NEWS RELEASE

I-SPY 2 Publication in Nature Communications Shows Signatera™ Can Predict Treatment Response and Recurrence Risk in Early-Stage Breast Cancer

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Latest findings from multicenter trial demonstrate Signatera's ability to improve risk stratification for patients with therapy-resistant disease

AUSTIN, Texas--(BUSINESS WIRE)-- **Natera, Inc.** (NASDAQ: NTRA), a global leader in cell-free DNA and precision medicine, together with Quantum Leap Healthcare Collaborative, today announced the publication of new findings from the I-SPY 2 trial in **Nature Communications**.

The study examined how Signatera can refine risk assessment in patients with early-stage breast cancer whose tumors resist neoadjuvant therapy (NAT). These cancers often leave behind substantial residual disease and carry a higher risk of metastasis, though only about 15–30% recur within three years1-3. Distinguishing which NAT-resistant tumors are more likely to recur could guide treatment decisions to potentially prevent or delay metastatic recurrence.

Researchers used Signatera to measure personalized circulating tumor DNA (ctDNA) in 723 women with high-risk, early-stage breast cancer receiving NAT at four time points: 1) before treatment; 2) after three weeks of paclitaxel with or without an investigational agent; 3) between paclitaxel- and anthracycline-based regimens; and 4) after completing neoadjuvant therapy. Key findings include:

- Signatera ctDNA testing improved prognostic precision beyond residual cancer burden (RCB) alone in patients with high RCB (RCB-II/III) following neoadjuvant therapy (NAT).

    - Signatera-negative patients, at either pretreatment or post-NAT, had a much lower risk of metastasis:
        - RCB-II: Post-NAT, pre-surgery (T3) 3-year DRFS = 88% (ctDNA–) vs. 57% (ctDNA+), adj HR = 0.29, p = 0.001
        - RCB-III: Post-NAT, pre-surgery (T3) 3-year DRFS = 83% (ctDNA–) vs. 22% (ctDNA+), adj HR = 0.14, p< 0.001
    - Persistent Signatera positivitypost-NAT (T3) was a strong independent predictor of metastatic recurrence (adj HR = 5.20, p< 0.001).
- Early Signatera ctDNA clearance at week 3 (T1) was strongly associated with favorable response to NAT, including regimens containing immune checkpoint inhibitors and HER2-targeted therapies, supporting its potential as an early, dynamic biomarker of treatment sensitivity.
- Personalized Signatera assay variants remained highly stable despite tumor evolution, with median conservation rates of 94–97% between pretreatment and post-NAT tumor samples.

"These findings show that ctDNA provided critical insight into which therapy-resistant tumors were most likely to recur and, importantly, which were not," said Laura Esserman, M.D., MBA, and Laura van 't Veer, Ph.D., professors at the UCSF and principal investigators of the I-SPY study. "That distinction is vital because it can help us identify who remains at higher risk for recurrence and who may not need more aggressive treatment. Our next step is to integrate these findings and examine how ctDNA, pathology and imaging can complement each other. The I-SPY trial provides a framework to optimize all of the information for the benefit of patients."

"The I-SPY 2 publication adds to a growing body of evidence supporting Signatera's role in early breast cancer," said Minetta Liu, M.D., chief medical officer of oncology and early cancer detection at Natera. "Building on our previous studies, this work provides further validation that Signatera can improve risk assessment for therapy-resistant disease. We are grateful for our ongoing collaboration with the I-SPY investigators on research that brings us closer to more personalized and effective care for patients."

References

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2. Symmans, W. F. et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol 35, 1049-1060, doi:10.1200/JCO.2015.63.1010 (2017).

3. Symmans, W. F. et al. Assessment of Residual Cancer Burden and Event-Free Survival in Neoadjuvant Treatment for

High-risk Breast Cancer: An Analysis of Data From the I-SPY2 Randomized Clinical Trial. JAMA Oncol 7, 1654-1663, doi:10.1001/jamaoncol.2021.3690 (2021).

About Natera

Natera™ is a global leader in cell-free DNA and precision medicine, dedicated to oncology, women's health, and organ health. We aim to make personalized genetic testing and diagnostics part of the standard-of-care to protect health and inform earlier, more targeted interventions that help lead to longer, healthier lives. Natera's tests are supported by more than 325 peer-reviewed publications that demonstrate excellent performance. Natera operates ISO 13485-certified and CAP-accredited laboratories certified under the Clinical Laboratory Improvement Amendments (CLIA) in Austin, Texas, and San Carlos, California, and through Foresight Diagnostics, its subsidiary, operates an ISO 27001-certified and CAP-accredited laboratory certified under CLIA in Boulder, Colorado. For more information, visit **www.natera.com**.

Forward-Looking Statements

All statements other than statements of historical facts contained in this press release are forward-looking statements and are not a representation that Natera's plans, estimates, or expectations will be achieved. These forward-looking statements represent Natera's expectations as of the date of this press release, and Natera disclaims any obligation to update the forward-looking statements. These forward-looking statements are subject to known and unknown risks and uncertainties that may cause actual results to differ materially, including with respect to whether the results of clinical or other studies will support the use of our product offerings, the impact of results of such studies, our expectations of the reliability, accuracy, and performance of our tests, or of the benefits of our tests and product offerings to patients, providers, and payers. Additional risks and uncertainties are discussed in greater detail in "Risk Factors" in Natera's recent filings on Forms 10-K and 10-Q, and in other filings Natera makes with the SEC from time to time. These documents are available at **www.natera.com/investors** and **www.sec.gov**.

Investor Relations: Mike Brophy, CFO, Natera, Inc., **investor@natera.com**
Media: Lesley Bogdanow, VP of Corporate Communications, Natera, Inc., **pr@natera.com**

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