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#### **Legal Manufacturer**

Siemens Healthcare Diagnostics Inc.  
1717 Deerfield Road  
Deerfield, IL 60015-0778  
USA

#### **Global Division**

Siemens Healthcare Diagnostics Inc.  
1717 Deerfield Road  
Deerfield, IL 60015-0778  
USA  
[www.siemens.com/diagnostics](http://www.siemens.com/diagnostics)

#### **Siemens Global Headquarters**

Siemens AG  
Wittelsbacherplatz 2  
80333 Muenchen  
Germany

#### **Global Siemens Healthcare Headquarters**

Siemens AG  
Healthcare Sector  
Henkestrasse 127  
91052 Erlangen  
Germany  
Telephone: +49 9131 84 - 0  
[www.siemens.com/healthcare](http://www.siemens.com/healthcare)

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## **Understanding the Clinical Utility of Serum HER-2/neu**

Answers for life.

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# Current Advances in HER-2/neu Biomarker Testing

## Follow HER-2/neu for Life

Serum HER-2/neu is a blood test for more precise management of HER-2/neu metastatic breast cancer patients and for monitoring the effectiveness of therapy.

These clinical references highlight data indicating that serum levels of HER-2/neu 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 regimen.

### **Serum HER-2/neu change predicts clinical outcome to trastuzumab-based therapy**

**Ali SM, Esteva FJ, Fournier M, et al. J Clin Oncol, ASCO Annual Meeting Proceedings Part 1, 2006;24(18S, 6/20 Supplement);Abstract No. 500.**

In this report, Ali et al. presented data from seven clinical institutions and 307 metastatic breast cancer (MBC) patients who had the Serum HER-2/neu test before and after treatment (30-120 days) with trastuzumab-based therapy.

The results of this study allowed the 307 MBC patients who had the Serum HER-2/neu test before and after trastuzumab-based treatment to be divided into those with a greater than 20 percent decrease from baseline to first follow-up visit and those with a less than 20 percent decrease from baseline to the first follow-up visit. The patients whose Serum HER-2/neu levels decreased by less than 20 percent had a lower response rate; shorter duration of response; shorter time to progression; and decreased overall survival rate. The authors concluded that patients with <20% change from baseline should be considered for investigative agents in addition to trastuzumab.

### **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, Wiltshcke C, Zielinski CC. Clin Cancer Res 2004;10(5):1618-1624.**

This study was performed to determine if early changes in Serum HER-2/neu levels during trastuzumab-based treatment would predict the clinical course of disease in patients with metastatic breast cancer. In patients responding to treatment,



Serum HER-2/neu levels decreased significantly as early as day eight of treatment onward. In contrast, no significant change in Serum HER-2/neu levels was observed in patients with progressive disease. Multiple logistic regression analyses identified kinetics of Serum HER-2/neu levels as the only factor that allowed for the accurate prediction of response likelihood as early as from day eight of trastuzumab-based treatment onward. In addition, determination of serial HER-2/neu levels allowed for the prediction of the risk for disease progression within the observed period as early as day 15 of treatment.

**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**

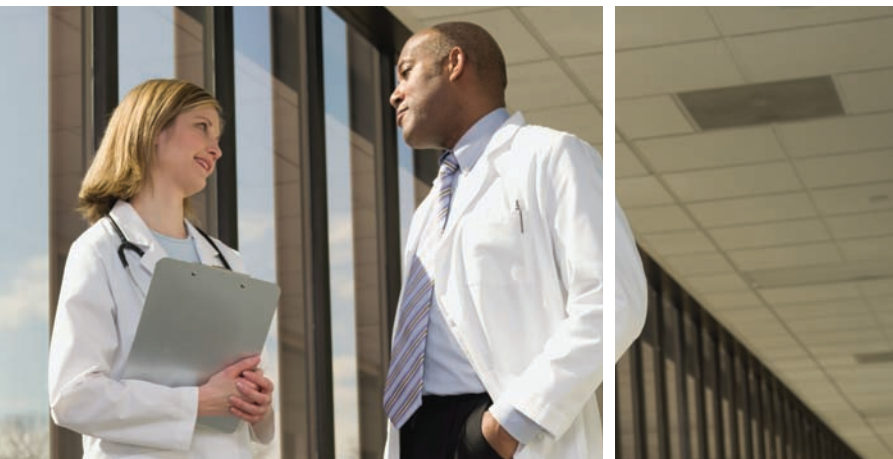
**Esteva FJ, Cheli CD, Fritsche H, Fornier M, Slamon D, Thiel RP, Lueftner D, Ghani F. Breast Cancer Res 2005;7(4):R436-443.**

The purpose of this retrospective study was to determine the clinical utility of Serum HER-2/neu in monitoring metastatic breast cancer patients undergoing trastuzumab-based therapy and to compare these results with those obtained using cancer antigen (CA) 15-3. Sera were obtained retro-

spectively from 103 women at four medical institutions. A baseline serum sample for each patient was taken before trastuzumab-based therapy was started. Patients were subsequently monitored over 12 to 20 months and serum samples were taken at the time of clinical assessment and tested with the Serum HER-2/neu or CA 15-3 tests.

Progression-free survival differed significantly ( $P = 0.043$ ) according to whether the patient's HER-2/neu concentration at 2 to 4 weeks after the start of therapy was  $>77\%$  or  $\leq 77\%$  of her baseline level. The median progression-free survival times for these two groups were 217 and 587 days, respectively.

These findings indicate that Serum HER-2/neu testing is clinically valuable in monitoring metastatic breast cancer patients undergoing trastuzumab-based treatment and provides additional value over the commonly used CA 15-3 test. The investigators concluded that the percentage of baseline HER-2/neu concentrations in the early weeks after the start 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.**

In this report, the investigators examined the relationship between Serum HER-2/neu levels and tissue HER-2 status as determined by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). They also examined the predictive value of Serum HER-2/neu in a cohort of metastatic breast cancer patients treated with weekly trastuzumab and paclitaxel.

In this study, the investigators reported a statistically significant association between pretreatment Serum HER-2/neu levels and tissue HER-2/neu status as assessed by IHC and FISH. A decrease in Serum HER-2/neu levels of over 55 percent from baseline was a significant predictor of response to trastuzumab-based therapy.

### **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 an elevated Serum HER-2/neu level (15 ng/mL or greater) occurred in approximately 26 percent of patients who received first-line hormone therapy with letrozole or tamoxifen. Conversion to Serum HER-2/neu-elevated 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.

**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, Krippel 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 levels. The study concluded that decrease of elevated Serum HER-2/neu to levels below 15 ng/mL and levels continuously  $\leq 15$  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 percentage of women with elevated Serum HER-2/neu due to the presence of a HER-2/neu-positive tumor is higher than generally known. Studies show on average that approximately

45.6 percent (range 23-80 percent) of patients with metastatic breast cancer have an elevated Serum HER-2/neu. The studies summarized in this review showed that serial changes in Serum HER-2/neu levels consistently paralleled the clinical course of metastatic breast cancer and provide a new tool for managing patients with HER-2/neu-positive breast cancer.



**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. However, evidence presented in this report shows HER-2/neu

tissue status can differ based on the test methods used at the time of HER-2/neu assessment. For instance, the HER-2/neu status of the primary breast cancer is used to determine if a patient will receive trastuzumab during MBC. However, not all HER-2/neu test results from the primary breast cancer are correct, which means there is a population of patients designated HER-2/neu negative by tissue tests that have HER-2/neu-positive tumors. This observation has important therapeutic implications for breast cancer patients with HER-2/neu-positive tumors who are not eligible for anti-HER-2/neu therapy.