SKIN

ORIGINAL RESEARCH

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)

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ABSTRACT

The incidence and mortality rates of cutaneous squamous cell carcinoma (cSCC) in the Medicare population are rapidly increasing. The current national guidelines are broad and the available staging systems for stratification are inadequate to accurately guide patient management. A prognostic 40-gene expression profile (40-GEP) test has demonstrated both analytical and clinical validity for assessment of metastatic risk of high-risk cSCC patients independent of traditional clinicopathologic factors. Real-world data have shown that clinicians can identify appropriate patients for 40-GEP testing and use this personalized, molecular risk stratification tool to guide risk-aligned clinical planning and patient management. The data herein focuses on 59 Medicare-eligible patients (≥65 years of age) enrolled within a multicenter, prospective Clinical Utility and Health Outcomes Study (UTILISE) conducted to demonstrate patterns of 40-GEP test utilization, distribution of results across clinicopathologic variables, and impact on clinician recommendations for clinical management of high-risk cSCC patients. Regarding management of patients under-study, more than 80% of clinicians reported that the 40-GEP had a positive impact and 42% stated a 40-GEP test result was the single most influential factor in determining management plans. Overall, 24% of clinicians made changes to their treatment plan after receiving the 40-GEP result- a clinical actionability rate comparable to those of currently covered molecular tests for cancer patients. This analysis demonstrates the positive impact the 40-GEP is having on clinicians' assessment of risk for their high-risk cSCC patients, which, in line with guidelines, is driving risk-aligned changes in treatment plans.

INTRODUCTION

The most common cancer in the United States is non-melanoma skin cancer (NMSC). It has been reported to have a steadily increasing incidence, in part due to enhanced detection methods and an aging population.[1–6] Cutaneous squamous cell carcinoma (cSCC) has recently been noted to account for up to half of NMSCs with estimates of 1.8 million new cases per year.[2]

Studies have also calculated not only a significant increase cSCC in the general population, but an even more dramatic increase in the Medicare population.[4, 7] Approximately 6% of cSCC patients will develop regional or distant metastatic lesions,[3, 5, 8–12] after which prognosis is usually poor, with 5-year survival rates ranging from 26-34% and 10-year survival rates of 16%.[13] The total number of deaths resulting from cSCC are estimated to be equal to or greater than those attributed to melanoma, due to the large number of cSCC diagnoses every year, and account for the majority of NMSC-related deaths.[4, 5, 14, 15]

Risk stratification and staging systems for cSCC are based on clinical and pathological features and include the National Comprehensive Cancer Network (NCCN) guidelines criteria, the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th Edition, AJCC8), and the Brigham and Women's Hospital (BWH) tumor classification system.[3, 16–20] These systems are limited in their ability to predict adverse events (i.e. have low positive predictive value [PPV] for metastasis)[18–22] and thus pose a challenge for implementing risk-directed patient management. PPV is low for both the NCCN and AJCC systems (14%–17%),[17–20, 22] and slightly higher for BWH (24%-38%), meaning that many patients categorized as high risk do not develop advanced disease.[16, 23] Data concerning cSCC is not collected in national cancer registries, contributing to the limitations of the efforts of staging systems at prognostication and making knowledge of costs associated with procedures utilized for this population scarce. One study did analyze 999 cSCC patients collected from Truven MarketScan® claims databases from 2012-2016 who had at least one lymph node dissection, ≥1 chemotherapy with radiation therapy in ≥2 treatment fields, or a metastasis.[24] With an average follow-up time of 16 months, the average total costs were $18,409.05 per-patient-per-month (PPPM) and average cSCC-specific costs were $7,385.82 PPPM. The authors compared these costs to that of metastatic melanoma, which was reported to have a total cost of $12,111 PPPM in 2013. Equally important, due to the lack of standardized care for high-risk cSCC patients, improved risk stratification methods would reduce unnecessary procedures for a patient population that is often elderly and at higher risk for complications. Given the discordance between staging systems and the generalization of treatment guidelines, [21, 22, 25, 26] there has been a clinical unmet need requiring better methods to identify truly high-risk lesions with regard to outcomes, particularly molecular biomarkers that can be objectively evaluated.

Gene expression profile (GEP) signatures have been shown to have powerful, independent, risk-stratification (aka prognostic) value for many tumor types, such as cutaneous melanoma, uveal melanoma, breast, prostate and others, improving risk-stratification treatment plan decisions by complementing staging based on clinicopathologic factors and have shown a significant impact on clinical management.[27–31] In these diseases, GEP signatures help improve risk estimates, independent of or in combination with traditional clinical staging, and are impactful in determining management strategies within established clinical guidelines. Consistent with this clinical actionability, many GEP signatures are now standard of care in oncology and covered by national insurance providers, including Medicare. A 40-gene expression profile (40-GEP) test has been validated to improve metastasis risk prediction in high-risk cSCC patients (high risk cSCC is defined as patients diagnosed with invasive cSCC

and the presence of one or more clinicopathologic risk factors) using archival, formalin-fixed paraffin-embedded (FFPE) primary cSCC tissue.[32] This test stratifies clinicopathologically-confirmed high-risk cSCC tumors into three risk groups based on low (Class 1), moderate (Class 2A), and high (Class 2B) risk for regional or distant metastasis at 3 years after diagnosis.[32] A substantially higher PPV (60.0%) was found for the 40-GEP test for Class 2B relative to that found for the AJCC8 and BWH staging systems, while maintaining a negative predictive value (NPV) of approximately 90.0% (which is similar to that of the AJCC8 and BWH systems).[32] Further, several studies have demonstrated that use of the 40-GEP test results impacted management decisions in a clinically and statistically significant and risk-appropriate manner for high-risk cSCC patient scenarios.[33–36]

The overarching goal of this ongoing, multicenter, prospective Clinical Utility and Health Outcomes Study (UTILISE) is to demonstrate patterns of test utilization, the distribution of results across clinicopathologic variables, and the impact on clinician recommendations for clinical management of high-risk cSCC patients. This analysis focuses on the Medicare-eligible, clinically tested population to evaluate the utility of 40-GEP results on clinician recommendations regarding therapeutic management for their high-risk cSCC patients.

METHODS

To evaluate the utility of the 40-GEP in the Medicare-eligible, clinically tested population (≥65 years old), patient clinicopathologic factors, 40-GEP test results and changes in clinical management were recorded and analyzed in a prospective, multi-center clinical study (Clinical Utility and Health Outcomes Study [UTILISE]). The study cohort consisted of patients diagnosed with a primary cSCC who qualified for 40-GEP testing and elected to be part of the clinical care plan. Institutional Review Board approval was obtained at each institution and all patients were required to meet study inclusion criteria as listed in Table 1 along with having a signed informed consent secured.

The study consisted of two sequential phases: the Lead-in Phase and the Clinical Utility Phase (Figure 1). The Lead-in Phase opened to enrollment of patients on August 31, 2021. During the Lead-in Phase, clinicians recorded a treatment plan assessment before receiving the 40-GEP test results for at least five patients. Details of patient demographics, clinicopathological features, disease management and outcomes were collected via a review of medical records and entered into an electronic Case Report Form. After completion of the treatment plan assessment for these five patients, clinicians were then able to enroll new patients into the Clinical Utility Phase.

The ongoing Clinical Utility Phase began enrolling patients on November 24, 2021. Data collection for the Clinical Utility Phase was identical to the Lead-in Phase with the addition of a second treatment assessment plan to be completed after receipt of the 40-GEP results (i.e., post-test). Patient management decisions and outcomes were reported as described above. Patients were either enrolled in the Lead-in Phase or the Clinical Utility Phase, but not both.

Statistical Analysis

Wilcoxon signed rank tests with continuity correction were used to compare pre- and post-40-GEP test treatment impact changes

Table 1. Patient eligibility criteria for UTILISE

Inclusion Criteria	Exclusion Criteria
Patient is willing and able to provide informed consent.	Direct employees and family members of an Investigator
Newly diagnosed cSCC with no more than six months before patient consent, with pathologically confirmed invasive cSCC for whom the clinician has determined the 40-GEP to be clinically appropriate (as previously described[36]) and will order the 40-GEP test as part of their clinical care	Patient whose primary cSCC tumor is not considered invasive (e.g., Bowens disease) or not pathologically confirmed as invasive cSCC
Patient must be ≥18 years of age at time of diagnosis of the tumor under study.	Patient who does not meet the guidelines for testing with 40-GEP[36] or is enrolled in another Castle Biosciences Inc. study.
Patient must likely follow up with enrolling clinicians for three years, or enrolling clinicians must have access to relevant medical records from other medical providers.	Patient who is in the Investigator's opinion, unlikely to survive the three-year study duration in the absence of cSCC.

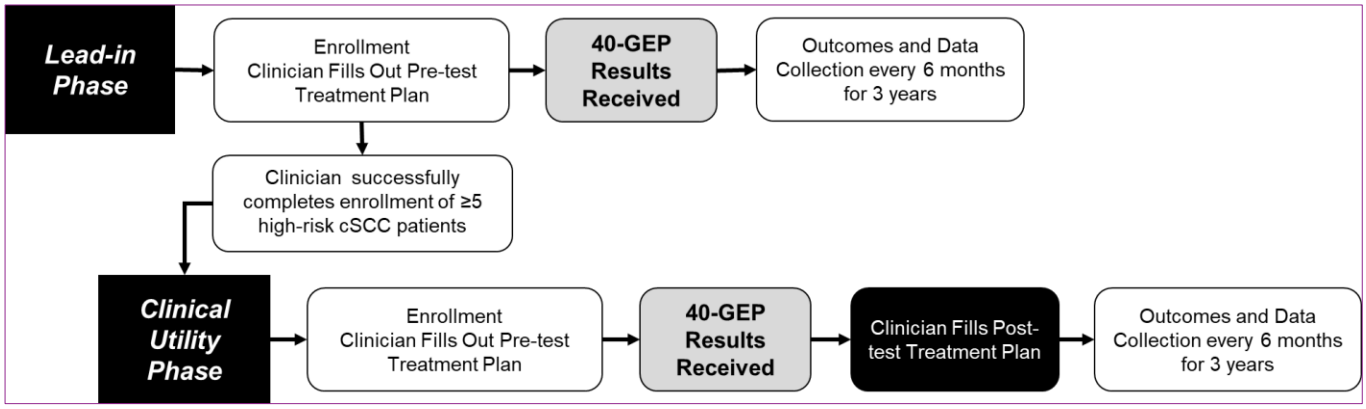

Figure 1. Study schematic of UTILISE (the Clinical Utility and Health Outcomes Study of the prognostic 40-GEP test)

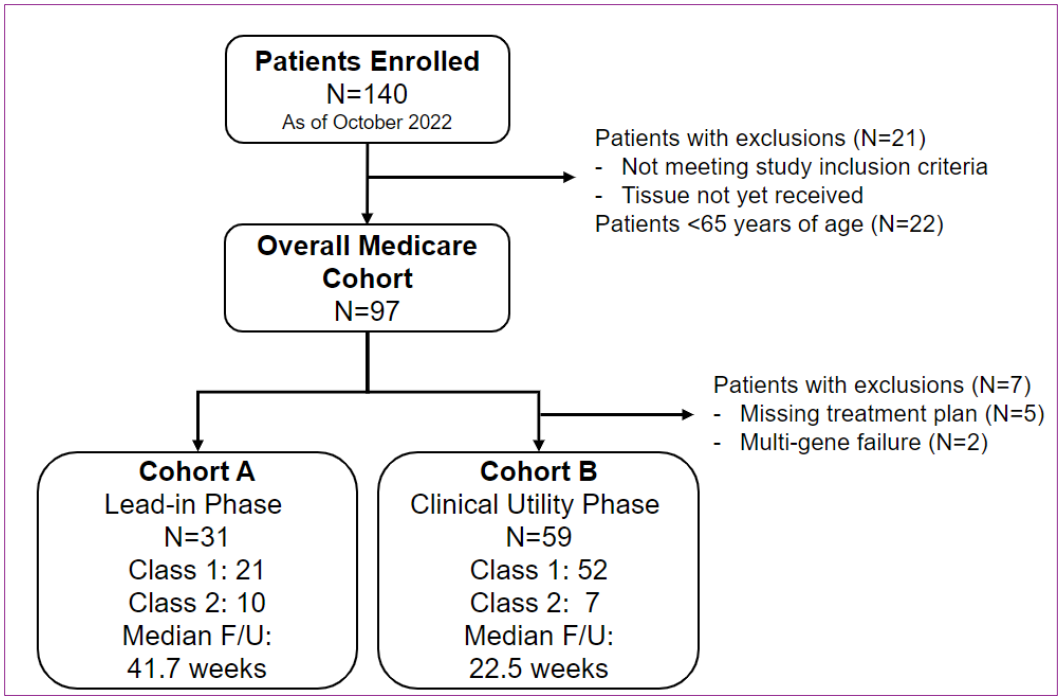

Figure 2. Consort diagram for enrollment of Medicare-eligible patients

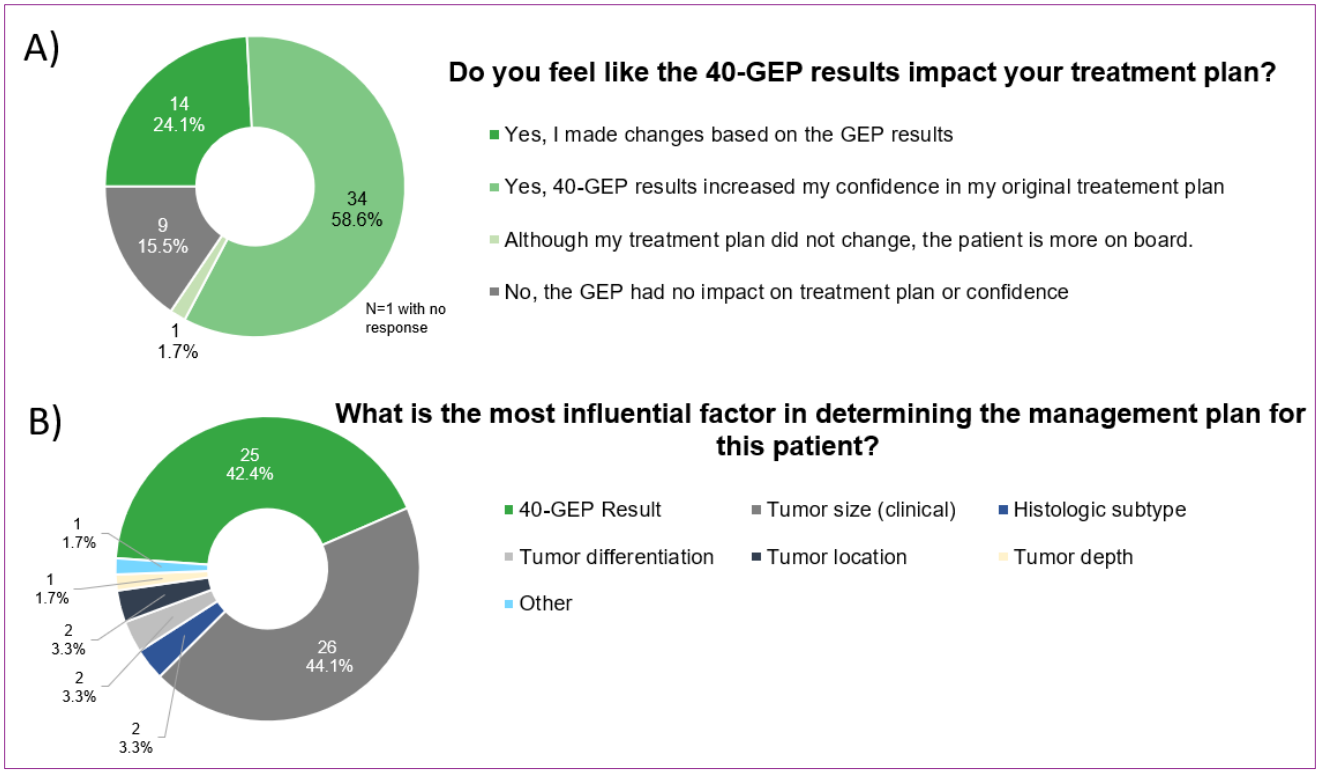

Figure 3. Do 24% of clinicians made changes in patient management due to 40-GEP testing and 42% reported 40-GEP results as the most influential factor in determining the management plan for their patient

Table 2. Patient demographics of clinical utility cohort of Medicare-eligible patients

Feature	Clinical Utility Cohort, n (%)
Medicare-eligible patients	59 (100)
Age: Average years (range)	78.2 (65-90)*
Male	38 (64.4)
Location on Head or Neck	43 (72.9)
Patient immunosuppressed	2 (3.4)
Neurologic symptoms at tumor site	1 (1.7)
Chronic inflammation at tumor site	2 (3.4)
Tumor diameter ≥2cm	21 (35.6)
Rapidly growing tumor	6 (10.2)
Poorly defined borders	10 (17.2)
Poor differentiation	1 (1.7)
Depth of Invasion**	
Beyond subcutaneous fat	1 (1.7)
Clark level IV or V	18 (30.5)
Breslow's Thickness ≥2mm	3 (5.1)
Lymphovascular invasion	1 (1.7)
Perineural invasion	2 (3.4)
40-GEP Result	
Class 1	52 (88.1)
Class 2A	7 (11.9)
Class 2B#	---

*To maintain confidentiality, any age >90 was reported as 90
**Investigators were allowed to report depth of invasion using various options
No Class 2B test results were observed at the time of analysis

with alpha set at 0.05. All data analysis was performed using open-access packages running in R (v4.1.2).

RESULTS

Five clinical sites and eleven unique clinicians have enrolled patients qualifying for inclusion in the current analyses. Eight (72%) clinicians were board certified dermatologists (with an average/median practice time of 21.6 years) of which seven identified as Mohs surgeons, and three were dermatology-based physician assistants who had been practicing in dermatology for an average of 3.3 years. At the time of this current analysis (October 2022), 140 patients were enrolled in the study and had received their GEP test result (Figure 2). Twenty-one patients were excluded due to insufficient tissue for testing or other technical issue, patient withdrawal due to relocation, or post-enrollment site review indicating failure to qualify. The focal population for current analysis is the Medicare population, therefore patients <65 years of age were also excluded (n=22), leaving 97 patients for potential analysis. These 97 patients were inclusive of n=31 patients enrolled in the Lead-in Phase and n=59 patients in the Clinical Utility Phase. To note, five patients in the latter cohort had been excluded for further analysis due to incomplete treatment assessment forms and two patients due to a multi-gene failure received from analysis of their tumor biopsy tissue.

Lead-in Cohort

Completion of the Lead-in Phase ensured that the site/clinicians were familiar and comfortable with use of the 40-GEP test and data entry before moving to the Clinical Utility Phase. At the time of analysis, the Lead-in cohort included 31 Medicare-eligible patients with the average age being 76.4 years old (±7.3). The median follow-up time for these patients was 41.7 weeks. 81% of the patients in this cohort had ≥2 risk factors (mean=2.5) with location on the head or neck (71%), depth of invasion (Clark level ≥IV, 71%), and tumor diameter ≥2cm (36%) being the three most observed clinicopathologic high-risk factors. 90.3% of this cohort underwent Mohs micrographic surgery (MMS) as their definitive surgery. This high-risk cSCC cohort was comprised of 68% 40-GEP Class 1, 25% Class 2A, and 6% Class 2B cases. At the time of analysis, the one patient who had regional metastasis after definitive surgery had received a Class 2A result. Based on 40-GEP class results and clinicopathologic risk factor distribution, participating clinicians received ample experience with prognostic molecular testing for individual patients.

Clinical Utility Cohort

The Clinical Utility cohort analyzed in this study included 59 Medicare-eligible patients with the average age being 78.2 years old (±7.9) (Table 2). The median follow-up timeframe for these patients was 22.5 weeks. 40-GEP tests were ordered by the treating clinicians for patients diagnosed with cutaneous squamous cell carcinoma (SCC) with one or more risk factors. 39.7% of the patients had 1 risk factor, 37.9% had 2 risk factors, and the remaining had more than 2 risk factors. Location on the head or neck (73%), tumor diameter ≥2cm (36%), and depth of invasion (Clark level ≥IV, 31%) were the three most common clinicopathologic high-risk factors observed. 96.6% of this cohort underwent MMS as their definitive treatment. This high-risk cSCC cohort was comprised of 88% 40-GEP Class 1 and 12% Class 2A cases.

Notably, 82.7% of clinicians reported a valuable impact to their patient management

when incorporating 40-GEP results (chi-square statistic=15.6; p-value<0.001) (Figure 3A); wherein 58.6% and 24.1% gained an increased confidence in and made changes to their original treatment plan, respectively. When analyzing these data by 40-GEP class result, 64.7% of clinicians reported increased confidence in their pre-test treatment plan and 17.6% reported a direct impact on treatment decisions for their patients receiving a Class 1 result. For clinicians whose patients received a Class 2A result, 14.3% reported increased confidence in their pre-test treatment plan and 71.4% reported a direct impact on treatment plans. Positive changes in patient attitude after receiving a 40-GEP Class 2A test result were also reported (14.3%). To further support the reported changes in management, 42.4% of clinicians noted a 40-GEP test result as the most influential factor in guiding the management of their patient (Figure 3B).

This cohort was used to evaluate 40-GEP-driven effects on treatment action plans and perception of risk by comparing clinician answers between the pre- and post-GEP treatment assessment forms. Based on the low-risk Class 1 results, clinician perception of metastatic likelihood decreased in a risk-aligned manner for 25.5% of patients (Table 3). In contrast, clinician perception of metastasis risk likelihood increased for 71.4% of patients that received a Class 2A result for an overall change in perception of metastatic likelihood of 31.0% (p<0.001). All changes to perception of risk for development of nodal or distant metastasis were aligned with 40-GEP class result. Overall, there was a statistically significant and clinically impactful change in intensity of management as a consequence of 40-GEP testing (22.4%, p=0.003). The intensity of management was decreased for 15.7% patients from moderate to low intensity due to a Class 1 test result. Class 2A results increased the pre- to post-test management from low to moderate intensity or from moderate to high for a total of 57.1% of patients (Table 3).

DISCUSSION

Management decisions for patients with cSCC are determined by the clinician's evaluation of the risk of disease progression. This evaluation can be challenging for implementing risk-appropriate high-risk cSCC patient management and lead to variability in outcomes due to the limitations of clinical and pathologic based risk-assessment and staging systems in predicting poor outcomes, coupled with the broad range of treatment options outlined in guidelines. The 40-GEP was developed as an objective, personalized, molecular test to better identify patients at risk for regional/nodal or distant metastasis, such that they receive more accurate risk-aligned treatment plans. The 40-GEP has proven to provide improved stratification independent of traditional clinicopathologic risk factors and staging systems.[32, 37]

The clinically tested population analyzed in this manuscript is focused on the Medicare-eligible population primarily because the majority of cSCC patients with high-risk clinicopathologic risk factors are older than 65 years of age with a majority of their cSCCs occurring on the head and neck, both are factors that elevate the morbidity arising from adjuvant treatments. Thus, as an objective, molecular test that better predicts poor outcomes for high-risk cSCC compared to clinicopathologically based risk-assessment or staging systems, use of the 40-GEP should efficiently reduce unnecessary interventions, improve identification of patients who may benefit from these interventions and have an overall

Table 3. Clinicians' perception of metastasis likelihood and overall management intensity changes with 40-GEP results in pre- and post-test comparison

Clinician perception of risk: What is the patient's risk of developing nodal or distant metastasis?							
40-GEP Class 1				**40-GEP Class 2A**			
Pre-GEP	Post-GEP	n	% of Class 1*	Pre-GEP	Post-GEP	n	% of Class 2A
<5%	<5%	37	72.5%	<5%	10-30%	3	42.8%
5-10%	<5%	12	23.5%	5-10%	5-10%	2	28.6%
5-10%	5-10%	1	2.0%	5-10%	10-30%	2	28.6%
10-30%	<5%	1	2.0%				
GEP-driven change:		**13**	**25.5%**	**GEP-driven change:**		**5**	**71.4%**
Overall GEP-driven change in risk perception 18/58 = 31.0% (p<0.001)							
Intensity of management: What is the overall management recommendation for this patient?							
40-GEP Class 1				**40-GEP Class 2A**			
Pre-GEP	Post-GEP	n	% of Class 1*	Pre-GEP	Post-GEP	n	% of Class 2A
Low	Low	36	70.6%	Low	Low	1	14.3%
Low	Moderate	1	2.0%	Low	Moderate	3	42.8%
Moderate	Low	8	15.7%	Moderate	Moderate	1	14.3%
Moderate	Moderate	6	11.8%	Moderate	High	1	14.3%
				High	High	1	14.3%
GEP-driven change:		**9**	**17.7%**	**GEP-driven change:**		**4**	**57.2%**
Overall GEP-driven change in intensity of management: 13/58 = 22.4% (p=0.0033)							
*n=1 case with no response							

improvement in healthcare resource utilization.

Use of the 40-GEP is recommended for patients with primary cSCC having one or more high-risk factors. The real-world clinical use population for 40-GEP testing (Hooper, et al,.[36]) does align with the UTILISE population both by number of risk factors and in percent of patients ≥65 years old (data presented here and Castle Biosciences data on file). While the focus of this analysis was on decision making pre- and post-40 GEP results a limitation to this prospective study is that a formal assessment of patient outcomes could not be performed due to abbreviated follow-up time for both cohorts. However, one nodal metastasis was observed in the Lead-in Cohort, which, as expected, was observed in the higher risk 40-GEP class, Class 2A.

While several clinician specialty types may be involved in the multidisciplinary care team for patients with high-risk cSCC, dermatologists or dermatologists/Mohs surgeons do serve as the hub for patient management decisions. Although highly experienced clinicians were involved in this study, a potential limitation is the minimal number currently participating (n=11) for the Clinical Utility Cohort. However, their specialties were encompassing of those most accessed for initial evaluation and treatment of high-risk cSCC patients, and with their 'graduation' from the Lead-in Phase, confidence in their assessment of how to implement the results of the 40-GEP can be considered steadfast. It is important to note that all clinicians participating in this study practiced in dermatology, 72% are board-certified dermatologists Mohs surgeons, indicating that this prospective study represents the same clinician type utilizing the test and making management decisions for patients with this nonmelanoma skin cancer type.

This analysis of the prospective UTILISE study demonstrates the positive impact of 40-GEP test results on clinician recommendations and actions for management of their Medicare-eligible high-risk cSCC patients. Hooper, *et al.*,[36] identified that the 40-GEP test had a significant impact on clinician decision making in a real-world setting, particularly for those ≥65 years of age. This data led us to analyze the impact on treatment plans within the Medicare-eligible population in the prospective UTILISE study. The results of this study identified the 40-GEP test as the single most influential factor in determining management plans for 42% of patients, along with a test result positively impacting patient management for over 80% of patients. Importantly, 15.7% of patients with a Class 1 result had a de-escalation in management that was aligned with their lower predicted risk of metastasis compared to clinicopathologic factors alone. Consistent with this alignment, 57.2% of patients with a Class 2A result had an escalation in management plans. These data show that risk-aligned changes in management planning are made and that these clinicians do incorporate the objective biological information that the 40-GEP test provides and use the information to prevent over treatment in those with a biologically low risk of metastasis and appropriately elevate the treatment in those with a greater biologic risk of metastasis to prevent poor outcomes.

These clinical treatment plan actions are not surprising given that GEP tests have been widely used and advocated for as risk-stratification factors that influence treatment plans in various cancer types.[38–47] Specifically, the results described here and within Hooper *et al.,*[36] mirror those of other risk-stratification gene expression profile tests (Table 4). For example, for stage I-II,

Table 4. Overall management change in patients tested with the 40-GEP compared to commonly used Medicare covered prognostic GEP tests in other cancers

Publication	GEP (Cancer)	Intended Use	Management Change
Current	40-GEP (cSCC)	To guide treatment decisions in patients with cSCC with one or more high-risk factors	24%
Soliman 2020[39]	70-GEP (breast)	To guide chemotherapy decisions in patients with early-stage breast cancer	24%
*Martin 2015[40]	50-GEP (breast)	To guide adjuvant treatment selection in patients with early-stage breast cancer	20%
Asad 2008[43]	21-GEP (breast)	To guide adjuvant treatment selection in patients with early-stage breast cancer	~~44~~%
Gore 2017[38]	22-GEP (prostate)	To guide decisions about adjuvant radiation therapy	18%
Badani 2021[41]	17-GEP (prostate)	To guide treatment decisions, including active surveillance, prostatectomy, and radiation therapy	18%
Lee 2021[42]	23-GEP (lung)	To guide invasive procedures versus surveillance in low/intermediate risk of lung malignancy	25%

hormone receptor-positive, HER2-negative breast cancer patients, the Medicare-covered 70-gene risk of recurrence signature (70-GS) IMPACT trial reported a 24% change in chemotherapy treatment recommendations post-70-GS results[39] and a study by Martín *et al*.,[40] reported a similar change in overall treatment recommendations (20%) post-50-GEP results. Another Medicare-covered GEP test, the 21-GEP, has been reported to impact treatment decisions in 44% of breast cancer patients[43] and TAILORx trial results demonstrated a net savings of $49 million per year.[48] In a Medicare-eligible enriched cohort, the 22-GEP for prostate cancer, another Medicare-covered GEP test, reported an 18% change in treatment recommendation for adjuvant radiation therapy and less anxiety post-test results among patients.[38] The 17-gene expression assay test for prostate cancer reported a 85% increase in urologists confidence in recommending treatments with incorporation of test results and an overall 18% change in recommendations between active surveillance and immediate treatment post-test results.[41] The 23-GEP test demonstrated that within the cohort of patients with low/intermediate risk lung nodules, 25% had a change in management plan from invasive procedure to surveillance when receiving a negative 23-GEP result.[42] In summary, GEP tests help to 1) identify patients at risk for poor outcomes or those who may be good candidates for adjuvant therapy, 2) prevent unwarranted treatments, 3) increase savings and better allocation of healthcare resources, 4) increase confidence among clinicians and decrease anxiety among patients.

CONCLUSION

In this analysis of the prospective Clinical Utility and Health Outcomes Study (UTILISE), the 40-GEP positively impacts a majority of clinicians' assessments of risk for their Medicare eligible patients with high-risk cSCC, which, in line with guidelines, is driving risk-aligned changes in treatment plans. It is also noteworthy that the clinical actionability rates of the 40-GEP for cSCC are comparable to those of currently covered molecular tests for cancer patients. Overall, 40-GEP results can help focus treatment options in a risk-appropriate manner, allowing for optimized utilization of healthcare resources and assisting in the development of a more standardized approach to the management of high-risk cSCC.

Conflict of Interest Disclosures: ES and KB participated as investigators for Castle Biosciences, Inc. (CBI) during this study; AF and JS are employees and options holders for CBI; SI is an investigator, advisor, and speaker for CBI.

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