NEWS RELEASE

Castle Biosciences Announces Publication of Study Demonstrating the Integration of DecisionDx®-Melanoma and Clinicopathologic Factors Provides Optimized, Personalized Survival Prognoses for Patients with Cutaneous Melanoma

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DecisionDx-Melanoma integrates a patient's clinicopathologic factors with his/her tumor biology to provide precise, personalized risk estimates, including five-year melanoma-specific survival, recurrence-free survival and distant metastasis-free survival

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 study in the Journal of the American Academy of Dermatology validating the performance of DecisionDx®-Melanoma's proprietary algorithm, i31-ROR. i31-ROR is designed to integrate a patient's tumor biology with clinicopathologic factors to provide the patient's personalized risk of melanoma recurrence. The study, accessible **here**, found that DecisionDx-Melanoma's integrated algorithms (i31-ROR and i31-SLNB) provide more precise risk-stratification and individualized risk estimates, compared to those based on clinicopathologic factors alone, and can ultimately improve treatment decisions.

As expected in the study, the most significant factor in predicting melanoma-specific survival (MSS) was the tumor biology risk as identified by DecisionDx-Melanoma's 31-gene expression profile (GEP) (multivariate hazard ratio (HR)=20.00). Additionally, DecisionDx-Melanoma, including both algorithms (i31-SLNB and i31-ROR), identified 44% of patients who could potentially forego the sentinel lymph node biopsy (SLNB) surgical procedure while

maintaining high survival rates (>98% for recurrence-free survival (RFS), distant metastasis-free survival (DMFS) and MSS) or were re-stratified as being at a higher or lower risk of recurrence or death than initially staged using the American Joint Committee on Cancer 8th edition (AJCC8) staging criteria.

"Current staging practices use key characteristics of a patient's melanoma tumor to determine how aggressive it is as a means to inform important cancer management decisions, such as intensity of follow-up, surveillance imaging and the need for adjuvant therapy," said first author Abel Jarell, M.D., dermatologist and dermatopathologist at Northeast Dermatology Associates, PC, Portsmouth, New Hampshire. "DecisionDx-Melanoma takes many of these same characteristics and combines them with the biology of a patient's tumor to provide patients and clinicians with personalized – instead of population-based – risk estimates that can allow for tailored treatment plans aligned to the patient's individual risk."

Integrating Clinicopathologic Factors with Tumor Biology for Precise, Personalized Risk Estimates

DecisionDx-Melanoma is Castle's molecular risk stratification GEP test that analyzes the expression of 31 genes (31-GEP) within tumor tissue. DecisionDx-Melanoma's 31-GEP has been shown to be a significant predictor of recurrence and metastatic risk, independent of other clinical factors.[1] In addition to the 31-GEP class score (low risk (Class 1A), increased risk (Class 1B/2A) or high risk (Class 2B) of recurrence or metastasis), the test now provides results from two proprietary algorithms, i31-SLNB and i31-ROR, that combine a patient's 31-GEP score with his/her clinicopathologic factors to provide precise, personalized risk assessments that inform two clinical questions in the management of cutaneous melanoma:

1) A patient's individual risk of sentinel lymph node (SLN) positivity (i31-SLNB algorithm, previously validated);[2] and

2) A patient's personal risk of recurrence and/or metastasis (i31-ROR algorithm).

The paper, titled "Optimizing treatment approaches for patients with cutaneous melanoma by integrating clinical and pathologic features with the 31-gene expression profile test," discusses the development and validation of the i31-ROR algorithm and its use in conjunction with the i31-SLNB algorithm for more comprehensive and refined patient prognoses.

i31-ROR Highlights:

- DecisionDx-Melanoma's i31-ROR algorithm integrates a patient's 31-GEP score with his/her clinicopathologic factors, including Breslow thickness, ulceration, mitotic rate, SLN status, age and tumor location. The most

significant factor in predicting MSS was the tumor biology risk as identified by the 31-GEP (multivariate HR=20.00).
- With these inputs, i31-ROR provides personalized, not population-based, predictions of five-year MSS, and two additional endpoints not available in AJCC8, RFS and DMFS.

Study highlights:

- In the study, DecisionDx-Melanoma's i31-ROR algorithm identified patients at the highest and lowest risk for recurrence or metastasis; patients with a low-risk i31-ROR result had significantly higher RFS (91% vs. 45%, P<0.001), DMFS (95% vs. 53%, P<0.001) and MSS (98% vs. 73%, P<0.001) than patients with a high-risk i31-ROR result.
- Additionally, i31-ROR correctly reclassified patient risk as being higher or lower than predicted by AJCC8 for MSS, demonstrating the ability of the algorithm to further refine patient risk and help inform more individualized melanoma management plans.
- The i31-ROR also had higher sensitivity and higher negative predictive value (NPV) for RFS, DMFS and MSS than SLN status alone (sensitivity of i31-ROR vs. SLN status alone: RFS (66% vs. 46%), DMFS (78% vs. 49%) and MSS (71% vs. 57%); NPV of i31-ROR vs. SLN status alone: RFS (93% vs. 89%), DMFS (97% vs. 93%) and MSS (98% vs. 97%)).
- When patients with an i31-SLNB estimated likelihood of SLN positivity of ≥5% (n=298) were analyzed by the i31-ROR algorithm, those with a negative SLN but high-risk i31-ROR result had lower RFS, DMFS and MSS rates than patients with a negative SLN and a low-risk i31-ROR result. Among this same subset of patients, those with a positive SLN but a low-risk i31-ROR result had higher RFS, DMFS and MSS rates than patients with a high-risk i31-ROR result.
- Moreover, the study showed that the number of patients undergoing SLNB could potentially be reduced as a subset of patients with an i31-SLNB predicted risk of <5% all received a low-risk i31-ROR result and had RFS, DMFS and MSS rates >98%.

Study conclusions:

- Overall, the study demonstrated that DecisionDx-Melanoma, with integrated algorithms that combine the 31-GEP score with a patient's clinicopathologic factors, provides personalized and accurate survival prognoses, which can help guide risk-aligned patient management.
- Further, the study showed that using DecisionDx-Melanoma test results in conjunction with current staging guidelines can help refine patient risk, reduce unnecessary procedures and ultimately improve patient care.
- As the National Comprehensive Cancer Network (NCCN) guidelines recommend risk-aligned decisions for individual patients, the use of DecisionDx-Melanoma test results could aid in identifying patients with more or less aggressive cases of melanoma to align treatment decisions more accurately with patient risk and help

ensure a more appropriate allocation of healthcare resources.

About DecisionDx®-Melanoma

DecisionDx-Melanoma is a gene expression profile risk stratification test. It is designed to inform two clinical questions in the management of cutaneous melanoma: a patient's individual risk of sentinel lymph node (SLN) positivity and a patient's personal risk of melanoma recurrence and/or metastasis. By integrating tumor biology with clinical and pathologic factors using a validated proprietary algorithm, DecisionDx-Melanoma is designed to provide a comprehensive and clinically actionable result to guide risk-aligned patient care. DecisionDx-Melanoma has been shown to be associated with improved patient survival and has been studied in more than 9,000 patient samples. DecisionDx-Melanoma's clinical value is supported by more than 35 peer-reviewed and published studies, providing confidence in disease management plans that incorporate the test's results. Through June 30, 2022, DecisionDx-Melanoma has been ordered 105,239 times for patients diagnosed with cutaneous melanoma. More information about the test and disease can be found at **www.CastleTestInfo.com**

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, uveal melanoma, Barrett's esophagus and mental health conditions. Additionally, the Company has active research and development programs for tests in other diseases with high clinical need, including its test in development to predict systemic therapy response in patients with moderate-to-severe psoriasis, atopic dermatitis and related conditions. To learn more, please visit **www.CastleBiosciences.com** and connect with us on **LinkedIn**, **Facebook**, **Twitter** 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 our DecisionDx®-Melanoma test and proprietary algorithms to help refine

patient risk, reduce unnecessary procedures, improve resource allocation, and ultimately improve patient care and treatment decisions; allow for tailored treatment plans aligned to the patient's individual risk; reduce the number of patients undergoing SLNB; help guide risk-aligned patient management; and aid in identifying patients with more or less aggressive cases of melanoma to align treatment decisions more accurately with patient risk and help ensure a more appropriate allocation of healthcare costs. The words "can," "could," "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 results obtained in this study, including with respect to the discussion of DecisionDx®-Melanoma in this press release; actual application of our DecisionDx®-Melanoma test may not provide the aforementioned benefits to patients; and the risks set forth under the heading "Risk Factors" in our Quarterly Report on Form 10-Q for the three months ended June 30, 2022, 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]Greenhaw BN, Covington KR, Kurley SJ, et al. Molecular risk prediction in cutaneous melanoma: a meta-analysis of the 31-gene expression profile prognostic test in 1,479 328 patients. Journal of the American Academy of Dermatology. 2020;83(3):745-753. doi:10.1016/j.jaad.2020.03.053

[2]Whitman ED, Koshenkov VP, Gastman BR, et al. Integrating 31-Gene expression profiling with clinicopathologic features to optimize cutaneous melanoma sentinel lymph node metastasis prediction. JCO Precision Oncology. 2021;(5):1466-1479. doi:10.1200/PO.21.00162

Investor Contact:

Camilla Zuckero

czuckero@castlebiosciences.com

Media Contact:

Allison Marshall

amarshall@castlebiosciences.com

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