NEWS RELEASE

Landmark Study Shows Combination of Castle Biosciences' DecisionDx®-UM and PRAME Outperforms Gene Mutation Analysis in Predicting Survival Outcomes in Uveal Melanoma

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FRIENDSWOOD, Texas, Dec. 17, 2025 (GLOBE NEWSWIRE) -- Castle Biosciences, Inc. (Nasdaq: CSTL), a company improving health through innovative tests that guide patient care, today announced new data from the largest prospective, multicenter study to date comparing next-generation sequencing (NGS)-based gene mutation analysis with the combination of DecisionDx-UM and Preferentially Expressed Antigen in Melanoma (PRAME) gene expression for predicting outcomes in patients with uveal melanoma (UM). The study, titled “Early Genetic Evolution of Driver Mutations in Uveal Melanoma,” was conducted by the Collaborative Ocular Oncology Group (COOG) and recently published in **Nature Communications**.

"The recently published COOG2 study validated that combining DecisionDx-UM test results and PRAME gene expression data provides more precise metastatic risk prediction for patients with UM than either test used independently," said J. William Harbour, M.D., ocular oncologist, and professor and chair of the Department of Ophthalmology at UT Southwestern Medical Center in Dallas.[1] "Our latest research builds on these findings and shows that the combination of DecisionDx-UM and PRAME delivers superior predictions of metastasis-free survival and overall survival compared to NGS-based mutation analysis. While gene mutation analysis remains valuable for other purposes, such as confirming tumor sampling quality and identifying patients for appropriate clinical trials, the DecisionDx-UM + PRAME combination offers the most comprehensive risk stratification available to guide more informed treatment pathway decisions for patients with UM.”

UM is a rare but aggressive eye cancer with a high risk of metastasis, often leading to fatal outcomes. Notably, UM

tumors are most likely to spread when they are still small, making them difficult to distinguish from benign lesions during early detection. This study aimed to better understand the genetic changes that drive the progression from benign nevi to malignant melanoma at the molecular level. Researchers analyzed 1,140 primary UM tumors, including 131 small, early-stage tumors, using NGS to assess seven clusters of recurrent genetic mutations. They then compared the predictive accuracy of these mutations with the combined DecisionDx-UM + PRAME result in assessing metastatic risk.

Key findings of the study include:

- DecisionDx-UM + PRAME, when used together, provide superior predictions of both metastasis-free survival (MFS) and overall survival (OS) when compared to individual gene mutation analysis using NGS.
- While the BAP1, SF3B1 and EIF1AX gene mutations were individually associated with high, medium and low metastatic risk (respectively), their ability to predict both MFS and OS became non-significant and redundant when DecisionDx-UM + PRAME were included in multivariate analysis.
- The study authors attribute the superior performance of DecisionDx-UM + PRAME to DecisionDx-UM's ability to measure gene activity from both tumor cells and surrounding immune cells, which provides a more comprehensive view of the tumor microenvironment. Conversely, targeted NGS analyzes DNA mutations in tumor cells alone. By capturing this broader biological context, DecisionDx-UM is designed to offer a more accurate assessment of a tumor's potential to metastasize.

Castle currently offers three tests for patients with UM – DecisionDx-UM, DecisionDx®-PRAME and DecisionDx®-UMSeq, an NGS-based test – all from a single biopsy sample. Together, these tests provide the most comprehensive molecular insights currently available on the market for patients with UM, supporting precise risk assessment and informed treatment planning.

About the Collaborative Ocular Oncology Group

The Collaborative Ocular Oncology Group (COOG) is the largest collaborative working group in North America of ocular and medical oncologists specialized in the treatment of patients with intraocular cancers, currently focusing on uveal melanoma. The COOG comprises more than 25 leading academic and private ocular oncology centers of excellence and has been continually funded by the National Cancer Institute for over a decade. The COOG has conducted two large multicenter prospective studies of prognostic biomarkers in uveal melanoma, the first and only such studies ever conducted in this cancer, and is planning a major expansion into adjuvant and metastatic clinic trials in patients with uveal melanoma.

About DecisionDx-UM

DecisionDx-UM is a gene expression profile (GEP) test that uses a patient's tumor biology to predict their personalized risk of metastasis from uveal melanoma, a rare and aggressive eye cancer. By stratifying patients into

low-, intermediate- or high-risk groups, the test helps guide personalized care decisions, including surveillance intensity, medical oncology referral and clinical trial consideration. Since 2009, DecisionDx-UM has been widely adopted as the standard of care in the U.S. and is included in the American Joint Committee on Cancer (AJCC) Staging Manual and the National Comprehensive Cancer Network (NCCN) Guidelines. The test is supported by more than 25 peer-reviewed publications involving more than 5,000 patients, representing the largest evidence base of any prognostic test for uveal melanoma. Today, nearly 80% of newly diagnosed patients undergo DecisionDx-UM testing. Learn more at **www.CastleBiosciences.com**.

About Castle Biosciences
Castle Biosciences (Nasdaq: CSTL) is a leading diagnostics company improving health through innovative tests that guide patient care. With a primary focus in dermatologic and gastroenterological disease, we develop personalized, clinically actionable solutions that help improve disease management and patient outcomes.

We put people first—empowering patients and clinicians and informing care decisions through rigorous science and advanced molecular tests that support more confident treatment planning. To learn more, visit **www.CastleBiosciences.com** and connect with us on **LinkedIn**, **Instagram**, **Facebook** and **X**.

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 clinical utility and performance of our diagnostic tests, including DecisionDx-UM, DecisionDx-PRAME and DecisionDx-UMSeq; the ability of the DecisionDx-UM + PRAME combination test to guide more informed, risk-aligned management decisions through the precise risk-stratification of patients with UM; and the potential increased risk stratification from including PRAME gene expression information to a patient's DecisionDx-UM test result. The words "believe," "can" 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 these studies, including with respect to the discussion of our tests 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 year ended December 31, 2024 and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2025, each filed with the SEC, 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. Harbour JW, Correa ZM, Schefler AC, et al. 15-Gene Expression Profile and PRAME as Integrated Prognostic Test for Uveal Melanoma: First Report of Collaborative Ocular Oncology Group Study No. 2 (COOG2.1). J Clin Oncol. 2024;42(28):3319-3329. doi:10.1200/JCO.24.00447

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