doi:10.36849/JDD.7691

 ORIGINAL ARTICLE

Incorporating a Prognostic Gene Expression Profile Test Into the Management of Cutaneous Squamous Cell Carcinoma: An Expert Consensus Panel Report

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ABSTRACT

Background: Cutaneous squamous cell carcinoma (cSCC) is a growing health concern with a rapidly increasing incidence. Disease-specific mortality is typically preceded by a metastasis, but current staging systems have significant limitations in predicting this event. The 40-gene expression profile (40-GEP) test is a validated method of further stratifying patients based on the risk of regional or distant metastasis, but limited guidelines exist for incorporating this test into clinical practice.

Objective: To review the available literature on the use of gene expression profile (GEP) testing to assess prognosis in cSCC and create consensus statements to guide dermatology clinicians on its use.

Methods: A comprehensive literature search of PubMed, EMBASE, and Scopus was completed for English-language original research articles on the use of GEP testing to assess cSCC prognosis. A panel of 8 dermatologists with significant expertise in diagnosing and managing cSCC gathered to review the articles and create consensus statements. A modified Delphi process was used to approve each statement and a strength of recommendation was assigned using the Strength of Recommendation Taxonomy (SORT) criteria.

Results: The literature search produced 157 articles that met the search criteria. A thorough screening of the studies for relevance to the research question resulted in 21 articles that were distributed to the panelists for review prior to the roundtable discussion. The panel unanimously voted to adopt 7 consensus statements and recommendations, 6 of which were given a strength of "A" and 1 of which was given a strength of "C".

Conclusion: The 40-GEP test provides accurate and independent prognostic information beyond standard staging systems that only incorporate pathologic data. Incorporation of GEP testing into national guidelines can help further stratify patients based on risk of metastasis, and thus may improve morbidity and mortality.

J Drugs Dermatol. 2024;23(2):54-60. doi:10.36849/JDD.7691

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, occurring in 1.8 million people in the United States (US) annually.[1-4] Its incidence is on the rise, likely due to an aging population and possibly an increased emphasis on skin cancer screening.[1-5] Although typically found at a 1:4 ratio to basal cell carcinoma (BCC), the most common skin cancer in the general US population, one study identified a 1:1 ratio between cSCC and BCC in a Medicare fee-for-service population in 2012.[5] While cSCC typically carries an excellent prognosis, with 5-year cure rates greater than 90%, a subset of these tumors exhibit aggressive behavior such as local recurrence and metastasis.[6-9] The frequency of regional and distant metastasis may be underreported due to a lack of nonmelanoma skin cancer (NMSC) registries.[1,8] As a result, these numbers are primarily

estimated by retrospective cohort studies, which cite a rate between 2% to 6%.[7-10] Furthermore, disease-specific mortality is typically estimated to be 1.5% to 3%.[4,9,11,12] Despite this relatively low mortality rate, the absolute number of deaths attributable to cSCC in the US was estimated to be between 3932 and 8971 in 2012 and may already exceed deaths from cutaneous melanoma.[3,12-14] The vast majority of these deaths arise in patients with metastasis, at which point the 5-year survival rate can drop to 50% to 83% for regional metastasis and even below 40% for distant metastasis.[8,9,11]

There are several staging systems for cSCC designed to stratify patients based on the risk of recurrence and metastasis. The most commonly used systems include the individual risk factor-based National Comprehensive Cancer Network (NCCN) system, American Joint Committee on Cancer Eighth Addition (AJCC8) staging system, and the Brigham and Women's Hospital (BWH) classification.[15-17] These systems are based on clinical and/or pathological features, such as tumor size and thickness, perineural invasion, cell differentiation, and tumor location. However, these factors may be limited in their utility, as biopsy specimens are often transected, precluding accurate measurement of tumor depth.[9,12] Additionally, interobserver variability in dermatopathology has been reported throughout the literature,[18-20] with one study identifying discrepancies in 22% of the 405 cases reviewed, 40% of which related to nonmelanocytic neoplasms.[18] The combination of these limitations have resulted in a low sensitivity (23-46%) and positive predictive value (PPV) (12-13%) for these staging systems.[16,17,21,22]

Given these relatively low sensitivity and PPV values, more precise methods of predicting the risk of recurrence, metastasis, and mortality are needed for skin cancer. Precision medicine has already become commonplace throughout many specialties, including dermatology. Genomic testing with the use of gene expression profile (GEP) assays is a validated and commonly used tool to aid in diagnosis and prognostic assessment for cutaneous malignancies.[23-27] For cSCC, there is one commercially available GEP test, the 40-gene expression profile test (40-GEP), that uses formalin-fixed paraffin-embedded (FFPE), primary cSCC tissue to stratify tumors into low (Class 1), high (Class 2A), and highest (Class 2B) risk for regional or distant metastasis at 3 years after diagnosis.[14] The test was initially validated by Wysong et al in 2020,[28] but several other studies since then have demonstrated the test's analytical validity, clinical validity, accuracy, and clinical utility.[11,14,28-36] Despite the abundant data, limited guidelines exist on how to incorporate this test into clinical practice. The purpose of this study was for a panel of experts in cSCC diagnosis and management to review the available literature and produce appropriate use recommendations for dermatology practitioners for GEP testing for this cancer.

MATERIALS AND METHODS

Literature Search and Study Selection

A comprehensive literature search of PubMed, EMBASE, and Scopus was completed on December 2, 2022, using the keywords cutaneous squamous cell carcinoma, prognosis, and gene expression along with the Boolean term AND for English-language original research articles, systematic reviews, and meta-analyses without date restrictions. Articles were screened for relevance to the topic of measuring gene expression to assess prognosis in cSCC. The studies that met the inclusion criteria were then distributed to the panelists. Each member of the panel reviewed the selected articles and assigned them a level of evidence based on Strength of Recommendation Taxonomy (SORT) criteria.[37] These levels include level 1 (good-quality patient-oriented evidence, such as systematic reviews or meta-analyses of good-quality cohort studies or a prospective cohort study with good follow-up), level 2 (limited-quality patient-oriented evidence, such as retrospective cohort studies or prospective cohort studies with poor follow-up), or level 3 (other evidence, such as consensus guidelines, usual practice, opinion, or disease-oriented evidence).[37] Of note, a level 2 or 3 designation does not necessarily indicate a deficient study, but is requisite for retrospective studies or basic science articles that focus on disease states, respectively.

Development of Consensus Statements

The panel consisted of 8 dermatologists with expertise in diagnosing and managing cSCC. They convened on January 13, 2023, to review and discuss the studies and create consensus statements to guide clinicians on the use of GEP testing to assess prognosis for cSCC. A modified Delphi process was used to reach a consensus for each statement.[38] This process requires supermajority approval to adopt a recommendation through multiple rounds of real-time voting and has been utilized frequently to create expert recommendations in dermatology.[39-42]

RESULTS

Literature Search and Study Selection

The initial literature search produced 157 articles that met the search criteria. A thorough screening of the studies for relevance to the research question resulted in 21 articles that were distributed to the panelists for review prior to the roundtable discussion.

Levels of Evidence Designation

Of the 21 articles that were reviewed, the panel assigned level 1 evidence to 2 articles,[28,35] level 2 evidence to 8 articles,[11,14,29,43-47] and level 3 evidence to 11 articles[30-34,36,48-52] (Table 1 and 2).

Consensus Statements

The panel created seven consensus statements related to cSCC and the use of GEP testing to assess prognosis. All 7 statements received a unanimous (8/8) vote for adoption. Each of the

TABLE 1.

SORT Criteria Level Of Evidence for Articles Pertaining to the 40-GEP Test	
Article	**Level of Evidence**
Wysong A, Newman JG, Covington KR, et al. Validation of a 40-gene expression profile test to predict metastatic risk in localized high-risk cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 2021;84(2):361-369.	1
Saleeby E, Bielinski K, Fitzgerald A, et al. A Prospective, Multi-Center Clinical Utility Study Demonstrates That the 40-Gene Expression Profile (40-GEP) Test Impacts Clinical Management for Medicare-Eligible Patients with High-Risk Cutaneous Squamous Cell Carcinoma (cSCC). *SKIN The Journal of Cutaneous Medicine.* 2020;6(6):482–496.	1
Arron ST, Wysong A, Hall MA, et al. Gene expression profiling for metastatic risk in head and neck cutaneous squamous cell carcinoma. *Laryngoscope Investig Otolaryngol.* 2022;7(1):135-144.	2
Farberg AS, Hall MA, Douglas L, et al. Integrating gene expression profiling into NCCN high-risk cutaneous squamous cell carcinoma management recommendations: impact on patient management. *Curr Med Res Opin.* 2020;36(8):1301-1307.	2
Ibrahim SF, Kasprzak JM, Hall MA, et al. Enhanced metastatic risk assessment in cutaneous squamous cell carcinoma with the 40-gene expression profile test. *Future Oncol.* 2022;18(7):833-847.	2
Arron ST, Blalock TW, Guenther JM, et al. Clinical Considerations for Integrating Gene Expression Profiling into Cutaneous Squamous Cell Carcinoma Management. *J Drugs Dermatol.* 2021;20(6):5s-s11.	3
Au JH, Hooper PB, Fitzgerald AL, Somani AK. Clinical utility of the 40-gene expression profile (40-gep) test for improved patient management decisions and disease-related outcomes when combined with current clinicopathological risk factors for cutaneous squamous cell carcinoma (cscc): case series. *Dermatol Ther (Heidelb).* 2022;12(2):591-597.	3
Borman S, Wilkinson J, Meldi-Sholl L, et al. Analytical validity of DecisionDx-SCC, a gene expression profile test to identify risk of metastasis in cutaneous squamous cell carcinoma (SCC) patients. *Diagn Pathol.* 2022;17(1):32.	3
Hooper PB, Farberg AS, Fitzgerald AL, et al. Real-world evidence shows clinicians appropriately use the prognostic 40-gene expression profile (40-gep) test for high-risk cutaneous squamous cell carcinoma (cscc) patients. *Cancer Invest.* 2022;40(10):911-922.	3
Litchman GH, Fitzgerald AL, Kurley SJ, et al. Impact of a prognostic 40-gene expression profiling test on clinical management decisions for high-risk cutaneous squamous cell carcinoma. *Curr Med Res Opin.* 2020;36(8):1295-1300.	3
Rebeca T, Giselle P, Litchman GH, et al. Impact of gene expression profile testing on the management of squamous cell carcinoma by dermatologists. *J Drugs Dermatol.* 2019;18(10):980-984.	3

TABLE 2.

SORT Criteria Level of Evidence for Articles Related to the Measurement of Gene Expression to Assess Prognosis in cSCC but Not Pertaining to the 40-GEP Test	
Article	**Level of Evidence**
Cañueto J, Cardeñoso-Álvarez E, Cosano-Quero A, et al. The expression of podoplanin is associated with poor outcome in cutaneous squamous cell carcinoma. *J Cutan Pathol.* 2017;44(2):144-151.	2
Chen MK, Cai MY, Luo RZ, et al. Overexpression of p300 correlates with poor prognosis in patients with cutaneous squamous cell carcinoma. *Br J Dermatol.* 2015;172(1):111-119.	2
Li YY, Hanna GJ, Laga AC, et al. Genomic analysis of metastatic cutaneous squamous cell carcinoma. *Clin Cancer Res.* 2015;21(6):1447-1456.	2
Vinicius de LV, Scapulatempo C, Perpetuo NM, et al. Prognostic and risk factors in patients with locally advanced cutaneous squamous cell carcinoma of the trunk and extremities. *J Skin Cancer.* 2011;2011:420796.	2
Xu R, Cai MY, Luo RZ, et al. The expression status and prognostic value of cancer stem cell biomarker cd133 in cutaneous squamous cell carcinoma. *JAMA Dermatol.* 2016;152(3):305-311.	2
Al-Rohil RN, Tarasen AJ, Carlson JA, et al. Evaluation of 122 advanced-stage cutaneous squamous cell carcinomas by comprehensive genomic profiling opens the door for new routes to targeted therapies. *Cancer.* 2016;122(2):249-257.	3
Campos MA, Macedo S, Fernandes MS, et al. Prognostic significance of RAS mutations and P53 expression in cutaneous squamous cell carcinomas. *Genes (Basel).* 2020;11(7):751. Published 2020 Jul 6.	3
Kitrell BM, Blue ED, Siller A Jr, et al. Gene expression profiles in cutaneous oncology. Dermatol Clin. 2023;41(1):89-99.	3
Newman JG, Hall MA, Kurley SJ, et al. Adjuvant therapy for high-risk cutaneous squamous cell carcinoma: 10-year review. *Head Neck.* 2021;43(9):2822-2843.	3
Zilberg C, Lee MW, Yu B, et al. Analysis of clinically relevant somatic mutations in high-risk head and neck cutaneous squamous cell carcinoma. *Mod Pathol.* 2018;31(2):275-287.	3

TABLE 3.

Consensus Statements and Recommendations for Incorporating the 40-GEP Test into Clinical Practice and Their Corresponding Strengths Using SORT Criteria

Consensus Statement/Recommendation	Strength of Recommendation	Consensus Vote
There is data to support that specific genes influence cSCC clinical behavior.	A	8/8
The data supports the 40-GEP test's ability to identify a subset of cSCCs that are at a high risk for metastasis.	A	8/8
The 40-GEP test provides clinically useful data for cSCC prognosis independent of the AJCC8 and BWH staging systems.	A	8/8
Adding 40-GEP data to the AJCC8 and BWH staging systems enhances the prognostic assessment of cSCC.	A	8/8
The 40-GEP test results can increase the precision and confidence in cSCC management decisions.	A	8/8
The 40-GEP test should be considered for use on cSCC tumors with at least 1 high-risk feature per AJCC8 and/or BWH and/or NCCN guidelines.	A	8/8
The 40-GEP test should not be used on cSCC in situ or invasive cSCC without high-risk features, or for patients that are not candidates for additional procedures or therapies.	C	8/8

statements and recommendations were given a strength of recommendation according to SORT criteria (Table 3).

Statement 1: *There are data to support that specific genes influence cSCC clinical behavior. (SORT Level A)*

Several studies have demonstrated a correlation between the upregulation or downregulation of certain genes and aggressive clinicopathologic features, poor outcomes, or both.[43-52] Campos et al retrospectively evaluated 162 cases of cSCC and found that RAS mutations were more frequently associated with an infiltrative than expansive pattern of invasion and were also associated with features of local aggressiveness.[49] Additionally, p53 overexpression was shown to be a predictor of recurrence in the univariate analysis, although not in the multivariate analysis.[49] Cañueto et al analyzed podoplanin expression in a series of 94 cSCCs and found that moderate-to-intense expression was associated with the presence of desmoplasia, an infiltrative growth pattern, the presence of lymphovascular invasion, and the presence of ulceration.[43] These higher levels of expression were also associated with a higher risk of nodal metastasis during follow-up and shorter periods of disease-free relapse.[43] Additional studies have shown that overexpression of p300 correlates with decreased recurrence-free survival (RFS) and overall survival (OS),[44] and that high CD133 expression is greater in patients with advanced tumor stage and it also correlated with decreased RFS and OS.[47]

Statement 2: *The data support the 40-GEP test's ability to identify a subset of cSCCs that are at high risk for metastasis. (SORT Level A)*

The original validation study for the 40-GEP test consisted of a prospective cohort of 321 primary cSCC cases, all of which had 1 or more clinicopathologic risk factors, of which 52 had documented regional or distant metastasis vs 269 that did not. Regarding metastatic risk, the test designated 203 cases as Class 1 (low risk), 93 as Class 2A (high risk), and 25 as Class 2B (highest risk). Kaplan-Meier survival analysis then demonstrated that the 3-year metastasis-free survival (MFS) rates were 91.6% for Class 1, 80.6% for Class 2A, and 44.0% for Class 2B.[28] Furthermore, the hazard ratios for metastasis for the Class 2A and 2B cases were 2.44 and 10.15, respectively.[28]

Since that original study, several others have demonstrated that the 40-GEP test can accurately identify a subset of cSCCs at high risk for metastasis. Arron et al used the test to assess 278 cases of cSCC of the head and neck and found that 3-year MFS rates were 92.1% for Class 1, 76.1% for Class 2A, and 44.4% for Class 2B.[29] Ibrahim et al used the 40-GEP test to analyze a retrospective cohort of 420 cases of cSCC without at least 1 high-risk feature as defined by NCCN guidelines or AJCC or BWH staging systems.[11] In this study, 3-year MFS rates for Class 1, Class 2A, and Class 2B were 93.9%, 80.5%, and 47.8%, respectively.[11] All 3 studies demonstrated concordant 3-year MFS rates for each 40-GEP class and verified the ability of the test to predict the risk of metastasis.

Statement 3: *The 40-GEP test provides clinically useful data for cSCC prognosis independent of the AJCC8 and BWH staging systems. (SORT Level A)*

The utility of the 40-GEP test depends on its ability to accurately assess cSCC prognosis independent of established staging systems such as AJCC8 and BWH. Several studies compared the 40-GEP test to these staging systems and found that the test is an independent predictor of risk. In the original validation study, a 40-GEP Class 2B result had a PPV of 60% compared to 32.8%, 35.1%, and 16.7% for the AJCC, BWH, and NCCN high-risk groups, respectively.[28] Furthermore, a Class 1 result

had a negative predictive value of 91.1% compared to 87.7%, 86.3%, and 90.5% for the AJCC, BWH, and NCCN low-risk groups, respectively. Similarly, Ibrahim et al found that the PPV for a Class 2B result in their cohort was 52.2% compared with 30.0% and 33.9% for high-stage AJCC8 and BWH tumors, respectively.[11] Likewise, in a cohort of cSCCs on the head and neck, Arron et al found that the sensitivity of a Class 2 result for metastasis was significantly greater than high-stage AJCC8 T3/T4 and BHW T2b/T3 results and the specificity of a Class 2B result was significantly greater than the high-stage AJCC8 and BWH results.[29]

Statement 4: *Adding 40-GEP data to the AJCC8 and BWH staging systems enhances the prognostic assessment of cSCC. (SORT Level A)*

Not only does the literature support the independent prognostic value of the 40-GEP test, but it also establishes that incorporating these results into current staging systems and guidelines further improves prognostic assessment. Patients classified as NCCN high risk and very high risk that also received a 40-GEP result of Class 2B had a metastasis occurrence rate of 37.5% and 60.0% respectively, compared to a rate of 9.8% for NCCN high risk and a rate of 23% for NCCN very high risk alone.[11]

Statement 5: *The 40-GEP test results can increase the precision and confidence in cSCC management decisions. (SORT Level A)*

As previously noted, applying 40-GEP test results has the potential to re-categorize NCCN-defined high-risk cSCC patients into lower intensity management groups.[11,28] This can have a large impact on management decisions, such as frequency of follow-up, method of nodal assessment (ie, palpation vs biopsy), use of advanced imaging, and use of adjuvant therapy. The NCCN guidelines for high-risk cSCC are broad and have the potential to lead to overtreatment, as 63.0% of the high-risk NCCN cases in the original 40-GEP validation cohort were identified as low-risk Class 1.[28] By incorporating additional data from 40-GEP testing into management decisions, clinicians can better adjust their management intensity based on risk. In a survey of 162 dermatologists, Litchman et al showed that a 40-GEP Class 1 result caused clinicians to substantially increase their avoidance of additional interventions while a Class 2B result led clinicians to choose a higher intensity management plan with increases in recommendations for sentinel lymph node biopsy, adjuvant radiation, adjuvant chemotherapy, and shorter follow-up intervals.*34* Hooper et al also conducted a clinical utility study by surveying 34 clinicians who ordered 10 or more 40-GEP tests in its first year of availability. Using 6 real-world cases spanning the spectrum of risk levels, they found that clinicians were overall well-aligned regarding the baseline risk levels and subsequent management changes based on 40-GEP results.[33] Farberg et al analyzed a cohort of 300 NCCN-defined high-risk cSCC patients and found that 40-GEP test results, after adjusting for AJCC8 or BWH tumor stage, were able to recommend low management intensity for 53.0% or 57.7% of patients, respectively.[14]

Statement 6: *The 40-GEP test should be considered for use on cSCC tumors with at least 1 high-risk feature per AJCC8 and/or BWH and/or NCCN guidelines. (SORT Level A)*

The validation study for the 40-GEP test consisted of a cohort of patients with at least 1 high-risk feature as defined by these staging systems and NCCN guidelines.[28] Additional studies demonstrating the test's accuracy and clinical validity also utilized similar inclusion criteria.[11,14] Therefore, the panel recommends considering the test for cSCC cases with at least 1 high-risk feature in order to maximize prognostic accuracy and utility.

Statement 7: *The 40-GEP test is not recommended to be used on cSCC in situ or invasive cSCC without high-risk features, or for patients that are not candidates for additional procedures or therapies. (SORT Level C)*

Similarly, the available literature does not support the use of the test for in situ cSCC or cSCC without high-risk features. Until further studies are completed on these tumors, the use of the test would result in unnecessary healthcare costs that outweigh the benefits of the results. Additionally, if a patient is not a candidate for additional procedures or therapies, the panel believes that there is limited value in the test's results, as it will not lead to an alteration in management.

CONCLUSION

cSCC is a growing health concern with a rapidly rising incidence and poor survivability in cases of metastatic disease.[1-5,8,9,11] Existing clinicopathologic staging systems have significant limitations in their ability to predict which patients will experience a metastasis, as only 14% to 17% of patients with AJCC8 T3/T4 tumors and 24% to 38% of patients with BWH T2b/T3 tumors develop one.[16,21,22] A more accurate method of assessing this risk is critical to reduce the morbidity and mortality associated with both cSCC and unnecessary interventions. This comprehensive review demonstrated that the 40-GEP test has been validated as an independent predictor of cSCC risk of metastasis beyond AJCC8 and BWH staging systems. Furthermore, when 40-GEP testing is used in conjunction with these systems, multiple studies have shown that more accurate prognostic assessment is possible.[11,14,28]These consensus recommendations put forth by the panel can help guide dermatology clinicians on appropriate test usage to make better risk-aligned management decisions, thereby ultimately improving patient outcomes.

DISCLOSURES

DZ and NB have participated in a research fellowship partially funded by Castle Biosciences. BB has served as a consultant for Castle Biosciences. RC, TAC, JQDR, LKF, and GG have no conflicts of interest. DS has served as a consultant to DermTech.

Funding: This study was funded in part by an unrestricted educational grant from Castle Biosciences.

REFERENCES

1. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: Incidence, risk factors, diagnosis, and staging. *J Am Acad Dermatol.* 2018;78(2):237-247. doi:10.1016/j.jaad.2017.08.059
2. Muzic JG, Schmitt AR, Wright AC, et al. Incidence and trends of basal cell carcinoma and cutaneous squamous cell carcinoma: a population-based study in Olmsted County, Minnesota, 2000 to 2010. *Mayo Clin Proc.* 2017;92(6):890-898. doi:10.1016/j.mayocp.2017.02.015
3. Waldman A, Schmults C. Cutaneous squamous cell carcinoma. *Hematol Oncol Clin North Am.* 2019;33(1):1-12. doi:10.1016/j.hoc.2018.08.001
4. Skin Cancer Foundation: Skin Cancer Facts & Statistics [Internet]. *The Skin Cancer Foundation.* Updated January 2023. Accessed April 1, 2023. https://www.skincancer.org/skin-cancer-information/skin-cancer-facts
5. Rogers HW, Weinstock MA, Feldman SR, et al. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. *JAMA Dermatol.* 2015;151(10):1081-1086. doi:10.1001/jamadermatol.2015.1187
6. Stratigos AJ, Garbe C, Dessinioti C, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 1. epidemiology, diagnostics and prevention. *Eur J Cancer.* 2020;128:60-82. doi:10.1016/j.ejca.2020.01.007
7. Brougham ND, Dennett ER, Cameron R, et al. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. J Surg Oncol. 2012;106(7):811-815. doi:10.1002/jso.23155
8. Dessinioti C, Pitoulias M, Stratigos AJ. Epidemiology of advanced cutaneous squamous cell carcinoma. *J Eur Acad Dermatol Venereol.* 2022;36(1):39-50. doi:10.1111/jdv.17709
9. Schmults CD, Karia PS, Carter JB, et al. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. *JAMA Dermatol.* 2013;149(5):541-547. doi:10.1001/jamadermatol.2013.2139
10. Brougham ND, Dennett ER, Cameron R, et al. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk factors. *J Surg Oncol.* 2012;106(7):811-815. doi:10.1002/jso.23155
11. Ibrahim SF, Kasprzak JM, Hall MA, et al. Enhanced metastatic risk assessment in cutaneous squamous cell carcinoma with the 40-gene expression profile test. *Future Oncol.* 2022;18(7):833-847. doi:10.2217/fon-2021-1277
12. Thompson AK, Kelley BF, Prokop LJ, et al. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. *JAMA Dermatol.* 2016;152(4):419-428. doi:10.1001/jamadermatol.2015.4994
13. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol.* 2013;68(6):957-966. doi:10.1016/j.jaad.2012.11.037
14. Farberg AS, Hall MA, Douglas L, et al. Integrating gene expression profiling into NCCN high-risk cutaneous squamous cell carcinoma management recommendations: impact on patient management. *Curr Med Res Opin.* 2020;36(8):1301-1307. doi:10.1080/03007995.2020.1763284
15. National Comprehensive Cancer Network: Squamous Cell Skin Cancer, NCCN Guidelines Version 1.2023, in NCCN Clinical Practice Guidelines in Oncology [Internet]. Published 2023. Accessed April 1, 2023. https://www.nccn.org/professionals/physician_gls/default.aspx#site
16. Ruiz ES, Karia PS, Besaw R, et al. Performance of the American Joint Committee on Cancer Staging Manual, 8th Edition vs the Brigham and Women's Hospital Tumor Classification System for Cutaneous Squamous Cell Carcinoma. *JAMA Dermatol.* 2019;155(7):819-825. doi:10.1001/jamadermatol.2019.0032
17. Karia PS, Jambusaria-Pahlajani A, Harrington DP, et al. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. *J Clin Oncol.* 2014;32(4):327-334. doi:10.1200/JCO.2012.48.5326
18. Gaudi S, Zarandona JM, Raab SS, et al. Discrepancies in dermatopathology diagnoses: the role of second review policies and dermatopathology fellowship training. *J Am Acad Dermatol.* 2013;68(1):119-128. doi:10.1016/j.jaad.2012.06.034
19. van Dijk MC, Aben KK, van Hees F, et al. Expert review remains important in the histopathological diagnosis of cutaneous melanocytic lesions. *Histopathology.* 2008;52(2):139-146. doi:10.1111/j.1365-2559.2007.02928.x
20. Shoo BA, Sagebiel RW, Kashani-Sabet M. Discordance in the histopathologic diagnosis of melanoma at a melanoma referral center. *J Am Acad Dermatol.* 2010;62(5):751-756. doi:10.1016/j.jaad.2009.09.043
21. Karia PS, Morgan FC, Califano JA, et al. Comparison of tumor classifications for cutaneous squamous cell carcinoma of the head and neck in the 7th vs 8th edition of the AJCC cancer staging manual. *JAMA Dermatol.* 2018;154(2):175-181. doi:10.1001/jamadermatol.2017.3960
22. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol.* 2013;149(4):402-410. doi:10.1001/jamadermatol.2013.2456
23. Jarell A, Gastman BR, Dillon LD, et al. Optimizing treatment approaches for patients with cutaneous melanoma by integrating clinical and pathologic features with the 31-gene expression profile test. *J Am Acad Dermatol.* 2022;87(6):1312-1320. doi:10.1016/j.jaad.2022.06.1202
24. Marchetti MA, Coit DG, Dusza SW, et al. Performance of gene expression profile tests for prognosis in patients with localized cutaneous melanoma: a systematic review and meta-analysis. *JAMA Dermatol.* 2020;156(9):953-962. doi:10.1001/jamadermatol.2020.1731
25. Clarke LE, Warf MB, Flake DD, 2nd, et al. Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma. *J Cutan Pathol.* 2015;42:244-52.
26. Gerami P, Yao Z, Polsky D, et al. Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma. *J Am Acad Dermatol.* 2017;76:114-20.e2.
27. Zakria D, Brownstone N, Rigel D. The Integrated 31-Gene Expression Profile (i31-GEP) Test for cutaneous melanoma outperforms a clinicopathologic-only nomogram at identifying patients who can forego sentinel lymph node biopsy. *SKIN The J Cutan Med.* 2020;6(6):463–473. doi:10.25251/skin.6.6.3
28. Wysong A, Newman JG, Covington KR, et al. Validation of a 40-gene expression profile test to predict metastatic risk in localized high-risk cutaneous squamous cell carcinoma [published correction appears in J Am Acad Dermatol. 2021 Jun;84(6):1796]. *J Am Acad Dermatol.* 2021;84(2):361-369. doi:10.1016/j.jaad.2020.04.088
29. Arron ST, Wysong A, Hall MA, et al. Gene expression profiling for metastatic risk in head and neck cutaneous squamous cell carcinoma. *Laryngoscope Investig Otolaryngol.* 2022;7(1):135-144. doi:10.1002/lio2.724
30. Arron ST, Blalock TW, Guenther JM, et al. Clinical considerations for integrating gene expression profiling into cutaneous squamous cell carcinoma management. *J Drugs Dermatol.* 2021;20(6):5s-s11. doi:10.36849/JDD.2021.6068
31. Au JH, Hooper PB, Fitzgerald AL, Somani AK. Clinical Utility of the 40-Gene Expression Profile (40-GEP) Test for improved patient management decisions and disease-related outcomes when combined with current clinicopathological risk factors for cutaneous squamous cell carcinoma (cSCC): case series. *Dermatol Ther (Heidelb).* 2022;12(2):591-597. doi:10.1007/s13555-021-00665-y
32. Borman S, Wilkinson J, Meldi-Sholl L, et al. Analytical validity of DecisionDx-SCC, a gene expression profile test to identify risk of metastasis in cutaneous squamous cell carcinoma (SCC) patients. *Diagn Pathol.* 2022;17(1):32. doi:10.1186/s13000-022-01211-w
33. Hooper PB, Farberg AS, Fitzgerald AL, et al. Real-world evidence shows clinicians appropriately use the prognostic 40-gene expression profile (40-gep) test for high-risk cutaneous squamous cell carcinoma (cscc) patients. *Cancer Invest.* 2022;40(10):911-922. doi:10.1080/07357907.2022.2116454
34. Litchman GH, Fitzgerald AL, Kurley SJ, et al. Impact of a prognostic 40-gene expression profiling test on clinical management decisions for high-risk cutaneous squamous cell carcinoma. *Curr Med Res Opin.* 2020;36(8):1295-1300. doi:10.1080/03007995.2020.1763283
35. Saleeby E, Bielinski K, Fitzgerald A, et al. A prospective, multi-center clinical utility study demonstrates that the 40-gene expression profile (40-gep) test impacts clinical management for medicare-eligible patients with high-risk cutaneous squamous cell carcinoma (cSCC). *SKIN The Journal of Cutaneous Medicine.* 2022;6(6): 482–496. https://doi.org/10.25251/skin.6.6.5
36. Rebeca T, Giselle P, Litchman GH, et al. Impact of Gene Expression Profile Testing on the Management of Squamous Cell Carcinoma by Dermatologists. *J Drugs Dermatol.* 2019;18(10):980-984.
37. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician.* 2004;69(3):548-556.

38. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Pract. Assess. Res. Eval.* 2007;12:1-8.
39. Berman B, Ceilley R, Cockerell C, et al. Appropriate use criteria for the integration of diagnostic and prognostic gene expression profile assays into the management of cutaneous malignant melanoma: an expert panel consensus-based modified delphi process assessment. *SKIN The J Cutan Med.* 2019;3(5):291–306. doi:10.25251/skin.3.5.1
40. Thiboutot DM, Dréno B, Abanmi A, et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2018;78(2 Suppl 1):S1-S23.e1. doi:10.1016/j.jaad.2017.09.078
41. Richard MA, BarnetcheT, Rouzaud M, et al. Evidence-based recommendations on the role of dermatologists in the diagnosis and management of psoriatic arthritis: systematic review and expert opinion. *J Eur Acad Dermatol Venereol.* 2014;28 Suppl 5:3-12. doi:10.1111/jdv.12560
42. Zakria D, Brownstone N, Berman B, et al. Incorporating prognostic gene expression profile assays into the management of cutaneous melanoma: an expert consensus panel report. S*KIN The J Cutan Med.* 2023;7(1):556–569. https://doi.org/10.25251/skin.7.1.1
43. Cañueto J, Cardeñoso-Álvarez E, Cosano-Quero A, et al. The expression of podoplanin is associated with poor outcomes in cutaneous squamous cell carcinoma. *J Cutan Pathol.* 2017;44(2):144-151. doi:10.1111/cup.12859
44. Chen MK, Cai MY, Luo RZ, et al. Overexpression of p300 correlates with poor prognosis in patients with cutaneous squamous cell carcinoma. *Br J Dermatol.* 2015;172(1):111-119. doi:10.1111/bjd.13226
45. Li YY, Hanna GJ, Laga AC, Haddad RI, Lorch JH, Hammerman PS. Genomic analysis of metastatic cutaneous squamous cell carcinoma. *Clin Cancer Res.* 2015;21(6):1447-1456. doi:10.1158/1078-0432.CCR-14-1773
46. Vinicius de LV, Scapulatempo C, Perpetuo NM, et al. Prognostic and risk factors in patients with locally advanced cutaneous squamous cell carcinoma of the trunk and extremities. *J Skin Cancer.* 2011;2011:420796. doi:10.1155/2011/420796
47. Xu R, Cai MY, Luo RZ, et al. The Expression Status and Prognostic Value of Cancer Stem Cell Biomarker CD133 in Cutaneous Squamous Cell Carcinoma. *JAMA Dermatol.* 2016;152(3):305-311. doi:10.1001/jamadermatol.2015.3781
48. Al-Rohil RN, Tarasen AJ, Carlson JA, et al. Evaluation of 122 advanced-stage cutaneous squamous cell carcinomas by comprehensive genomic profiling opens the door for new routes to targeted therapies. *Cancer.* 2016;122(2):249-257. doi:10.1002/cncr.29738
49. Campos MA, Macedo S, Fernandes MS, et al. Prognostic Significance of RAS Mutations and P53 Expression in Cutaneous Squamous Cell Carcinomas. *Genes (Basel).* 2020;11(7):751. Published 2020 Jul 6. doi:10.3390/genes11070751
50. Kitrell BM, Blue ED, Siller A Jr, et al. Gene Expression Profiles in Cutaneous Oncology. *Dermatol Clin.* 2023;41(1):89-99. doi:10.1016/j.det.2022.07.018
51. Newman JG, Hall MA, Kurley SJ, et al. Adjuvant therapy for high-risk cutaneous squamous cell carcinoma: 10-year review. *Head Neck.* 2021;43(9):2822-2843. doi:10.1002/hed.26767
52. Zilberg C, Lee MW, Yu B, et al. Analysis of clinically relevant somatic mutations in high-risk head and neck cutaneous squamous cell carcinoma. *Mod Pathol.* 2018;31(2):275-287. doi:10.1038/modpathol.2017.128

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