Incorporating the 40-gene expression profile (40-GEP) test for poorly differentiated cutaneous squamous cell carcinoma (cSCC) tumors mitigates risk assessment uncertainty from histologic grading

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Background

- With 1.8 million new cases diagnosed each year, cutaneous squamous cell carcinoma (cSCC) is the second most prevalent skin cancer in the U.S.[1] While >95% of cSCC cases are cured by surgery, an estimated 5% progress to nodal or distant metastasis, where survival rates drop to 50-83% and <40%, respectively.[2,3]
- The degree of differentiation plays a critical role in the progression of cSCC. Multiple studies have established poorly differentiated histology as an independent predictor of poor outcomes.[2,4,5]
- For patients with primary cSCC and one or more risk factors, the clinically available 40-GEP test accurately classifies likelihood of regional, nodal, or distant metastasis at 3 years post diagnosis (Class 1=low risk, Class 2A=moderate risk, Class 2B= high risk).[1,2] The 40-GEP has also demonstrated independent and additive prognostic value in a multivariate model when compared to commonly utilized high-risk factors or Brigham and Women's Hospital (BWH) staging system (**Table 1**).[6,7]

Table 1. Independent risk assessment by the 40-GEP complements existing systems[7]

- Class 2A result has similar risk to well-established high-risk factors
- Class 2B result 3-4x as risky as high-risk clinicopathologic factors or T-stage

		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
Immunosuppression	103	---	---
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**

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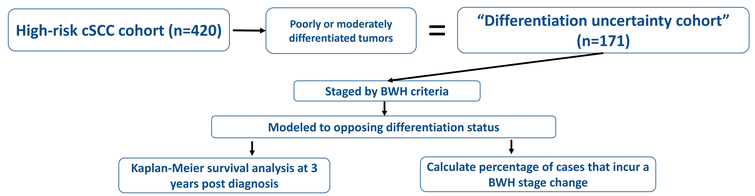
Methods

Figure 1. Development of a 'differentiation uncertainty cohort'



- A high-risk cSCC cohort[7] (n=420) was divided into moderately and poorly differentiated statuses based on clinical pathology reports and by an independent dermatopathologist review. If differentiation status differed between the report and the independent review, poorly differentiated was chosen as the status. The "differentiation uncertainty cohort" (n=171) was then staged by BWH criteria (**Table 2A**). To represent the subjectivity and inconsistent evaluation that commonly happens with this risk factor, differentiation status was manually changed to the opposing status (i.e., poorly changed to moderately, moderately changed to poorly). Determination of changes to BWH staging were documented to then note wherein changes of management may occur. Kaplan-Meier analysis was used to determine statistical significance of metastasis free survival (MFS) when incorporating the 40-GEP test.

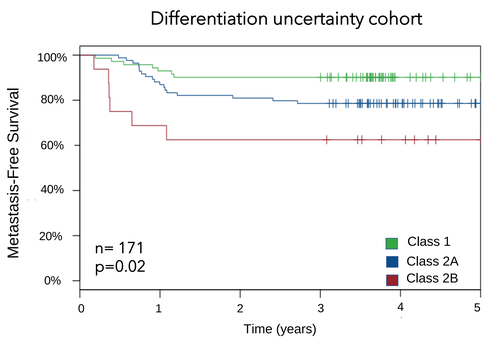
Clinical Issue and Objective

There is a lack of widely accepted criteria for grading of cSCC tumor tissue. This has led to subjectivity when determining differentiation status, complicated by different specialties' usage of different staging criteria.[8] Multiple studies have shown concordance for cSCC histologic grading is overall weak, especially when comparing moderately differentiated tumors.[9,10] The inconsistency in the assessment of this risk factor can adversely impact its value as a prognostic factor due to its direct impact on clinicopathologic tumor staging.[9]

The objective of this study was to evaluate the ability of the 40-GEP to risk stratify among a high-risk cSCC "differentiation uncertainty cohort" and its impact on staging, therefore its potential to influence treatment decisions.

Results

Figure 2. The 40-GEP stratifies risk among a histologically ambiguous high-risk cSCC cohort



40-GEP Risk Class	3- year MFS (95% CI)	Overall Event Rate	Non-metastatic (n)	Metastatic (n)
Class 1	90.1% (97.3-83.5%)	11.3%	63	8
Class 2A	78.6% (87.9-70.3%)	21.4%	66	18
Class 2B	62.5% (91.4-42.8%)	37.5%	10	6
Without 40-GEP	81.9% (87.9-76.3%)	18.7%	139	32

Within the 'differentiation uncertainty cohort' (n=171), Kaplan-Meier survival analysis demonstrated statistically significant 3-year metastasis-free survival between all 40-GEP classes. Assessment of number of samples with metastatic outcomes was also evaluated and arranged by 40-GEP class.

Table 2. Differentiation status was altered for 40% of the cohort, impacting BWH stage and potentially treatment decisions

A)

BWH T-stage	
T1	0 high risk factors
T2	T2a: 1 high risk factors T2b: 2-3 high risk factors
T3	4 high risk factors

High-risk factors
- Poorly differentiated histology
- Tumor diameter ≥2cm
- Perineural invasion ≥0.1mm
- Deep tumor invasion (beyond subcutaneous fat but excluding bone invasion, which qualifies as T3)

B)

Number of patients upstaged			
BWH T-stage			n
T1	→	T2a	76
T2a	→	T2b	55
T2b	→	T3	1
Total			132
Number of patients downstaged			
T2a	→	T1	22
T2b	→	T2a	17
Total			39

A) Risk factors comprising the Brigham and Women's Hospital (BWH) staging system.[5] B) Overall, 40% of the high-risk cSCC cohort would change differentiation status, with 77.2% being upstaged and 22.8% being downstaged by BWH criteria. This 'differentiation uncertainty cohort' is representative of how inconsistencies in assessment of cSCC tissue grading can directly impact staging and potentially treatment decisions.

Conclusions

- For clinicians who follow BWH staging, uncertainty in differentiation status may impact patient management.
- The 40-GEP provides objective and reproducible prognostic information, including in situations where the distinction between poorly and moderately differentiated histological grading is challenging.
- Within this cohort of high-risk cSCC patients, whose BWH stage would change solely due to an alteration in differentiation status, the 40-GEP was able to significantly stratify risk of metastasis.
- Incorporating the personalized 40-GEP test results into clinical cSCC risk assessment could enhance current patient management decisions, therefore improving patient outcomes.

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Disclosures

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