Gastroesophageal adenocarcinoma (GEA) is estimated to represent up to 41,570 cancer cases in the US in 2015, and represents the eighth (esophageal) and fifth (stomach) most common cancers worldwide. HER2 (also known as 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. Amplification and/or overexpression of this gene has been reported in 7 to 38% of patients with GEA.

In 2010, results of an open-label, international, phase 3 randomized controlled trial (Trastuzumab for Gastric Cancer, ToGA), showed that the anti-HER2/neu humanized monoclonal antibody trastuzumab (Herceptin) is effective in prolonging survival compared with chemotherapy alone in patients with HER2–positive adenocarcinoma of the stomach and the gastroesophageal junction. For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or GE junction for whom Trastuzumab is being considered, assessment for tumor HER2 overexpression using IHC, FISH or other in-situ hybridization is recommended by the NCCN.

In 2007, a joint expert panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) met to develop guidelines for when and how to test for the HER2 gene, which is amplified and/or
overexpressed in up to 30% of primary breast cancers. In 2012, ASCO and CAP convened an Update Committee to conduct a formal and comprehensive review of the peer reviewed literature published since 2006 and to revise the guideline recommendations as appropriate. This information was used to help the Update Committee develop new algorithms (for pathologists and oncologists) for testing, specify testing requirements and exclusions, and facilitate the necessary quality assurance monitoring that will make HER2 testing less variable and ensure more analytic consistency between laboratories. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer were published in February of 2014 in the Archives of Pathology and Laboratory Medicine and in the Journal of Clinical Oncology.\(^9\)

There is currently no CAP/ASCO/ASCP-approved HER2 testing guideline for GEA, and the HER2 scoring criteria for GEA are different than the ASCO/CAP guidelines scoring criteria for breast cancer. A HER2 guideline for gastroesophageal cancer (that includes a scoring methodology) was recommended. The CAP, ASCP and ASCO convened an international and national expert panel to systematically review published documents and develop an evidence-based guideline to establish recommendations for HER2 testing in GEA. The team is co-chaired by two pathologists and one oncologist, and the expert and advisory panels consist of pathologists, oncologists, gastroenterologists, a patient advocate, and a support staff that includes a librarian and a methodologist.
A face to face meeting was convened in April of 2015 in Chicago with the co-chairs and members of the expert panel present. Here, the key questions were drafted and discussed, and criteria for a systematic review were decided. There were two clinical questions asked initially including:

1. What is the optimal testing algorithm for the assessment of HER2 status in patients with GEA?  
   – this question led to six main key questions.
2. What strategies can help ensure optimal performance, interpretation and reporting of established assays in patients with GEA?  
   – this led to ten other key questions.

Under Clinical question one, the six questions that arouse were:

1. Should HER2 testing be requested for every patient diagnosed with GEA?
2. Which of the following tissue specimen is the most appropriate to use for the test? (biopsy specimen from primary tumor, resection specimen, tissue from metastatic site, FNA or cytology specimen from primary or metastatic tumor)?
3. In patients with HER2 positive results, under what clinical scenario should HER2 targeted therapy be initiated?
4. Should HER2 directed therapy be delayed if HER2 status cannot be confirmed as positive or negative (i.e. if an equivocal result is found with IHC)?
5. Under what circumstances should patient samples be retested?
6. What are the clinical performance characteristics of IHC and ISH?

Under the second clinical question, ten additional questions arouse including:

7. What are the analytic performance characteristics of IHC and ISH?
8. What are the acceptable methodologies for HER2 IHC and ISH?

9. What is the optimal testing algorithm for the assessment of HER2 status?

10. What are the steps/procedures needed to analytically validate a laboratory developed HER2 GEA assay before reporting results on patient samples?

11. What is the best scoring method for IHC and ISH in GEA specimens?

12. How should HER2 results be reported?

13. What is adequate specimen handling for gastroesophageal adenocarcinoma testing?

14. What is the appropriate morphologic correlation for interpretation of ISH?

15. What are the optimal quality assurance/quality control standards that labs should adhere to?

16. Is there a role for HER2 genomic testing?

A comprehensive literature search was then conducted using Ovid MEDLINE as the primary database. Supplemental searches were also performed using PubMed, Scopus and from guideline repository sites such as the Agency for Healthcare Research and Quality (www.guidelines.gov) and Guidelines International Network (www.g-i-n.net). A total of 969 documents were obtained from all sources and a title/abstract review was performed. Two-hundred and eighty of these were moved forward for a full text review.

After the data extraction and quality assessment were performed and the evidence tables were made by the methodologist, the co-chairs and expert panel met face to face to discuss and review the data, tables and findings. The panel was guided by using the GuideLines Into DEcision Support (GLIDES) program which is a decision support program used to ensure standardization in the designation for the
strength of recommendations, as well as promoting transparency in the process and the Bridgewiz software \(^{(11)}\) to draft these actionable recommendations. The methodologist performed an assessment of all the articles included in the systematic review by examining the quality, quantity and consistency of the evidence. The quality of evidence was then included with each of the recommendations. Additionally, the expert panel gave its recommendations with regards to potential clinical impact by assessing benefits and harms for each recommendation, and then rated the quality of evidence for the recommendations as high, intermediate, low or insufficient. The Grading of Recommendations Assessment, Development and Evaluation, or GRADE method, was used to rate the quality of the evidence. \(^{(12)}\) As well, the CAP uses its own Strength of Recommendations, so during the face to face meeting, the panel also assessed the Strength of Recommendations and used the quality of evidence and mapped the CAP designation to the GLIDES designation.

The following preliminary draft recommendations were released in December of 2015 for a month long open public comment period through the CAP, ASCO and ASCP. A manuscript with comprehensive recommendations, explanations and supporting detail from the literature will follow and will be submitted for publication in the three society journals; Achieves of Pathology and Laboratory Medicine, American Journal of Clinical Pathology and the Journal of Clinical Oncology. Early online release is slated for Q2-Q3 2016.
PRELIMINARY DRAFT RECOMMENDATIONS:

(Note: These recommendations are in their draft form and are subject to change based upon the comments gathered during the open comment period.)

- **Strong Recommendation**: In patients with GEA who are potential candidates for HER2 targeted therapy, the treating clinician should request HER2 testing on tumor tissue. (Quality of evidence: High; Strength of recommendation: Strong)

- **Recommendation**: Treating clinicians or pathologist should request HER2 testing on tumor tissue in the biopsy or resection specimens (primary or metastasis) preferably prior to the initiation of trastuzumab therapy if such specimens are available and adequate. HER2 testing on FNA specimens (cell blocks) is an acceptable alternative. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

- **Strong Recommendation**: Treating clinicians should offer combination chemotherapy and HER2-targeted therapy as the initial treatment for appropriate patients with HER2 positive tumors who have metastatic or recurrent GEA. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong)

- **Strong Recommendation**: Treating clinicians should not offer HER2 targeted therapy as treatment for patients with metastatic or recurrent GEA until HER2 positivity by IHC or ISH is confirmed. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong)

- **Recommendation**: If there is documentation of a HER2 positive result in any specimen, the treating clinician does not need to request further HER2 testing.
Quality of evidence: Moderate/Intermediate; Strength of recommendation: Recommendation/Moderate)

- **Recommendation**: If there is no documentation of HER2 positive result and there is no available tumor tissue, the treating clinician and/or pathologist may obtain additional tumor tissue and request HER2 testing. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Recommendation/Moderate)

- **Strong recommendation**: Laboratories/pathologists must specify the antibodies and probes used for the test and ensure that assays are appropriately validated for HER2 IHC and ISH on GEA specimens. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong)

- **Strong Recommendation**: When GEA HER2 status is being evaluated, laboratories/pathologists should perform/order IHC testing first followed by ISH when IHC result is 2+ (equivocal). Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing. (Quality of evidence: High; Strength of recommendation: Strong)

- **Strong Recommendation**: The pathologist should use the Ruschoff/Hofmann method in scoring HER2 IHC and ISH results for GEA. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong)

- **Recommendation**: Pathologists should select the tissue block with the areas of lowest grade tumor morphology in biopsy and resection specimens. More than one tissue block may be selected if different morphologic patterns are present.
• **Strong Recommendation**: Pathologists should report HER2 testing results in GEA specimens using the CAP biomarker “Template for Reporting Results of HER2 (ERBB2) Biomarker Testing of Specimens from Patients with Adenocarcinoma of the Stomach or Esophagogastric Junction”. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong)

• **Strong Recommendation**: Pathologists should ensure that biopsies or resection specimens used for HER2 testing are rapidly placed in fixative, ideally within 1 hour (cold ischemic time) and are fixed in 10% neutral buffered formalin for 6 to 72 hours. Laboratories should test a sufficient number of such cases to ensure that assays consistently achieve expected results. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong)

• **Strong recommendation**: Pathologists should identify areas of invasive adenocarcinoma and also mark areas with strongest intensity of HER2 expression by IHC in GEA specimen for subsequent scoring when ISH is required. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong)

• **Strong Recommendation**: Laboratories must incorporate GEA HER2 testing methods into their overall laboratory quality improvement program, establishing appropriate quality improvement monitors as needed to assure consistent performance in all steps of the testing and reporting process. In particular, laboratories performing GEA HER2 testing must participate in a formal
proficiency testing program, if available, or an alternative proficiency assurance activity. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong)

- **No Recommendation**: There is insufficient evidence to recommend for or against genomic testing in GEA patients at this time.

- **Expert Consensus Opinion**: Laboratories must provide clinically appropriate turnaround times and optimal utilization of tissue specimens by using appropriate techniques (IHC and ISH) for HER2 in GEA. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Expert Consensus Opinion/Weak)

- **Expert Consensus Opinion**: In order to inform therapeutic decision-making, HER2 results should be reported promptly. (A benchmark of 90% of reports available within 10 working days from date of procedure for specimen acquisition). (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Expert Consensus Opinion/Weak)

- **Expert Consensus Opinion**: Laboratories that require send out of tests for HER2 testing in GEA should process and send specimens to reference laboratories in a timely manner. (The panel suggests a benchmark of 90% of specimens sent within 3 working days). (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Expert Consensus Opinion/Weak)

- **Expert Consensus Opinion**: Pathologists must evaluate candidate specimens for HER2 testing to ensure specimen adequacy taking into account tissue
viability, quantity, and malignant cell fraction. Specimen adequacy findings should be documented in the patient report. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Expert Consensus Opinion/Weak)

- **Expert Consensus Opinion**: Laboratories should establish policies to ensure efficient allocation and utilization of tissue for ancillary testing, particularly in small specimens. (Quality of evidence: Moderate/Intermediate; Strength of recommendation: Expert Consensus Opinion/Weak)
REFERENCES:


on rating quality of evidence and strength of recommendations. *BMJ.*
2008;336: 924–926.