Template for Reporting Results of HER2 (ERBB2) Biomarker Testing of Specimens From Patients With Adenocarcinoma of the Stomach or Esophagogastric Junction

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For the Members of the Cancer Biomarker Reporting Committee, College of American Pathologists
The College of American Pathologists offers these templates to assist pathologists in providing clinically useful and relevant information when reporting results of biomarker testing. The College regards the reporting elements in the templates as important elements of the biomarker test report, but the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these templates as educational tools to assist pathologists in the useful reporting of relevant information. It did not issue them for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the templates might be used by hospitals, attorneys, payers, and others. The College cautions that use of the templates other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: GastricHER2Biomarkers 1.0.0.0

Summary of Changes
This is a new template.
Gastric HER2 Biomarker Reporting Template

Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (e.g., a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient’s medical record and thus readily available to the treating clinical team.

STOMACH/ESOPHAGO Gastric JUNCTION

Select a single response unless otherwise indicated.

Note: Use of this template is optional.

+ RESULTS

+ HER2 (by immunohistochemistry)
  + __ Negative (score 0)
  + __ Negative (score 1+)
  + __ Equivocal (score 2+)
  + __ Positive (score 3+)
  + __ Indeterminate (explain): _________________________

+ HER2 (ERBB2) (by in situ hybridization)
  + __ Negative (not amplified)
  + __ Positive (amplified)
  + __ Indeterminate (explain): _________________________

+ Number of observers: _____
+ Number of invasive cancer cells counted: _____
+ __ Using dual-probe assay
  + Average number of HER2 (ERBB2) signals per cancer cell: _____
  + Average number of CEP17 signals per cancer cell: _____
  + HER2 (ERBB2):CEP17 ratio: _____
+ __ Using single-probe assay
  + Average number of HER2 (ERBB2) signals per cancer cell: _____

+ METHODS

+ HER2 (by immunohistochemistry)
  + __ US Food and Drug Administration (FDA) cleared (specify test/vendor): _________________________
  + __ Laboratory-developed test

+ Data elements preceded by this symbol are not required.
+ Primary Antibody
+ ___ 4B5
+ ___ HercepTest™
+ ___ A0485
+ ___ SP3
+ ___ C811
+ ___ Other (specify): __________________________

+ HER2 (ERBB2) (by in situ hybridization)
+ ___ FDA cleared (specify test/vendor): ______________
+ ___ Laboratory-developed test (specify probe): ______________


All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (www.hgvs.org/mutnomen/; accessed February 10, 2015).
HER2 (ERBB2) is a proto-oncogene located on chromosome 17 that encodes a 185-kd tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family whose phosphorylation initiates signaling pathways that lead to cell division, proliferation, differentiation, and apoptosis. The Human Genome Organisation (HUGO) Nomenclature Committee (HGNC) has designated ERBB2 as the approved symbol and CD340, HER-2, HER2, and NEU as synonyms (http://www.genenames.org/cgi-bin/gene_symbol_report?hgnc_id=3430). HER2 gene product is expressed in normal epithelial cells, and amplification and/or overexpression of this gene has been reported in up to 30% of breast cancers and in 9% to 27% of patients with gastric cancer. Overexpression in stomach cancer varies with histologic type (intestinal type greater than diffuse type) and differentiation (moderately differentiated greater than poorly differentiated).

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or esophageal gastric junction for whom trastuzumab (Herceptin) is under consideration for therapy, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) or in situ hybridization (ISH) is recommended by the National Comprehensive Cancer Network (NCCN). Results of an open-label, international, phase 3 randomized controlled trial in 2010 (Trastuzumab for Gastric Cancer [ToGA]) showed that the anti-HER2 humanized monoclonal antibody trastuzumab is effective in prolonging survival compared with chemotherapy alone in patients with HER2-positive adenocarcinoma of the stomach and the esophagogastric junction. HER2 (ERBB2) appears to be an important prognostic factor in gastric cancer, although the literature is conflicting, and not all studies have shown an association between HER2 overexpression and poor prognosis. Clinical trials with antibodies to HER2 in gastric cancer patients are in progress.

HER2 (ERBB2) status is assessed by testing either biopsy or surgical resection specimens. IHC evaluates membranous protein expression of cancer cells. Both intensity and percentage of immunoreactive cancer cells is assessed with scores ranging from 0 to 3+ (Table 1). ISH, which encompasses fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), and silver-enhanced in situ hybridization (SISH), identifies the presence or absence of gene amplification. Some assays use a single HER2 (ERBB2) probe to determine the number of HER2 (ERBB2) gene copies present, but most assays include a chromosome enumeration probe (CEP17) to determine the ratio of HER2 (ERBB2) signals to copies of chromosome 17. ISH has been used to verify IHC-equivocal cases. HER2-positive gastric cancer has been defined as IHC 3+ or ISH positive in the USA and Japan, and IHC 3+ or 2+ with ISH positivity in Europe. In the US, the FDA has approved trastuzumab in association with chemotherapy for metastatic gastric cancer utilizing the eligibility criteria of the ToGA trial, limited to patients with a score of IHC 3+ or 2+ and ISH positivity. No significant survival benefit was seen for patients who were IHC 0 or 1+ and FISH positive.

HER2 protein expression is more heterogeneous in gastric cancers than in breast cancers. The completeness of membrane staining required for positivity in breast cancers is infrequent in gastric adenocarcinomas, which often exhibit a basolateral staining pattern. Detection of HER2 (ERBB2) gene amplification by FISH is similar to that in breast cancer according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) 2013 guidelines, in which HER2 (ERBB2) amplification is defined as HER2 (ERBB2):CEP17 ratio of ≥2. Hoffman et al developed a four-tier scoring system for IHC (Table 1), also used in the ToGA trial, for gastric cancer by using the assessment area cutoff of at least 10% stained tumor cells for resection specimens and a small cluster of cells (≥5 neoplastic cells) for biopsy specimens. The NCCN guidelines recommend that assessment for HER2 status should be performed first using immunohistochemistry following the modified scoring system used in the ToGA trial. A score of 0 or 1+ is considered to be negative for HER2 expression. A score of 2+ is considered equivocal and should be confirmed with FISH or other in situ hybridization techniques. The NCCN panel recommends FISH only for cases with IHC 2+, although some institutions routinely perform
Background Documentation

both IHC and FISH on all cases. The guidelines recommend trastuzumab with chemotherapy only for patients with IHC 3+ and IHC 2+ with evidence of HER2 (ERBB2) amplification by ISH (HER2 (ERBB2):CEP17 ratio ≥2). Trastuzumab is not recommended if the IHC score is 0 or 1+.5

Table 1. Criteria Used in the ToGA Trial® for Scoring HER2 Expression by Immunohistochemistry (IHC) in Gastric and Esophagogastric Junction Adenocarcinoma

<table>
<thead>
<tr>
<th>HER2 IHC Score</th>
<th>HER2 IHC Pattern in Surgical Specimen</th>
<th>HER2 IHC Pattern in Biopsy Specimen</th>
<th>HER2 Expression Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No reactivity or membranous reactivity in &lt;10% of cancer cells</td>
<td>No reactivity or no membranous reactivity in any cancer cell</td>
<td>Negative by IHC</td>
</tr>
<tr>
<td>1+</td>
<td>Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane</td>
<td>Cancer cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive</td>
<td>Negative by IHC</td>
</tr>
<tr>
<td>2+</td>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in &gt;10% of tumor cells</td>
<td>Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive</td>
<td>Equivocal by IHC</td>
</tr>
<tr>
<td>3+</td>
<td>Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells</td>
<td>Cancer cell cluster with a strong complete basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

* Cancer cell cluster consisting of ≥5 neoplastic cells

References