ↑	31%	94%	97%
Very High Risk	26%	32%	54%	--	83% ↑

↑ Increased from a baseline (--)

Conclusions

- This larger combined cohort confirms that the 40-GEP provides significant risk stratification within high-risk cSCC patients.
- Multivariate and likelihood analyses demonstrate the significant and independent value of the 40-GEP in models that include NCCN, BWH or AJCC8 systems.
- Incorporation of 40-GEP test results into clinical assessment with traditional clinicopathologic risk factors demonstrates significant improvement in risk assessment and can lead to better personalized patient management decisions.

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