

# Incorporation of a prognostic 40-gene expression profile (40-GEP) test into clinicopathological risk assessment using newly published guidelines for cutaneous squamous cell carcinoma (cSCC)

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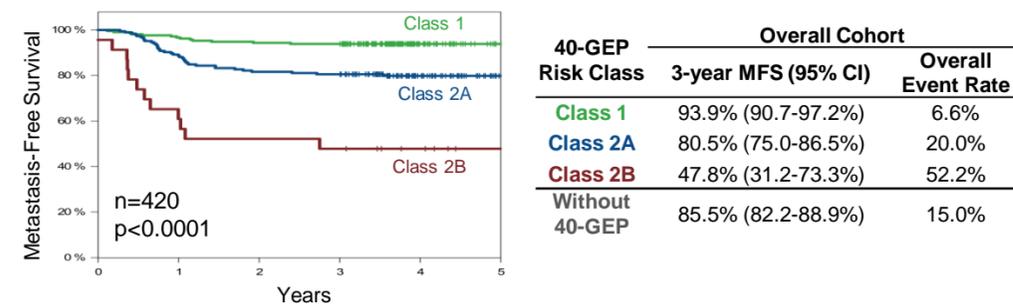
## BACKGROUND

- Although the fatality rate for cSCC is low, the overall incidence is high (~1-2.5 million cases/year) and rising, resulting in an estimated mortality rate likely to surpass that for melanoma.<sup>1,2</sup>
- The National Comprehensive Cancer Network (NCCN) Guidelines are a comprehensive set of recommendations to guide management decisions, including treatment options and follow-up recommendations. Guidelines for cSCC have recently been updated (February 2021) to include newly defined risk groups (low, high, or very high) based on risk factors that contribute to local recurrence, metastasis, or disease related death.<sup>3</sup>
- The clinically available 40-GEP test was developed and independently validated to accurately classify risk for regional or distant metastasis as low (Class 1), moderate (Class 2A), or high (Class 2B) in patients with primary cSCC and one or more high-risk factors<sup>4,5</sup> (Figure 1).

### Objective:

Within these revised NCCN guidelines, this study aimed to both validate the assessment of the high-risk cSCC 40-GEP cohort and evaluate the potential of 40-GEP test results to further stratify risk.

**Figure 1. Kaplan Meier analysis for metastasis free survival based on 40-GEP.** The 40-GEP test classifies patients based on risk for regional and/or distant metastasis. All cases (n=420) were either high-risk by NCCN guidelines for localized cSCC or met Mohs Micrographic Surgery (MMS) appropriate use criteria (AUC).<sup>5</sup> Kaplan-Meier analysis demonstrated a statistically significant difference between Class results.



## METHODS

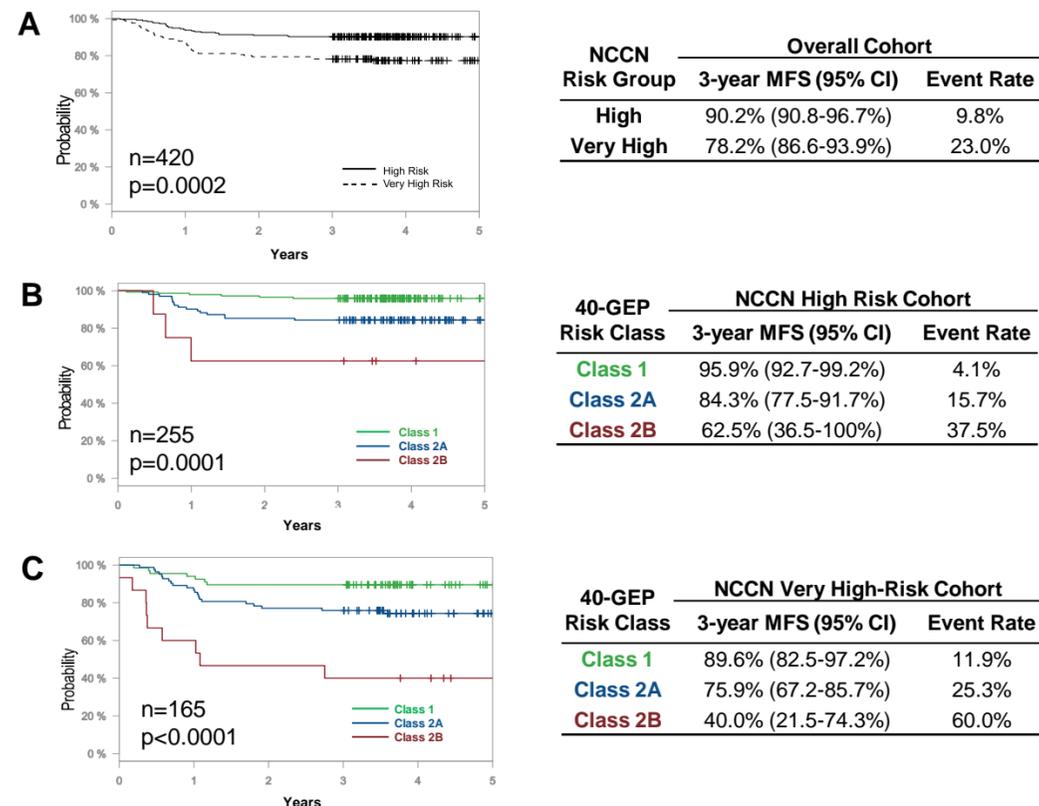
- In this IRB-approved, multi-center study, primary cSCC formalin-fixed paraffin-embedded (FFPE) archival tumor specimens with one or more risk factors and known 3-year outcomes were collected from 33 centers.
- Comprehensive assessment of clinicopathological risk factors was performed based on original biopsy reports, definitive surgical reports, and independent dermatopathologist review and assayed under clinical testing conditions by the 40-GEP test (n=420).
- Kaplan-Meier for metastasis-free survival (MFS) was performed and hazard ratios (HR) were determined by multivariate Cox regression analysis.

## RESULTS

**Table 1. Risk factors used in analysis.** Seven risk factors with the best supported evidence for metastasis<sup>5</sup> were assessed, and analysis was performed within newly developed cSCC NCCN risk groups.<sup>3</sup>

Risk Factor	High Risk	Very High Risk
Size/Location	Any size on the head, neck, genitalia, hands, feet or pretibial surface or ≥2 cm size on any other area of the body	≥4 cm
Perineural involvement	present	≥0.1mm
Immunosuppression	(+)	-----
Depth	-----	Invasion beyond subcutaneous fat or >6mm
Histologic features	Acantholytic/adenoid, adenosquamous or metaplastic/carcinosarcomatous subtypes	Desmoplastic SCC
Lymphovascular involvement	-----	(+)
Differentiation	-----	Poor

**Figure 2. Kaplan Meier analysis for metastasis free survival.** When applying criteria from the newly developed NCCN guidelines all 420 patients of the 40-GEP validation cohort were defined as either high or very high risk. A) Very high-risk cases demonstrate lower metastasis free survival rates than high risk cases. The 40-GEP further stratified risk within NCCN B) high-risk and C) very high-risk subsets.



**Table 2. Univariate and multivariate analysis of 40-GEP Classes and NCCN Risk Groups**

Variable	n	Univariate Cox Regression		Multivariate Cox Regression*	
		Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
<b>40-GEP Result</b>					
Class 1	212	1.00 (---)	---	1.00 (---)	---
Class 2A	185	3.22 (1.74-5.95)	<0.001	2.92 (1.57-5.44)	<0.001
Class 2B	23	11.61 (5.36-25.15)	<0.001	9.5 (4.33-20.9)	<0.001
<b>NCCN Risk Group</b>					
High risk	255	1.00 (---)	---	1.00 (---)	---
Very high risk	165	2.54 (0.26-3.62)	<0.001	1.99 (1.19-3.33)	0.009

\*The addition of interaction terms revealed no significant interactions (p<0.05)

## CONCLUSIONS

- These data demonstrate that the cSCC cohort used in validation of the 40-GEP test is representative of a high-risk population under the new NCCN guidelines.
- These findings also validate that the 40-GEP test adds independent prognostic value within the new NCCN guidelines and could be applied as an adjunct to enhance cSCC risk stratification.
- Overall, incorporating the 40-GEP into cSCC patient risk assessment could lead to more personalized and risk-appropriate pathways for improvement of patient management and disease related outcomes.

## REFERENCES

- Rogers *et al* JAMA Derm 2015 3. NCCN Guidelines Version 1.2021 5. Ibrahim *et al* Derm Surg. Under review
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