Serum HER-2/neu Simple. Direct. Definitive.

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For Providers: Integrating Serum HER-2/neu into Your Standard of Care

The following information describes the Serum HER-2/neu Test's role as a complement to tissue testing, recommends when to use the test and summarizes key investigations of the test's clinical utility.

American Cancer Society

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treatment should be modified.

The Serum HER-2/neu Test monitors an oncoprotein that is the specific target of certain HER-2/neu targeted therapies such as trastuzumab. In a certain population of patients, serum testing could help detect HER-2/neu-positive tumors in patients whose tissue tests were negative for HER-2/neu

Knowing a patient's serum HER-2/neu status can be critical to creating a more efficient treatment pathway for better quality of life.

The Serum HER-2/neu Test does not replace tissue tests such as HercepTest® but is complementary. The additional insight it offers can make a critical difference in getting the right treatment to the right patient at the right time.

Serum HER-2/neu and Tissue Testing

Immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) provides semi-quantitative measurement of a patient's HER-2/neu status at initial diagnosis of breast cancer. The Serum HER-2/neu Test complements tissue testing when a tumor metastasizes by monitoring response to therapy or time to disease progression. Serum HER-2/neu offers the following advantages:

- It is minimally invasive—a simple blood draw.
- HER-2/neu can be used for monitoring

women who are receiving hormone therapy, chemotherapy or combination therapies.

- It is the only test that can track a woman's HER-2/neu level once she is diagnosed with MBC.

In addition, studies have shown that serum testing could help identify HER-2/neu-positive tumors in a population of women with breast cancer who tested negative by IHC or FISH in the primary tumor.1,2 This may have important implications for determining whether a patient with MBC should receive HER-2/neu targeted treatment.

Serum HER-2/neu and Commonly Used Tumor Markers

Because it monitors an oncoprotein rather than a tumor marker, the Serum HER-2/neu Test can provide direct insight into monitoring patients with MBC.

For example, there are now specific HER-2/neu targeted therapies, but no therapies targeted at CEA, CA 15-3 or CA 27.29. HER-2/neu can guide the use of specific HER-2/neu targeted therapies; neither CEA nor CA 15-3 can direct specific therapies. CEA and CA 15-3 are tumor markers associated with tumor bulk, while HER-2/neu has been shown to be an independent factor with respect to tumor bulk.

DEFINITIVE: HER-2/neu LEVELS AT A GLANCE

RECOMMENDED TESTING GUIDELINES

- **Normal:** If the serum HER-2/neu level is in the normal range (<15 ng/mL), the Serum HER-2/neu Test should be repeated two times a year.
- **Above normal:** If the first Serum HER-2/neu Test shows a level that is above normal (>15 ng/mL), the test should be repeated four times a year.

With a cutpoint of 15 ng/mL, Serum HER-2/neu provides clear direction: rising levels indicate

disease progression; falling levels signify treatment response. This evolution in HER-2/neu testing is simple, direct and definitive.

The Biomarker Advantage

As a biomarker test, the Serum HER-2/neu Test differs from tumor marker tests in that it tracks the biological activity of an oncoprotein, HER-2/neu. HER-2/neu has emerged as an important cellular target of a variety of new cancer therapies. Monitoring rising and falling serum HER-2/neu can guide HER-2/neu therapy much like hormone receptors guide hormone therapy.

The advantages of HER-2/neu over commonly used tumor markers may be summarized below.

HER-2/NEU AND TUMOR MARKERS: A COMPARISON

	HER-2/neu	CEA	CA 15-3	CA 27.29
Converts normal cells to cancer cells	✓			
Is the target of specific therapies	✓			
Provides specific information about status of HER-2-positive tumors	✓			
Guides the use of HER-2/neu targeted therapies	✓			
Independent of tumor bulk	✓			

The Serum HER-2/neu Test may be used in conjunction with tumor marker tests; in fact, studies show that serum testing for HER-2/neu may provide additional insight to monitoring with tumor markers
CEAand CA15-3.[3-10]

References

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Clin Breast Cancer 2004;5(2):105–116.

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personalized HER-2 therapy. Personalized Medicine 2005;2(4):317–324.

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Including Serum HER-2/neu in Metastatic Breast Cancer Monitoring

About the Serum HER-2/neu Test

The Serum HER-2/neu Test is a simple biomarker blood test that measures and monitors the extracellular domain (ECD) of HER-2/neu that is shed into the serum of metastatic breast cancer (MBC) patients. Tumors in patients with elevated HER-2/neu concentrations tend to grow more aggressively and resist hormonal therapy and some chemotherapies, and patients generally have

a poorer prognosis.[1]

Serum levels of HER-2/neu directly reflect disease status and the effectiveness of HER-2/neu targeted or combination therapies.[2,3] Increases reflect progression; decreases reflect treatment response. This allows serum HER-2/neu to guide HER-2/neu therapy much like hormone receptors guide hormone therapy.[4]

The Serum HER-2/neu Test is a simple biomarker blood test that directly reflects disease progression and therapy response.

With the emergence of several HER-2/neu targeted therapies, knowing real-time HER-2/neu status may be considered critical to creating a more efficient treatment pathway for better quality of life in patients with metastatic breast cancer.

Clinical Utility of the Serum HER-2/neu Test

Allows more precise monitoring of hormone or chemotherapy.
Many studies of patients with MBC receiving hormone or chemotherapy have shown that longitudinal changes in serum HER-2/neu levels directly reflect the clinical course of a patient's disease.[5]

Data reported by Schippinger et al and Lipton et al indicated that patients with MBC who had an ECD level <15 ng/mL had improved overall survival and suggested that managing therapy to keep the ECD <15 ng/mL may improve the clinical outcome of patients with HER-2/neu-positive tumors.

Allows more precise monitoring of trastuzumab-based therapy.

Numerous reports of patients with MBC, including those by Esteva et al[6] and Schondorf et al,[7] have indicated that serial changes in HER-2/neu ECD highly correlate with the clinical course of disease in patients treated with trastuzumab-based therapies. These studies evaluated serum HER-2/neu's monitoring utility in patients treated with trastuzumab plus various combinations of chemotherapy that included docetaxel or paclitaxel.

May add greater insight to monitoring with tumor markers CEA and CA 15-3.
A number of published studies have investigated the clinical utility of monitoring HER-2/neu in combination with carcinoembryonic antigen (CEA) and CA 15-3.[8-14] In general, these studies have reported that monitoring serum HER-2/neu in combination with either CEA or CA [15-3] may improve sensitivity for early detection of recurrence of disease.

When to Include the Serum HER-2/neu Test
Upon a diagnosis of MBC, establish HER-2/neu positivity by testing the primary tumor (if available) using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH).

Whether the tissue tests negative or positive for HER-2/neu, establish a serum baseline using the Serum HER-2/neu Test. Studies have shown that serum testing could help identify HER-2/neu-positive tumors in a population of women with breast cancer (10–40 percent, approximately 20 percent on average) who tested negative by IHC or FISH in the primary tumor.[5]

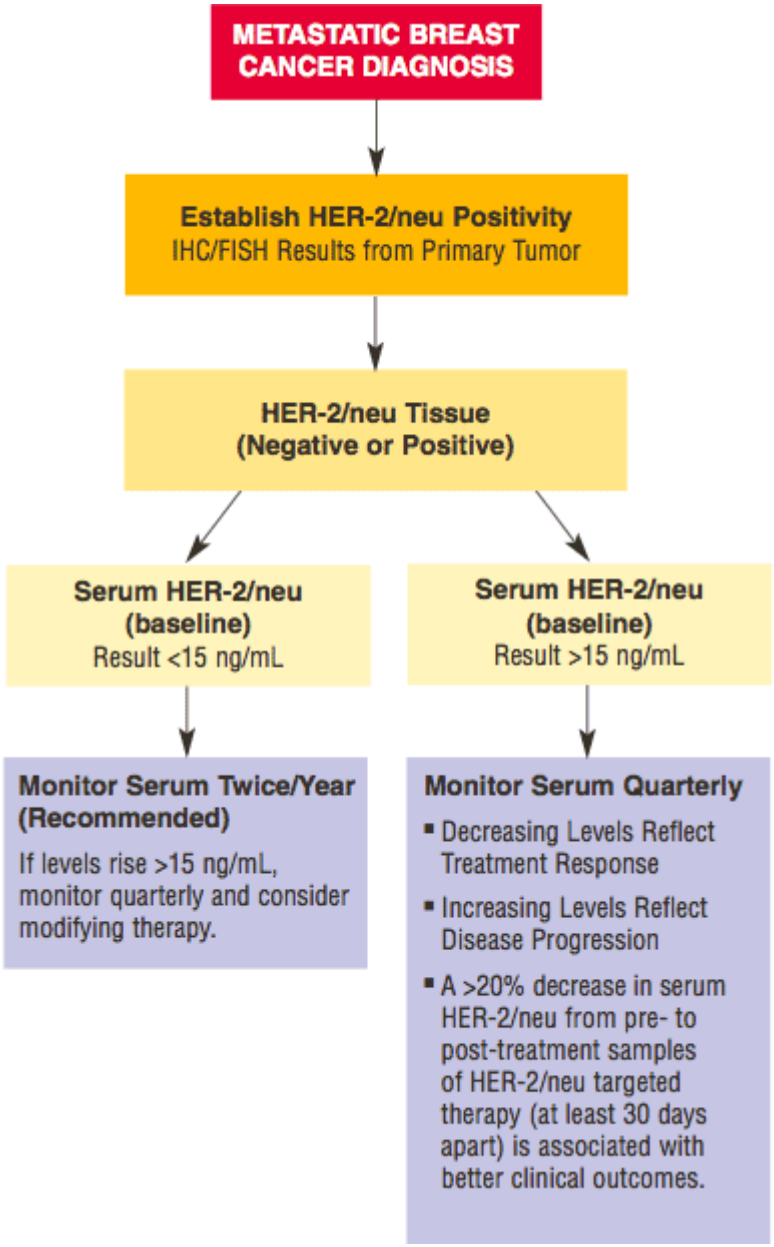
Recommended Testing Guidelines

- **If the serum baseline is <15 ng/mL**, continue to monitor the patient's serum twice a year. If levels rise to >15 ng/mL, monitor quarterly and consider modifying therapy.

- **If the serum baseline is >15 ng/mL**, monitor the patient's serum quarterly. Decreasing levels reflect treatment response, while increasing levels reflect disease progression.

The Serum HER-2/neu Test is the only test FDA-cleared for monitoring HER-2/neu status in patients with MBC. It is a simple, direct and definitive addition to the MBC standard of care.

Serum HER-2/neu Test Utility at a Glance



The Serum HER-2/neu Test is used to monitor a patient's HER-2/neu status once a diagnosis of metastatic breast cancer has been established. The chart above summarizes the test's clinical utility as a monitoring tool complementary to tissue testing.

Adapted from Carney, WP, et al. Clin Breast Cancer 2004;5(2):105–116.

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Understanding the Clinical Utility of Serum HER-2/neu

Follow HER-2/neu For Life

Serum HER-2/neu is a simple, direct biomarker blood test for more precise management of HER-2/neu metastatic breast cancer.

These clinical references highlight data indicating that serum concentrations of HER-2/neu directly reflect disease progression and response to therapy, and that serial monitoring of serum HER-2/neu may be a valuable tool in creating a more efficient treatment pathway for better patient quality of life.

Clinical utility of serum HER-2/neu in monitoring and prediction of progression-free survival in metastatic breast cancer patients treated with trastuzumab-based therapies

Esteva FJ, Cheli CD, Fritsche H, Fornier M, Slamon D, Thiel RP, Lueftner D, Ghani F. Breast Cancer Res 2005;7(4):R436–443. Epub 2005 Apr 8.

Serum HER-2/neu testing is proven clinically valuable in monitoring metastatic breast cancer patients undergoing trastuzumab-based treatment and provides additional value over the CA15-3 test. The percentage of baseline HER-2/neu concentrations in the early weeks of therapy may be an early predictor of progression-free survival.

Serum HER-2 extracellular domain in metastatic breast cancer patients treated with weekly trastuzumab and paclitaxel

Fornier MN, Seidman AD, Schwartz MK, et al. Ann Oncol 2005;16(2):234–239.

A statistically significant association exists between pretreatment serum HER-2 ECD and tissue HER-2 status as assessed by immunohistochemistry and fluorescence in situ hybridization. Adecreased HER-2 ECD serum level was a significant predictor of response to trastuzumab-based therapy.

Monitoring of serum HER-2/neu predicts response and progression-free survival to trastuzumab-based treatment in patients with metastatic breast cancer
Koestler WJ, Schwab B, Singer CF, Neumann R, Rucklinger E, Brodowicz T, Tomek S, Niedermayr M, Hejna M, Steger GG, Krainer M, Wiltschke C, Zielinski CC. Clin Cancer Res 2004;10(5):1618–1624.

This pilot study concluded that serial monitoring of serum HER-2/neu extracellular domain levels may be a valuable tool for early prediction of the probability of response and progression-free survival to trastuzumab-based treatment and is thus likely to contribute to an optimization of treatment and
resource allocation.

Serum HER-2/neu conversion to positive at the time of disease progression in patients with breast carcinoma on hormone therapy
Lipton A, Leitzel K, Ali SM, et al. Cancer 2005;104(2):257–263.

This study found that conversion to positive serum HER-2/neu status occurred in approximately 25 percent of patients who received first-line hormone therapy with letrozole or tamoxifen. Conversion to serum HER-2/neu-positive status with antiestrogen and aromatase-inhibitor therapy produced equal results. Serum conversion to HER-2/neu-positive status was shown to be an independent risk factor

for decreased survival in breast carcinoma patients.

Serum HER-2/neu in the management of breast cancer patients
Lueftner D, Luke C, Possinger K. Clin Biochem 2003;36(4):233–240.

This review notes that serum HER-2/neu levels are elevated beyond normal in 50 to 60 percent of stage IV breast cancer patients. The review also concludes that in longitudinal follow-up of patients during any kind of systemic therapy, serum HER-2/neu testing is complementary to HER-2/neu tissue results and to the determination of classical tumor markers such as CA15-3, CA27.29 and CEA, which are not targeted by specific forms of systemic therapy.

The course of serum HER-2/neu levels as an independent prognostic factor for survival in metastatic breast cancer
Schippinger W, Regitnig P, Bauernhofer T, Ploner F, Hofmann G, Krippl P, Wehrschutz M, Lax S, Carney W, Neumann R, Wernecke KD, Samonigg H. Oncol Rep 2004;11(6):1331–1336.

In this study, patients with continuously elevated serum HER-2/neu levels had a significantly poorer survival after disease recurrence compared to patients with continuously or temporarily nonelevated serum HER-2/neu values. The study concluded that decrease of elevated serum HER-2/neu to levels </=15 ng/ml and levels continuously </=15 ng/ml during the course of disease correlated significantly with longer survival.

HER-2/neu Summary Reviews

The following reviews summarize clinical experience with serum HER-2/neu testing to date, current clinical utility and possible future directions.

Monitoring the circulating levels of the HER-2/neu oncoprotein in breast cancer

Carney WP, Neumann R, Lipton A, Leitzel K, Ali S, Price CP. Clin Breast Cancer 2004;5(2):105–116.

This review notes that the prevalence of circulating HER-2/neu extracellular domain (ECD) is higher than generally known (about 18.1 percent in women with primary breast cancer; about 45.6 percent in women with metastatic breast cancer). Studies showed that serial changes in circulating HER-2/neu ECD levels consistently paralleled the clinical course of metastatic breast cancer. Conclusion: Serum HER-2/neu testing may be a new tool in detecting early evidence of metastatic disease.

HER-2 status is an important biomarker in guiding personalized HER-2 therapy

Carney, WP. Personalized Medicine 2005;2(4):317–324.

Among this review's conclusions: Identifying the HER-2/neu status of a patient is essential for guiding trastuzumab therapy; tissue tests indicate that 20-30 percent of patients with primary breast cancer have HER-2/neu-positive tumors, whereas an average 45 percent (23–80 percent) of metastatic breast cancer patients presented with HER-2-positive tumors by measuring HER-2/neu in their

serum. Serial monitoring studies with the serum HER-2/neu test have shown that an increase in levels may be reflective of progressive disease, while a decrease may indicate response to therapy or stable disease.

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Ordering Information

The following laboratories perform the Serum HER-2/ neu Test. Be sure to use the correct test number when ordering. The Serum HER-2/neu Test must be ordered by a physician.

Quest Diagnostics

Telephone: 1-800-222-0027
Test number: 15113X

Lab Corp

Telephone: 1-800-676-8033
Test number: 480136

Specialty Labs

Telephone: 1-800-421-7110
Test number S51008

ARUP(drawn in hospital labs and clinics)

Telephone: 1-800-522-2787
Test number: 0098615

HER2, IHC or FISH tissue testing is also available. Please call the lab for the correct code.

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