NEWS RELEASE

In Novel Cohort, New Data Confirms DecisionDx®-SCC Provides Significant, Independent and Clinically Actionable Risk-Stratification of Patients, Including in Various High-Risk Subgroups

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Largest study of gene expression profile testing in patients with high-risk cutaneous squamous cell carcinoma (SCC) supports test's ability to provide clinically actionable risk stratification to guide treatment decisions for patients diagnosed with this impactful skin cancer

FRIENDSWOOD, Texas--(BUSINESS WIRE)-- Castle Biosciences, Inc. (Nasdaq: CSTL), a company improving health through innovative tests that guide patient care, today announced the publication of a new multi-center performance study of its DecisionDx-SCC risk stratification test. The study, published in Dermatology and Therapy and available **here** , analyzed the independent performance of DecisionDx-SCC from risk factors and traditional staging systems (i.e., Brigham and Women's Hospital (BWH) and American Joint Committee on Cancer Staging Manual 8th Edition (AJCC8) staging), and demonstrated significantly improved predictive accuracy when the test's results were integrated with the staging systems and National Comprehensive Cancer Network® (NCCN) guidelines to guide risk-appropriate treatment pathway decisions that can improve patient outcomes.

"Data-driven risk assessment is the foundation of sound clinical decision-making," said Ashley Wysong, M.D., M.S., lead study author, professor, distinguished chair of dermatology and founding chair of the department of dermatology at the University of Nebraska Medical Center. "Incorporating DecisionDx-SCC test results into the management of high-risk SCC can help ensure patients receive the best care possible by incorporating their biological risk of metastasis into the treatment plan. Use of the test in clinical practice can help with optimization of healthcare resources by reducing both overtreatment of patients with a low biological risk of metastasis and

undertreatment of patients with aggressive tumor biology."

The DecisionDx-SCC test was developed and validated to improve the accuracy of metastatic risk prediction for patients with high-risk SCC, classifying patients as low (Class 1), higher (Class 2A) or highest risk (Class 2B) of regional or distant metastasis within three years based on the gene expression profile of their tumor. The data in this study support use of the test's results in the clinical management of high-risk SCCs as they can provide impactful risk-stratification to guide risk-appropriate treatment pathway decisions, such as the use of nodal assessment (i.e., imaging) and adjuvant radiation therapy (ART).

The goal of this study was to present an independent validation of the DecisionDx-SCC test in a novel performance cohort (n=534) and then merge it with the test's initial independent validation cohort (n=420) to evaluate the performance of the test in providing independent prognostic value to risk classification systems, individual clinicopathologic risk factors and clinically relevant patient populations.[1-2] In the study, DecisionDx-SCC demonstrated statistically significant risk-stratification of patients with high-risk SCC ($p<0.001$); 3-year metastasis-free survival rates were 94.1%, 81.1% and 56.8% for patients with Class 1, Class 2A and Class 2B test results, respectively. The entire population had 3-year metastasis-free survival of 87.5%. DecisionDx-SCC also provided significant and clinically actionable risk stratification in various patient subgroups, including NCCN high and very high-risk, lower-stage BWH tumors and Medicare-eligible patients, further stratifying risk to help guide important treatment decisions for these patients.

Generally, treatment pathways for patients with SCC are based on population-based estimates of risk, informed by guidelines and traditional staging systems (AJCC8 and BWH) which use various clinicopathological risk factors to predict a patient's risk of metastasis. Multivariate analyses demonstrated that DecisionDx-SCC Class 2A and 2B test results were independent and significant predictors of metastasis when evaluated in the context of NCCN risk stratification, AJCC8 and BWH staging, and various clinicopathologic risk factors, such as immunosuppression, poor differentiation and tumor thickness (>6mm) ($p<0.001$). Importantly, integrating DecisionDx-SCC with individual clinicopathologic risk factors or risk classification systems (AJCC8 and BWH) significantly improved the accuracy for prediction of metastatic events (ANOVA for model deviance, $p<0.0001$ for all models). These data support the use of DecisionDx-SCC test results, informed by a patient's tumor biology, to guide personalized patient treatment decisions aligned to a patient's risk of metastasis over three years. These decisions could include risk-aligned reductions in treatment intensity for patients with low risk (Class 1) test results and intensified treatment, such as consideration of ART, for patients at a higher risk of experiencing metastasis (Class 2A and 2B).

"Castle is committed to improving the care of patients with SCC through broader use of our DecisionDx-SCC test," said Matthew Goldberg, M.D., board-certified dermatologist and dermatopathologist, and senior vice president, medical, at Castle Biosciences. "As such, we continue to develop evidence showing that our test adds independent

prognostic value to the clinical and pathologic risk factors used for guiding risk-informed treatment plans within current guidelines. The DecisionDx-SCC test result is interpreted by the treating clinician in the context of what they already know about their patient's tumor to improve their prognostic accuracy and inform more closely risk-aligned management decisions with the goal of improving clinical outcomes for their patients with high-risk skin cancer."

About DecisionDx®-SCC

DecisionDx-SCC is a 40-gene expression profile test that uses an individual patient's tumor biology to predict individual risk of cutaneous squamous cell carcinoma metastasis for patients with one or more risk factors. The test result, in which patients are stratified into a Class 1 (low), Class 2A (higher) or Class 2B (highest) risk category, predicts individual metastatic risk to inform risk-appropriate management. Peer-reviewed publications have demonstrated that DecisionDx-SCC is an independent predictor of metastatic risk and that integrating DecisionDx-SCC with current prognostic methods can add positive predictive value to clinician decisions regarding staging and management.

About Castle Biosciences

Castle Biosciences (Nasdaq: CSTL) is a leading diagnostics company improving health through innovative tests that guide patient care. The Company aims to transform disease management by keeping people first: patients, clinicians, employees and investors.

Castle's current portfolio consists of tests for skin cancers, Barrett's esophagus, mental health conditions and uveal melanoma. Additionally, the Company has active research and development programs for tests in other diseases with high clinical need, including its test in development to help guide systemic therapy selection for patients with moderate-to-severe atopic dermatitis, psoriasis and related conditions. To learn more, please visit **www.CastleBiosciences.com** and connect with us on **LinkedIn**, **Facebook**, **X** and **Instagram**.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, which are subject to the "safe harbor" created by those sections. These forward-looking statements include, but are not limited to, statements concerning: the ability of DecisionDx-SCC to (i) significantly improve predictive accuracy to guide risk-appropriate treatment pathway decisions that can improve patient outcomes and (ii) optimize healthcare resources

in clinical practice. The words “can,” “potential” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements that we make. These forward-looking statements involve risks and uncertainties that could cause our actual results to differ materially from those in the forward-looking statements, including, without limitation: subsequent study or trial results and findings may contradict earlier study or trial results and findings or may not support the recommendations and guidelines presented in this report, including with respect to the discussion of DecisionDx-Melanoma in this press release; actual application of our tests may not provide the aforementioned benefits to patients; and the risks set forth under the heading “Risk Factors” in our Annual Report on Form 10-K for the twelve months ended December 31, 2023, and in our other filings with the SEC. The forward-looking statements are applicable only as of the date on which they are made, and we do not assume any obligation to update any forward-looking statements, except as may be required by law.

1. 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.
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.

Investor Contact:

Camilla Zuckero

czuckero@castlebiosciences.com

Media Contact:

Allison Marshall

amarshall@castlebiosciences.com

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