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Integrating Gene Expression Profiling into the Management of Cutaneous Squamous Cell Carcinoma

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INTRODUCTION Journal of Drugs in Dermatology

Bridging the Gap: Integrating Gene Expression Profiling into Clinical Practice

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Clinicians who treat patients with cutaneous squamous cell carcinoma (CSCC) face a unique set of management challenges. While the aim is to identify biologically aggressive tumors at earlier stages of progression and tumors that may be more advanced but pose lower than predicted risk, prognostication is not always accurate. Furthermore, even after careful clinical and histopathologic risk stratification, there remains significant variability in managing patients with high-risk CSCC. To address this challenge, experts are evaluating tools designed to improve risk stratification of these patients as discussed by the authors of this article.

Gene expression profile (GEP) testing has been shown, in combination with established clinical and histologic factors, to refine risk prediction for outcomes of interest for multiple diseases.[1] The recently developed and validated 40-GEP test for CSCC is the first clinically available GEP test used to predict the risk of nodal and distant metastasis and should only be considered for use in tumors with one or more high-risk factors.[2] The probability of nodal or distant CSCC metastasis varies based on established clinicopathologic risk factors, which current management algorithms use to provide recommendations appropriate for each individual patient. GEP testing for CSCC has the ability to provide clinicians with objective data from the primary tumor that can augment existing risk stratification, which could be an important and beneficial advance in patient care.

CSCC patients who ultimately experience poor outcomes have a variety of initial presentations and start their clinical journeys in diverse practice settings across the country. The clinician performing the initial biopsy may not be responsible for managing the advanced sequelae of that same lesion years after its diagnosis and primary treatment, and their initial assessment of patient risk may or may not be accurate. This article illustrates how collective decision making can help bridge existing gaps in current clinical guidelines to develop a plan of care for high-risk patients whose level of risk is unknown. The information gained from GEP testing provides more precise risk stratification and allows patients at highest risk of poor outcomes to be managed more aggressively and followed more closely. Because of the wide variety of risk-assessment approaches, treatment settings, and specialties involved in treating CSCC, it is unlikely that there will be a standardized approach to initiating GEP testing, but rather that a nuanced assessment of each patient's individual risk profile will be required to arrive at a decision. Furthermore, as the authors emphasize, GEP test results should be interpreted in the context of each patient's individual clinicopathologic risk factors to assess the appropriateness of nodal evaluation, the need for adjuvant radiation therapy, the frequency of follow-up intervals, and the level of required surveillance.

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Clinical Considerations for Integrating Gene Expression Profiling into Cutaneous Squamous Cell Carcinoma Management

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ABSTRACT

Gene expression profile (GEP) testing is now commercially available for metastatic risk prediction in patients with cutaneous squamous cell carcinoma (CSCC) and one or more high-risk factors. The purpose of this article is to provide an early framework for healthcare providers looking to integrate patient-specific tumor biology into their clinical practice using GEP testing. To develop a framework for clinical use, an expert panel was convened to identify CSCC management decision points where GEP testing may be immediately incorporated into practice until the definitive results of prospective trials become available. Based on their discussion, the expert panel focused on the areas of nodal evaluation, adjuvant radiation therapy, and follow-up and surveillance. The panel emphasized that GEP prognostic test results should not currently be used as a surrogate for standard of care treatment but as an additional data point when determining individualized management for patients with high-risk CSCC. Whenever possible, decisions on management plans for these patients should be developed with multidisciplinary input.

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INTRODUCTION

As the population of the United States continues to grow and age, the number of patients being diagnosed with nonmelanoma skin cancer (NMSC) is also changing. From 2006 to 2012, the annual incidence of NMSC increased by 35% with an estimated 710,000 people diagnosed with cutaneous squamous cell carcinoma (CSCC).[1] While the majority of CSCCs are curable with surgery, there is a subset of patients with tumors that have aggressive growth characteristics associated with a higher probability of metastasis, recurrence, or disease-specific death (ie, high-risk CSCC).[2,3] As the overall incidence of CSCC increases, it is likely that the incidence of these high-risk tumors will also increase, adding to the burden on patients, clinicians, and the healthcare system. Ideally, the goal is to identify patients with high-risk CSCC early and create personalized management plans that will reduce the risk of CSCC-related outcomes.

CSCC management plans are often based on using clinicopathologic staging and treatment guidelines to stratify patients by risk. However, CSCC is a heterogeneous disease and tumors in the same staging category may behave differently based on variations in tumor biology. The reported rates of

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metastasis can also differ depending on the study population, patient demographics, and practice setting. In addition, the predictive accuracy of staging systems in CSCC can vary; for instance, the positive predictive values for nodal metastasis using the American Joint Committee on Cancer (AJCC) Cancer Staging Manual and Brigham and Women's Hospital (BWH) staging system range from 14–17% and 24–38%, respectively.[4-7] These complexities make it difficult to know which treatment to select at which decision point for patients with high-risk CSCC.

Gene expression profile (GEP) testing can provide information about the biological characteristics of an individual patient's tumor beyond standard clinicopathologic risk factors. GEP tests have been used successfully in the clinical management of other cancer types (eg, breast, prostate, and melanoma) to identify tumors with high-risk characteristics and help guide prognosis and treatment options.[8-11] Recently, a prognostic GEP assay (the 40-GEP test) was developed for predicting the risk of metastasis in localized high-risk CSCC.[12] While it is premature to make definitive recommendations about CSCC management based on GEP test results, GEP testing has been validated to predict metastasis. By providing a clearer picture of a tumor's metastatic risk potential, the 40-GEP test result has the ability to inform risk-appropriate management decisions within established guidelines. GEP test results can be used to identify patients with biologically low-risk tumors who could be considered for de-escalation of treatment and surveillance. Conversely, GEP test results can also be used to identify patients with biologically high-risk tumors who may benefit from more intense treatment options.

One complexity associated with GEP testing for CSCC is identifying the optimal time frame for testing in order to have the greatest impact on treatment decisions. In addition, each specialist has a particular role in CSCC treatment with unique knowledge gaps and would prefer to have GEP test results prior to management decision points. For example, in surgical management decisions, the primary diagnosing provider would benefit from testing prior to referral to the surgeon while the surgeon would need to test prior to planning work-up and definitive management. For decisions on nodal evaluation and adjuvant therapy, GEP testing may help the primary diagnosing provider identify patients who may benefit from referral to the radiation/medical oncologist, while the radiation/medical oncologist may test as part of the treatment decision process. To maximize the utility of the GEP test, the test result needs to be available to the provider at the time in the patient's management plan when clinical decisions are being made. For this reason, it is recommended that GEP testing be pursued at the earliest point in high-risk CSCC management where the results will influence clinical decision making.

The purpose of this article is to provide an early framework for healthcare providers looking to integrate a GEP assay for CSCC into their clinical practice. Based on current risk data, it summarizes the clinical considerations identified by an expert panel reviewing the use of the 40-GEP test in the context of clinical management of high-risk CSCC.

METHODS

Panel Review

The panel consisted of Mohs surgeons, surgical oncologists, and a radiation oncologist from academic medical centers and community practices. Information on current clinical practice and considerations for including GEP testing when managing patients with high-risk CSCC was collected via structured one-on-one interviews and panel discussions. The panel reviewed existing clinicopathologic staging and treatment guidelines (eg, American Academy of Dermatology (AAD),[13] American College of Radiology (ACR),[14] AJCC,[15] American Society for Radiation Oncology (ASTRO),[16] BWH,[6] Mohs Appropriate Use Criteria (AUC),[17] and National Comprehensive Cancer Network (NCCN)[18]), and published expert recommendations and studies (Baum et al,[19] Farberg et al,[20] Ruiz et al,[21] Que et al,[22] Skulsky et al,[23] and Thompson et al[24]). The panel then discussed experiences, rationales, and scenarios where information from GEP testing may be helpful for CSCC treatment decisions. Note: The panel referenced Version 2.2020 of the NCCN Guidelines for squamous cell carcinoma; Version 1.2021 was released after the panel discussion.

GEP Assay

Data from the 40-GEP test (DecisionDx-SCC; Castle Biosciences, Inc.) was used as the reference for CSCC GEP testing recommendations; this assay is, currently, the only GEP test commercially available for CSCC healthcare providers.[12] The 40-GEP test separates CSCCs by risk of metastasis into low (Class 1), moderate (Class 2A), or high (Class 2B) categories (Figure 1). The assay was developed and validated with samples from patients with one or more high-risk factors (Table 1) and has been shown to have utility in scenarios classified as high-risk by existing guidelines.[6,15,17,18] Treatment modality thresholds including test results were synthesized based on overlaps between existing recommendations and 40-GEP data.

CLINICAL CONSIDERATIONS

For this article, the panel focused on decision-making points

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FIGURE 1. Metastasis-free survival rates for patients with Class 1, Class 2A, and Class 2B test results from the 40-GEP test validation study.
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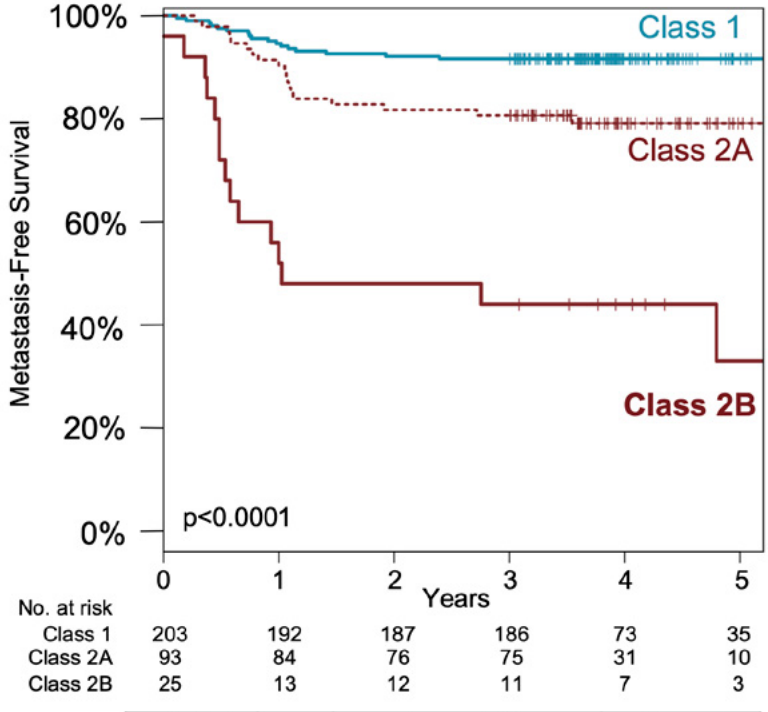

40-GEP Class	n	3-year MFS (95% CI)	Overall Event Rate
Class 1	203	91.6% (87.9-95.5%)	8.9%
Class 2A	93	80.6% (73.0-89.1%)	20.4%
Class 2B	25	44.0% (28.3-68.5%)	60%

TABLE 1.

High-Risk Factors Used to Identify Patients Who Qualified for 40-GEP Testing	
Patient History and Clinical Characteristics	**Surgical and Pathological Findings**
Tumor ≥2 cm anywhere on body[a,c,d]	Perineural involvement • Large (≥0.1 mm) or named nerve involvement[b,c] • Small (<0.1 mm) in caliber[a,d]
Tumor located on the head, neck, hands, genitals, feet or pretibial surface (Areas H[a,d] or M[a,d])	Poorly differentiated tumor histology[a,b,c,d]
Tumor at site of prior radiation therapy or chronic inflammation[a,d]	Tumor depth • Invasion beyond subcutaneous fat[a,b,c,d] • Breslow depth >2[a] or 6 mm[b,d] • Clark level ≥IV[a]
Rapidly growing tumor[d]	Aggressive histologic subtype[a,d]
Tumor with poorly defined borders[d]	Lymphovascular invasion[a,d]
Neurologic symptoms in region of tumor[d]	--
Immunosuppression[a*,d]	--

Guidelines referenced include the AAD/ACMS/ASDSA/ASMS 2012 Appropriate use criteria for Mohs micrographic surgery,[a] the AJCC Staging Manual, 8th Edition,[b] the BWH Tumor Classification System for CSCC,[c] and the NCCN Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer Ver 2.2020.[d]
*Except Area L primary nonaggressive <11 mm and keratoacanthoma-type <6 mm.

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TABLE 2.

GEP Test Results That May Impact Decisions for Baseline Radiologic Imaging or Sentinel Lymph Node Biopsy		
Decision Point	**Staging**	**GEP Test Result**
Baseline radiologic imaging of the draining nodal basin	BWH T2b/T3[a]	Class 2A[a] Class 2B[b]
Sentinel lymph node biopsy[c]	BWH T2b/T3[a]	Class 2B[b]

Reported risk of metastasis from Wysong et al was ≃20%[a] and >50%.[b]
[c]Dependent on trials investigating utility

where information from GEP testing might inform the clinical management of patients with high-risk CSCC. These areas included nodal evaluation, adjuvant radiation therapy (ART), and follow-up and surveillance. Information on using GEP test results to inform the use of systemic therapy and immunotherapy is outside the scope of this article as these treatments are currently reserved for patients with established metastatic disease.

Nodal Evaluation: Imaging and Sentinel Lymph Node Biopsy

One decision-making point in CSCC management is whether to examine local or regional lymph nodes further for evidence of metastasis and, if further evaluation is needed, what technique to use. For nodal evaluation, the panel considered whether GEP test results could help inform decisions on the utility of baseline radiologic or ultrasound imaging of the nodal basin or sentinel lymph node biopsy (SLNB) in CSCC management plans. Existing recommendations propose using baseline radiologic imaging (computed tomography/positron emission tomography) for nodal staging in patients with BWH T2b/T3 CSCC where the risk of metastasis is >20% (Table 2).[13,22] Multivariate analyses of Class 2A GEP test results and BWH T2b/T3 staging have demonstrated similar levels of metastatic risk. In addition, Class 2A and Class 2B GEP test results are associated with a 20% and >50% risk of a metastasis, respectively.[12] Clinicians may consider using radiologic imaging to examine regional lymph nodes and distant organs for metastasis in patients with a Class 2A or Class 2B GEP test result.

With respect to baseline imaging with ultrasonography or SLNB for nodal evaluation, there is currently not enough data available to make definitive recommendations. There is limited data on the utility of baseline ultrasonography since this modality is currently not part of standard clinical practice in the United States.[22] Studies examining the impact of SLNB on patient outcomes have been limited by retrospective design, sample size, and study populations with mixtures of risk factors.[18] However, there is thought that SLNB and pathologic nodal staging may be underutilized in high-risk CSCC.[25] Existing recommendations propose that patients with AJCC T4 or BWH T2b/T3 CSCC could be considered for nodal evaluation using baseline ultrasonography or SLNB but emphasize that clinical trials are needed to assess utility before including either modality in standard clinical practice.[18,22] In the absence of sufficient data to support BWH

TABLE 3.

GEP Test Results That May Impact Decisions on Follow-Up and Surveillance Intensity During the First Two Years after Diagnosis		
Decision Point	**Staging**	**GEP Test Result**
Clinical follow-up	<20% metastatic risk	Class 1[a]
Clinical follow-up + Nodal ultrasound/CT scan 1X/year	20% to <50% metastatic risk	Class 2A[b] Class 2B[c]
Clinical follow-up + Nodal ultrasound/CT scan 2X/year	>50% metastatic risk	Class 2B[c]

Reported risk of metastasis from Wysong et al was <7%,[a] ≃20%,[b] and >50%.[c]

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or AJCC stage as a sole determinant to guide the use of baseline ultrasonography or SLNB, a 40-GEP Class 2A or 2B result may provide additional evidence that a CSCC tumor has a high risk for metastasis.

Adjuvant Radiation Therapy

Another CSCC management decision-making point is whether or not to use ART for treatment. Using ART for cancer treatment involves balancing the potential to provide local cure against the potential to cause harm and illustrates an unmet need for personalized medicine in CSCC management. Knowledge of an individual tumor's biological potential could help with patient selection, allowing clinicians to reserve ART for patients with the greatest risk for metastasis and reduce the risk of overtreatment for a majority of patients. Existing guidelines recommend ART for any CSCC with AJCC T4 staging, extensive perineural involvement, positive tissue margins after definitive surgery, or after therapeutic lymphadenectomy in patients whose CSCC has metastasized to regional lymph nodes.[14,16,18] While randomized trials are lacking in this setting, several retrospective studies indicate that ART significantly reduced the risk of local recurrence.[26-28] However, the absolute benefit of ART depends on the risk of recurrence, which is difficult to quantify in many cases.

Importantly, the 40-GEP test was developed to specifically predict nodal or distant metastasis and may not apply to ART directly, which, historically, has focused on reducing loco-regional recurrence. However, there may be potential applications of the 40-GEP test in informing decision making about the use of ART. Tumors with BWH T2b/T3 or AJCC T3/T4 staging and a Class 2A GEP result were 4.6 to 5.8 times more likely to metastasize with a 35% risk of metastasis. Tumors with a Class 2B GEP result had an even higher risk of metastasis (≥50%) and were 15 times more likely to metastasize.[12] Patients with these 40-GEP test results could be considered for referral to a radiation oncologist for a multidisciplinary discussion. Conversely, radiation oncologists may reconsider the use of ART in patients with BWH T2b/T3 disease with a Class 1 GEP test result as their recurrence rates are low and the morbidities of treatment may outweigh the benefits.

Follow-up and Surveillance

With 75% of CSCC recurrences occurring within two years of the initial diagnosis, follow-up and surveillance are a critical part of the CSCC management plan.[3] Overall, the frequency of clinical follow-up should align with patient risk. Current recommendations propose that follow-up intervals be based on tumor risk classification with patients with high-risk CSCC receiving more extensive follow-up (Table 3).[19,20,22] The risk thresholds for metastasis from these recommendations align with 40-GEP test results. Clinicians may consider annual radiologic or ultrasound nodal surveillance with more frequent clinic visits for patients with a Class 2A GEP test result. For patients with a Class 2B GEP test result, clinicians may consider biannual radiologic/ultrasound surveillance with more frequent clinical visits. Patients with a Class 1 GEP test result may not require radiologic/ultrasound nodal surveillance.

SUMMARY

In this article, an expert panel has presented and reviewed situations where information from GEP testing could aid decision making in CSCC management. GEP testing has the potential to improve current high-risk CSCC assessment practices and allow clinicians to provide personalized care for patients. Further insight into tumor characteristics could help avoid unnecessary treatment and surveillance (eg, overtreatment with ART, radiologic surveillance in low-risk tumors) while allowing healthcare providers to add management modalities or increase treatment intensity or follow-up as needed. The additional information that can be gained from GEP testing could also be used to inform if and when to refer a patient for medical, surgical, or radiation oncology. There is also the potential in the future that GEP test results could be used to determine whether to consider SLNB or enroll a patient in an adjuvant immunotherapy clinical trial; however, additional studies are needed.

DISCLOSURES

S. Arron is employed by Rakuten Medical and is a consultant for Castle Biosciences and Enspectra Health. T. Blalock is the principal investigator on a research study funded by Castle Biosciences. J.M. Guenther is on the speaker bureau for Castle Biosciences. D. Hyams is on the speaker bureau for Castle Biosciences. S. Ibrahim has received advisor fees from Castle Biosciences, Regeneron Pharmaceuticals, and Sun Pharmaceutical Industries, research funding from Castle Biosciences, Galderma, and Regeneron Pharmaceuticals, and speaker fees from Castle Biosciences, Galderma, Genentech, Regeneron Pharmaceuticals, and Sun Pharmaceutical Industries. S. Koyfman has received research support from Merck and Bristol Myers Squibb, an honorarium from UpToDate, and is on advisory boards for Merck and Regeneron Pharmaceuticals. A. Wysong is a board member for the American College of Mohs Surgery, Women's Dermatologic Society, and Dermatology Foundation and is the principal investigator on an institutional research grant from Castle Biosciences.

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