

HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma:

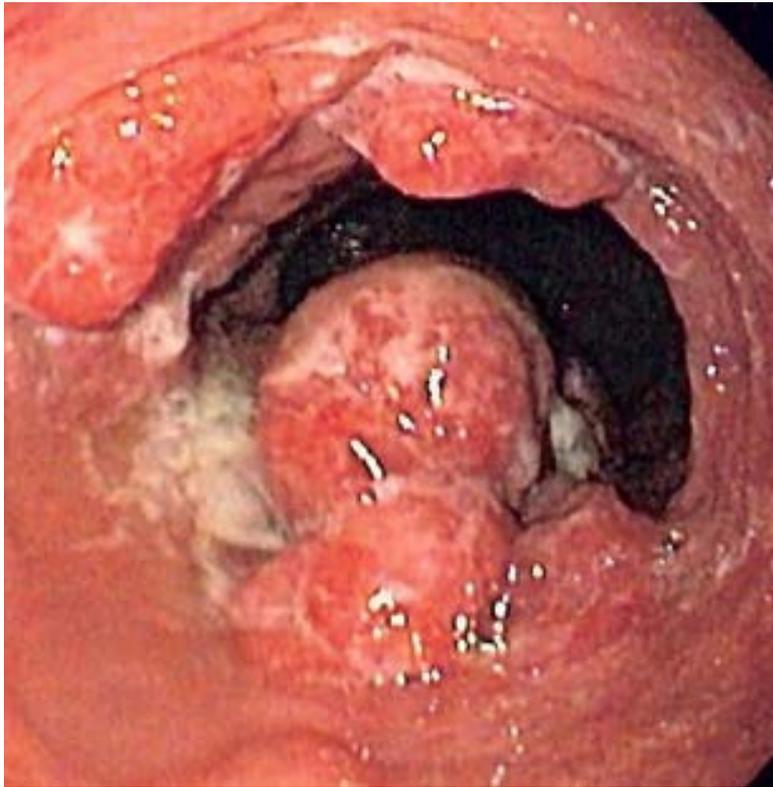
Guideline from the College of American Pathologists, American Society for Clinical Pathologists, and American Society of Clinical Oncology



Objectives

- **To establish an evidence-based guideline for HER2 testing in patients with gastroesophageal adenocarcinoma;**
- **To formalize the algorithms for methods to improve the accuracy of HER2 testing while addressing which patients and tumor specimens are appropriate**
- **To provide guidance on clinical decision making**

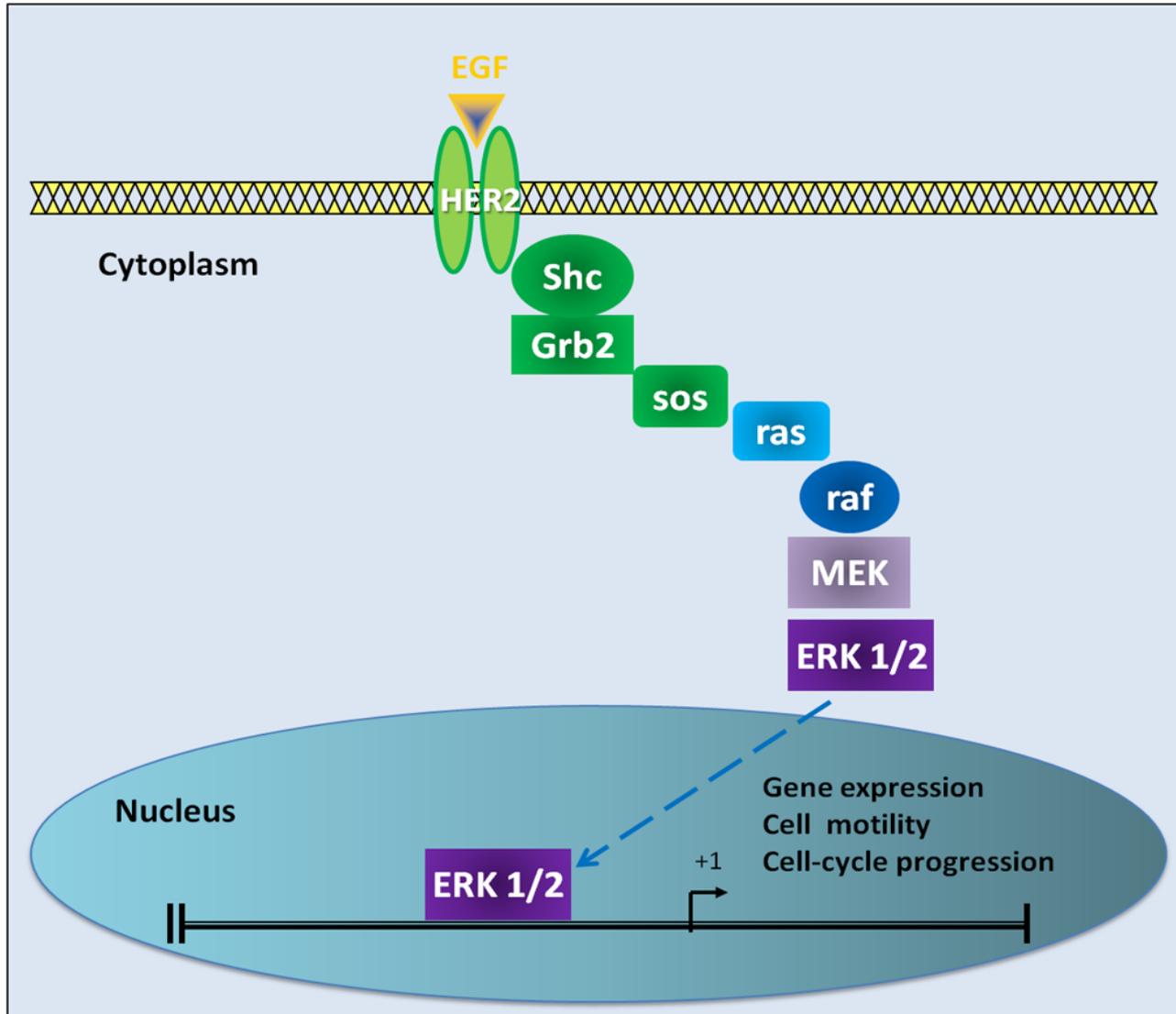
Gastroesophageal Adenocarcinoma (GEA)



<http://www.cancernetwork.com>

- **Esophageal: 8th**
 - **Stomach: 5th**
- Most common cancers worldwide**
- **Often diagnosed at an advanced stage**
 - **Therapies are limited**

HER2 (ERBB2)



Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

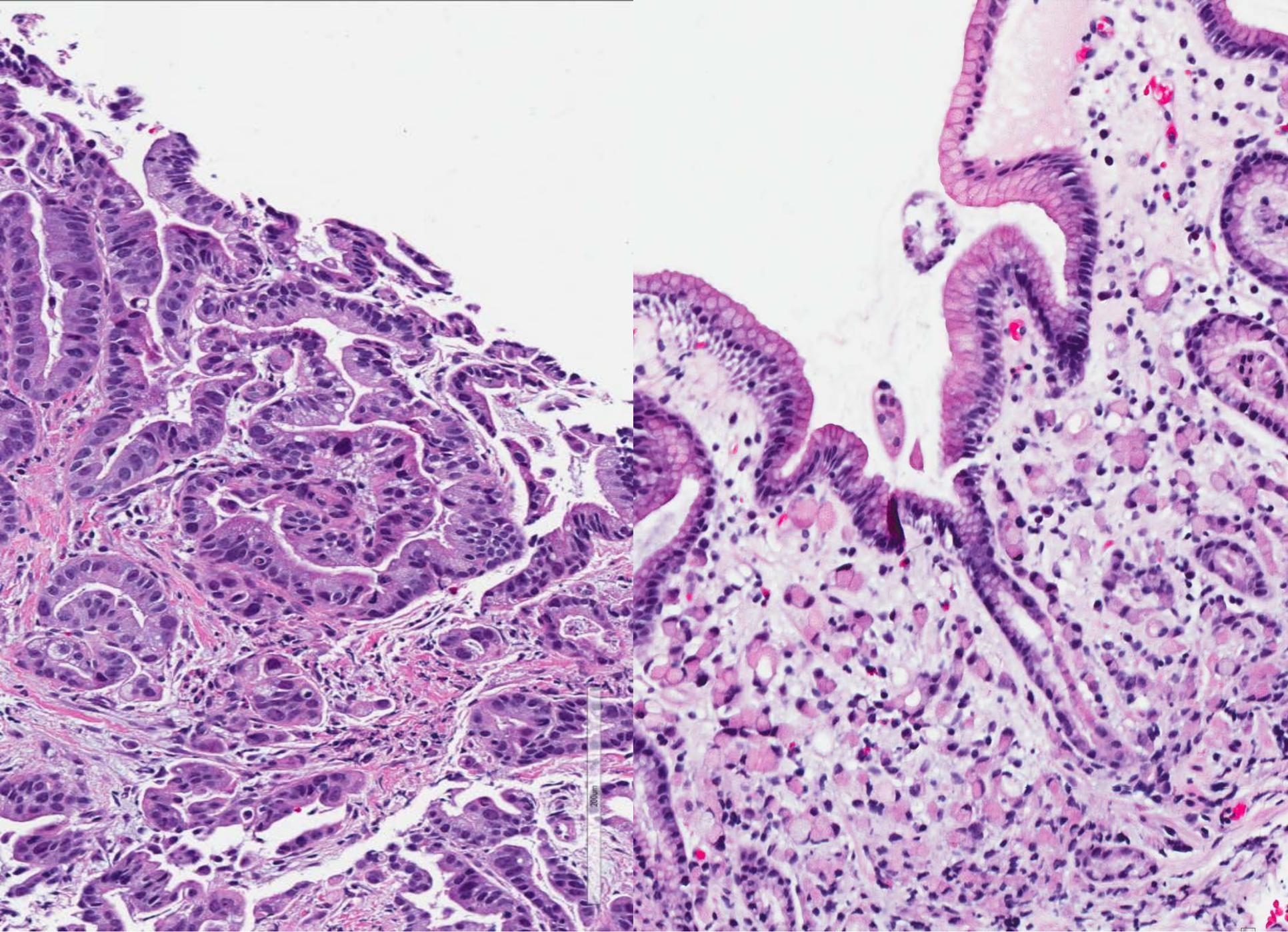
Yung-Jue Bang,* Eric Van Cutsem,* Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Satoh, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang, for the ToGA Trial Investigators†

Summary

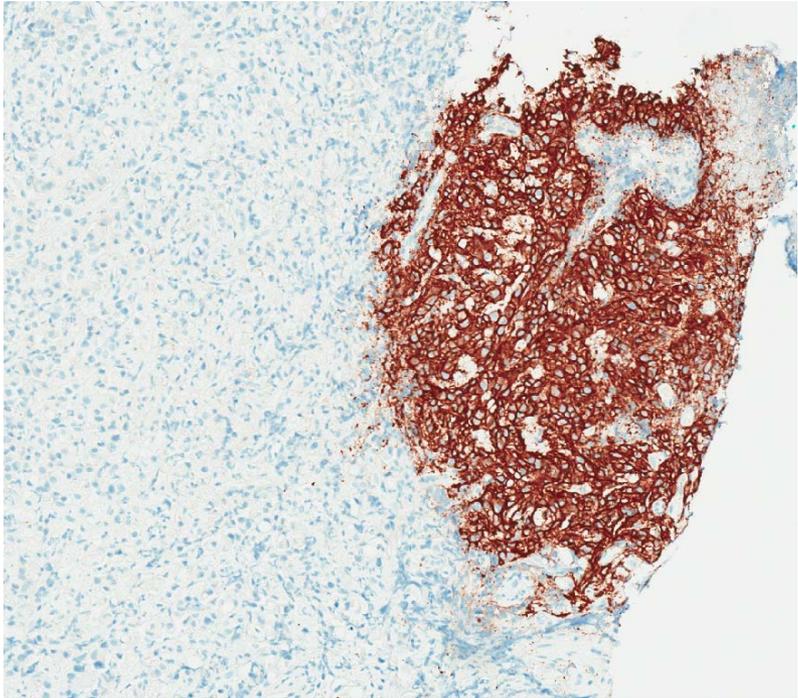
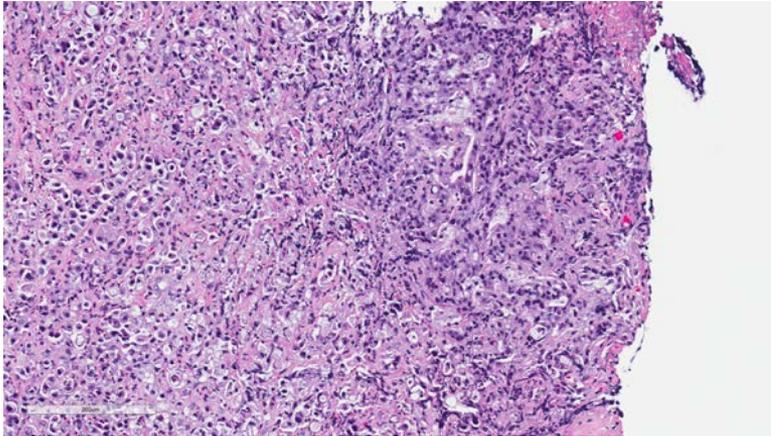
Background Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2; also known as ERBB2), was investigated in combination with chemotherapy for first-line treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer.

Methods ToGA (Trastuzumab for Gastric Cancer) was an open-label, international, phase 3, randomised controlled trial undertaken in 122 centres in 24 countries. Patients with gastric or gastro-oesophageal junction cancer were eligible for inclusion if their tumours showed overexpression of HER2 protein by immunohistochemistry or gene amplification by fluorescence in-situ hybridisation. Participants were randomly assigned in a 1:1 ratio to receive a chemotherapy regimen consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin given every 3 weeks for six cycles or chemotherapy in combination with intravenous trastuzumab. Allocation was by block randomisation stratified by Eastern Cooperative Oncology Group performance status, chemotherapy regimen, extent of disease, primary cancer site, and measurability of disease, implemented with a central interactive voice recognition system. The primary endpoint was overall survival in all randomised patients who received study medication at least once. This trial is registered with ClinicalTrials.gov, number NCT01041404.

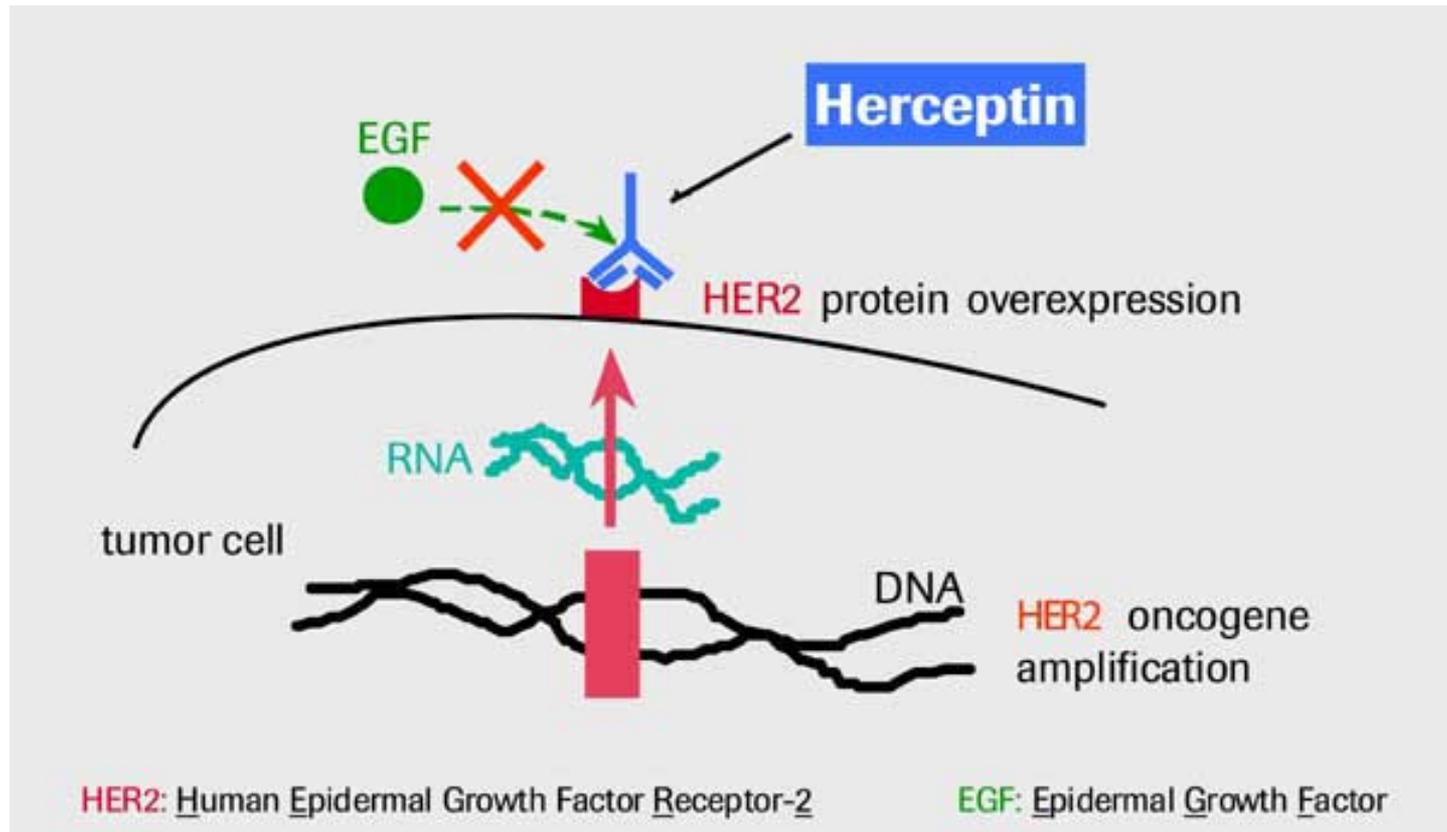
Source: Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010;376(9742):687-697.



HER2 expression by IHC



Trastuzumab (Herceptin)



Background

- **2007- expert panel with members from American Society of Clinical Oncology (ASCO) and the College of American Pathology (CAP)**
 - **Guidelines for when and how to test for the *HER2* gene in breast cancer**
 - **Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: the American Society of Clinical Oncology/College of American Pathologists Clinical Practice Update**

Source: Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997-4013.

Background, continued

- There are important, distinct differences in *HER2* expression, scoring, and outcomes in gastroesophageal adenocarcinoma relative to breast carcinoma
- There was a need for a HER2 Testing guideline for GEA
- The CAP (Pathology and Laboratory Quality Center), ASCP and ASCO convened a panel of pathologists, oncologists, and a gastroenterologist to develop an evidence-based guideline for optimal *HER2* testing in patients with gastroesophageal adenocarcinoma

HER2 Testing in GEA Project Team

Co-Chairs

Angela N. Bartley, MD – CAP
M. Kay Washington, MD – ASCP
Jaffer Ajani, MD - ASCO

Expert Panel

Al Benson, III, MD
Alfredo Carrato, MD, PhD
Margaret Gulley, MD
Dhanpat Jain, MD
Sanjay Kakar, MD
Srinadh Komanduri, MD
Helen Mackay, MD
Catherine Streutker, MD
Laura Tang, MD, PhD
Megan Troxell, MD, PhD

Advisory Panel

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Katherine Geiersbach, MD
Syma Iqbal, MD
Rahul Jawale, MD
Alyssa Krasinskas, MD
Shiwen Song, MD
William Sukov, MD
Hanlin Wang, MD, PhD
Christopher Willett, MD
Christa Whitney-Miller, MD

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Nofisat Ismaila, MD (ASCO)

Systematic Evidence Review

- **Identify key questions**
- **Literature search**
- **Data extraction**
- **Developed draft recommendations**
- **Open comment period**
- **Considered judgment process**
 - **Consider risk and benefits, cost, regulatory requirements, preferences, etc.**

Key Questions – For Clinicians

Clinical Question 1

What is the optimal testing algorithm for the assessment of HER2 status in patients with gastroesophageal adenocarcinoma?

- Should HER2 testing be requested for every patient diagnosed with GEA?
- Which of the following tissue specimen is the most appropriate to use for testing? (Biopsy specimen from primary tumor, resection specimen, tissue from metastatic site, or FNA or cytology specimen from primary or metastatic tumor)
- In patients with HER2 positive results, under what clinical scenario should HER2 targeted therapy be initiated?

Key Questions – For Clinicians, cont.

Clinical Question 1

What is the optimal testing algorithm for the assessment of HER2 status in patients with gastroesophageal adenocarcinoma?

- 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)?
- Under what circumstances should patient samples be retested?
- What are the clinical performance characteristics of IHC and ISH? (positive and negative predictive values, overall and progression free survival, response to treatment, outcomes, etc.)

Key Questions – For Pathologists

Clinical Question 2

What strategies can help ensure optimal performance, interpretation and reporting of established assays in patients with gastroesophageal adenocarcinoma?

- What are the analytic performance characteristics of IHC and ISH?
- What are the acceptable methodologies for HER2 IHC and ISH?
- What is the optimal testing algorithm for the assessment of HER2 status?

Key Questions – For Pathologists, cont.

Clinical Question 2

What strategies can help ensure optimal performance, interpretation and reporting of established assays in patients with gastroesophageal adenocarcinoma?

- What are the analytic performance characteristics of IHC and ISH?
- What are the acceptable methodologies for HER2 IHC and ISH?
- What is the optimal testing algorithm for the assessment of HER2 status? What are the steps/procedures needed to analytically validate a laboratory developed HER2 gastroesophageal adenocarcinoma assay before reporting results on patient samples?
- What is the best scoring method for IHC and ISH in gastroesophageal adenocarcinoma specimens?

Key Questions – For Pathologists, cont.

Clinical Question 2

What strategies can help ensure optimal performance, interpretation and reporting of established assays in patients with gastroesophageal adenocarcinoma?

- How should HER2 results be reported?
- What is adequate specimen handling for gastroesophageal adenocarcinoma testing?
- What is the appropriate morphologic correlation for interpretation of ISH?
- What are the optimal quality assurance/quality control standards that labs should adhere to?
- Is there a role for HER2 genomic testing?

Systematic Evidence Review Results

Literature Search

- Literature search for January 1, 2008 – June 1, 2015
- Title Abstract Review – 969 abstracts
- Full Text Review – dual review of 280 full text articles
- Data Extraction – 116 articles

Draft Recommendations

- Data from the systematic review helped the panel formulate 22 draft recommendations

Open Comment Period

- Public comment period hosted with 294 total comments with >80% agreement

Final Recommendations

- Expert panel finalized the recommendations, considering all the comments received during the open comment period.
- The expert panel drafted the supporting manuscript

Strength and Quality of Recommendations

- **Quality assessment, review and judgement of clinical impact (benefits and harms)**
- **Strength of recommendations: Guidelines Into Decision Support (GLIDES) program**
- **Quality of evidence: Grading of Recommendations Assessment, Development and Evaluation (GRADE) method**

Strength of Recommendations

CAP Designation	GLIDES Designation	Recommendation	Rationale
Strong Recommendation	Strong	Recommend For or Against a particular practice (Can include must or should)	Supported by high (convincing) or intermediate (adequate) quality of evidence and clear benefit that outweighs any harms
Recommendation	Moderate	Recommend For or Against a particular practice (Can include should or may)	Some limitations in quality of evidence (intermediate [adequate] or low [inadequate]), balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation.
Expert Consensus Opinion	Weak	Recommend For or Against a particular practice (Can include should or may)	Serious limitations in quality of evidence (low [inadequate] or insufficient), balance of benefits and harms, values or costs, but panel consensus is that a statement is necessary.
No Recommendation	N/A	No recommendation for or against a particular practice	Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation

Guideline Statement and Strength of Recommendations

Guideline statement 1

In patients with advanced GEA who are potential candidates for HER2 targeted therapy, the treating clinician should request *HER2* testing on tumor tissue.

Strength of recommendation: Strong

Quality of evidence: High

Guideline statement 1, continued

Rationale: HER2 status provides additional guidance for the addition of trastuzumab to therapy. Addition of *HER2*-targeted therapy can increase response rate and improve progression-free survival and overall survival

Guideline statement 2

Treating clinicians or pathologists 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.

Strength of recommendation: Recommendation

Quality of evidence: Moderate/Intermediate;

Guideline statement 2, continued

Rationale:

- **High degree of concordance between primary and metastatic**
- **FNA specimens are acceptable alternatives in the absence a primary or metastatic specimen**
 - **Minimum 5 biopsy fragments, optimally 6-8**

Guideline statement 3

Treating clinicians should offer combination chemotherapy and HER2-targeted therapy as the initial treatment for appropriate patients with *HER2* positive tumors who have advanced GEA.

Strength of recommendation: Strong

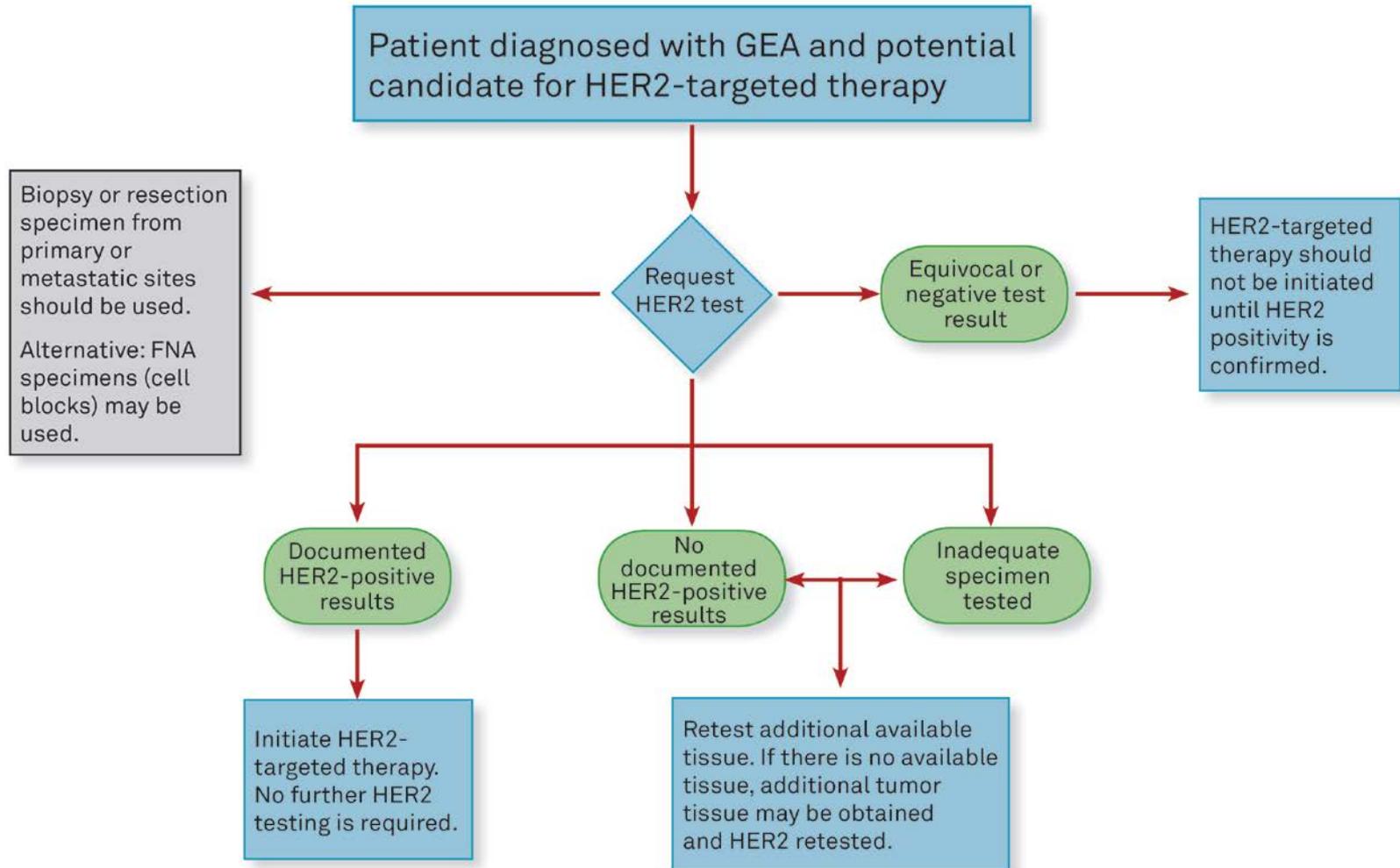
Quality of evidence: Moderate/Intermediate

Guideline statement 3, continued

Rationale:

- **HER2-targeted therapy was established as a new standard of care for the first-line treatment of patients with advanced GEA with HER2-positive tumors**
- **Treating clinicians must confirm HER2 positivity before offering HER2-targeted therapy**

HER2 Testing in Gastric Cancer: Algorithm for Clinicians



Guideline statement 4

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.

Strength of recommendation: Strong

Quality of evidence: Moderate/Intermediate

Guideline statement 4, continued

Rationale:

- **Multiple antibodies and methods available for HER2 IHC with good concordance.**
- **Various in-situ hybridization methods are comparable.**
- **Methods to determine HER2 status must be validated appropriately.**

Guideline statement 5

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.

Strength of recommendation: Strong

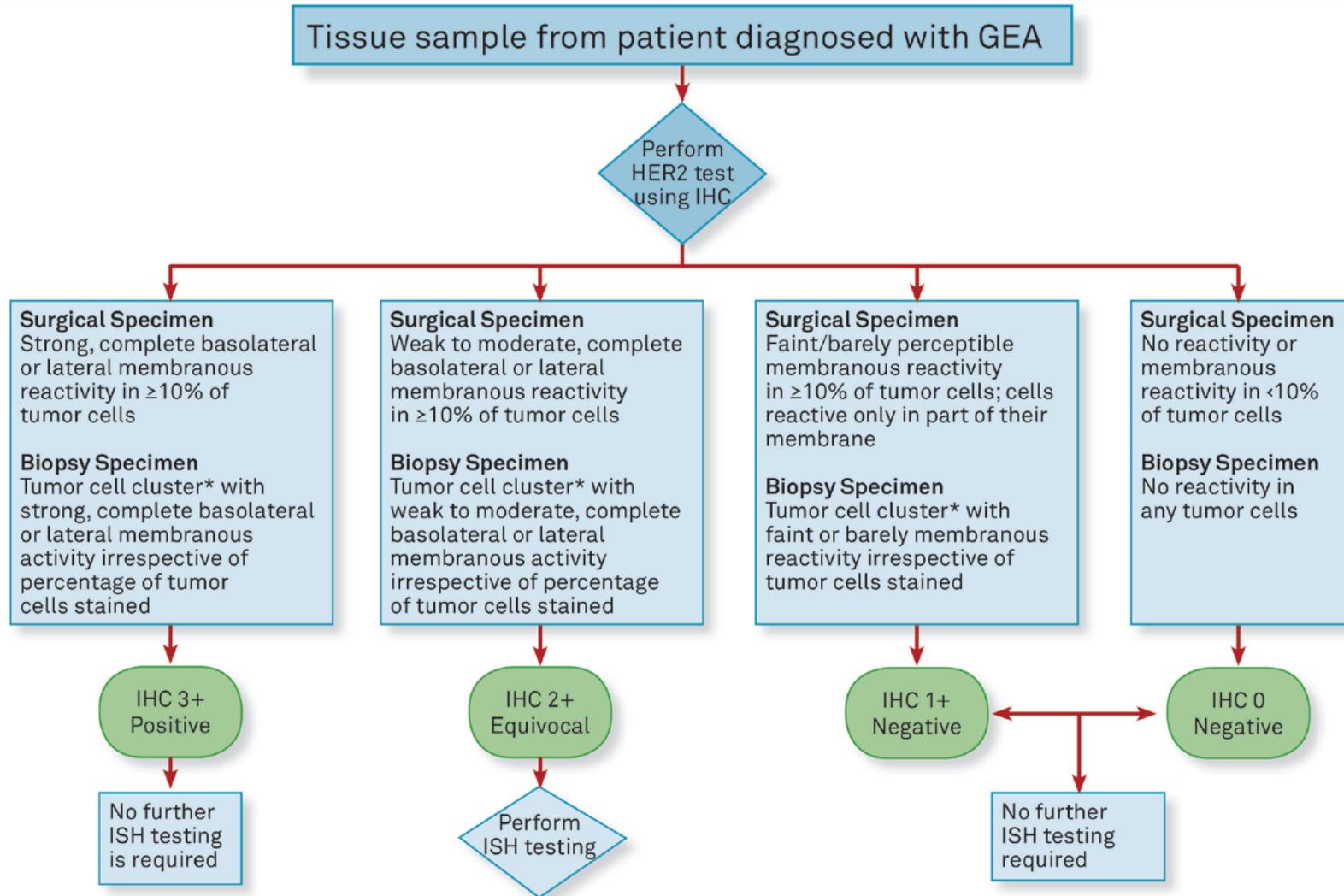
Quality of evidence: High

Guideline statement 5, continued

Rationale:

- **ISH testing only for 2+ IHC**
- **ISH testing not recommended for 0, 1+ and 3+ IHC**
- ***Note:* Interobserver variation can be seen with the 1+ and 2+ IHC. If IHC is borderline, ISH testing should be considered. However, this is not recommended for cases that show an obvious 1+ IHC score.**

HER2 Testing in Gastric Cancer: Algorithm for Pathologists



Guideline statement 6

Pathologists should use the Ruschoff/Hofmann method in scoring HER2 IHC and ISH results for GEA.

Strength of recommendation: Strong

Quality of evidence: Moderate/Intermediate

Guideline statement 6, continued

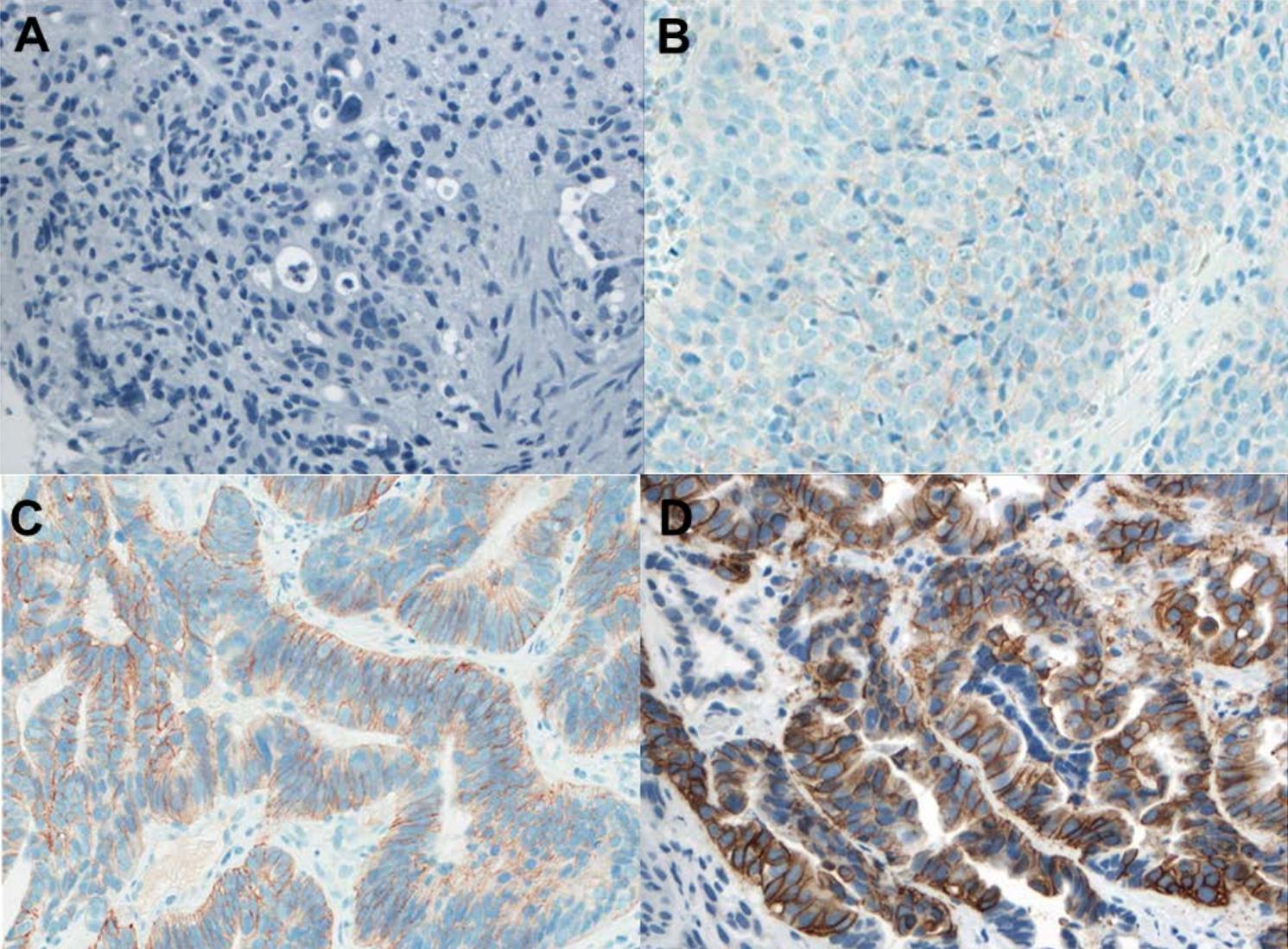
Rationale:

- **The scoring system (next slide) used in the ToGA trial and subsequently modified for biopsies has been used in many studies and has shown excellent correlation between IHC and gene amplification methods.**

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

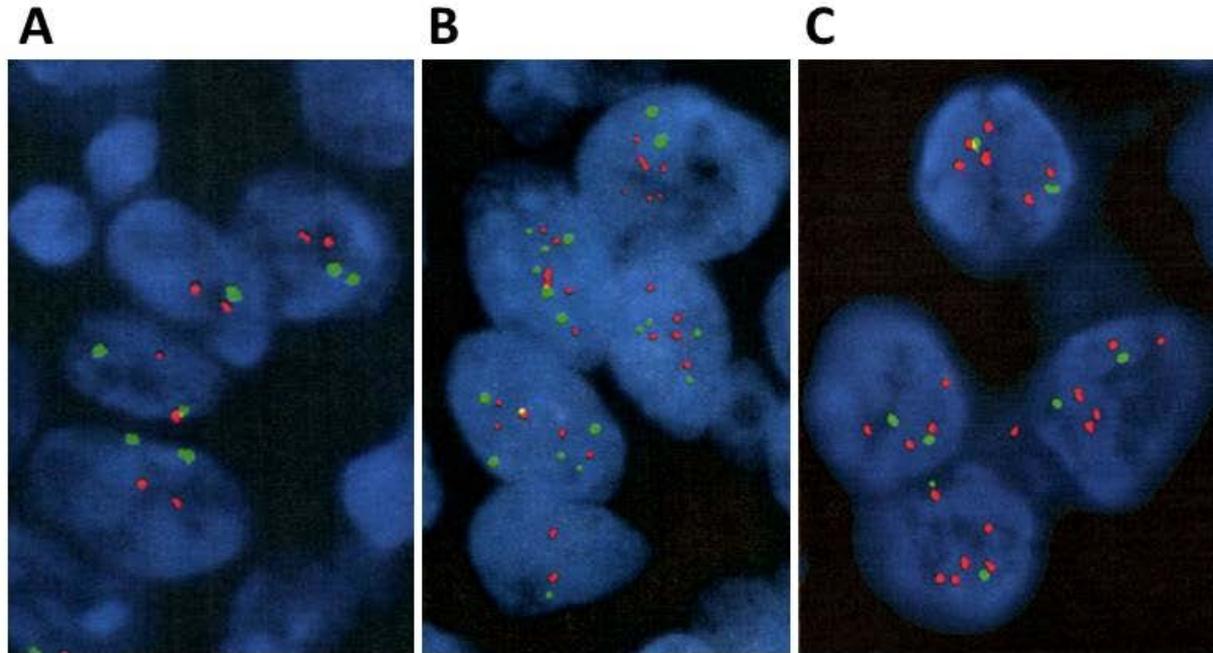
* Cancer cell cluster consisting of ≥5 neoplastic cells

Representative GEA IHC examples



A, Negative 0; B, Negative 1+; C, Equivocal 2+; D=Positive 3+

HER2 and CEP17 FISH Cases



HER2 and CEP 17 fluorescence in situ hybridization (FISH) shows scores of representative cases. (A) Not amplified: Ratio 1.0. Mean number of *HER2* signals per cell is 1.9; mean number of CEP 17 signals per cell is 1.8; (B) Not amplified: Ratio 1.3. Mean number of *HER2* signals per cell is 3.4; mean number of CEP 17 signals per cell is 2.7. Segmental duplication (or polysomy) likely accounts for signal numbers over 2 per cell; (C) Amplified: Ratio 3.0. Mean number of *HER2* signals per cell is 5.2; mean number of CEP 17 signals per cell is 1.7.

Abbreviation: CEP, chromosome enumeration probe. Figures courtesy of University of North Carolina Department of Pathology and Laboratory Medicine.

Guideline statement 7

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.

Strength of recommendation: Recommendation

Quality of evidence: Moderate/Intermediate

Guideline statement 7, continued

Rationale:

- **Selecting tissue blocks with the lower grade or intestinal morphology appears more likely to yield HER2-positive results**
- **If the cancer comprises substantially different grades or histologic patterns, test different areas, which may require selection of more than 1 block**

Guideline statement 8

Laboratories should report HER2 test results in GEA specimens in accordance with the CAP “Template for Reporting Results of *HER2 (ERBB2)* Biomarker Testing of Specimens From Patients With Adenocarcinoma of the Stomach or Esophagogastric Junction”

Strength of recommendation: Strong Recommendation

Quality of evidence: Moderate/Intermediate

Guideline statement 8, continued

Rationale:

- **The synoptic content of the CAP “Template for Reporting Results of *HER2 (ERBB2)* Biomarker Testing of Specimens From Patients With Adenocarcinoma of the Stomach or Esophagogastric Junction” lists essential reporting elements.**

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

Template web posting date: June 2014

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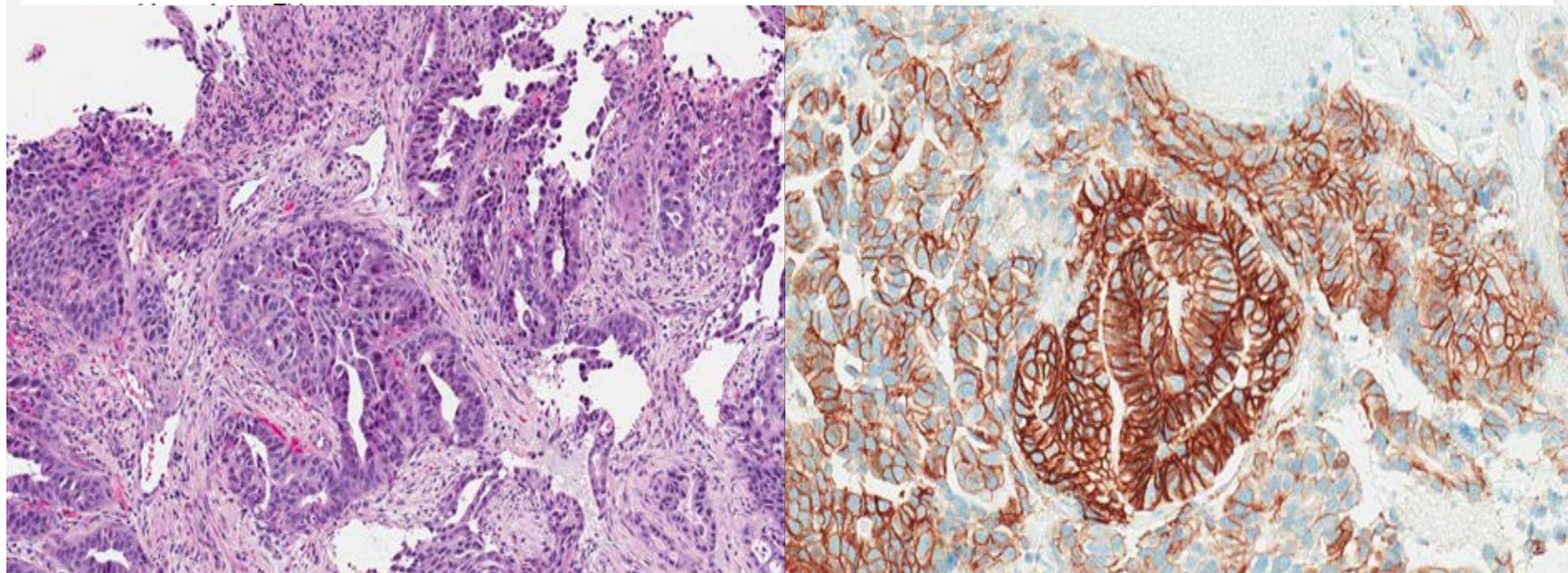
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Source: Bartley AN, Christ J, Fitzgibbons PL, et al. Template for reporting results of *HER2* (*ERBB2*) biomarker testing of specimens from patients with adenocarcinoma of the stomach or esophagogastric junction. *Arch Pathol Lab Med*. 2015;139(5):618-620.

Guideline statement 9

Pathologists should identify areas of invasive adenocarcinoma and also mark areas with strongest intensity of HER2 expression by IHC in GEA specimen for subsequent ISH scoring when required.

**Strength of recommendation: Strong
Recommendation**

Quality of evidence: Moderate/Intermediate

Guideline statement 9, continued

Rationale:

- **Areas of invasive cancer should be marked so that the scorer may scan these areas to identify regions enriched for amplification to prioritize for scoring.**
- **Good communication is essential to have between the histopathologist and the scorer to resolving difficult interpretations.**

Guideline statement 10

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 should participate in a formal proficiency testing program, if available, or an alternative proficiency assurance activity.

Strength of recommendation: Strong Recommendation

Quality of evidence: Moderate/Intermediate

Guideline statement 10, continued

Rationale:

- **Quality measures must be followed by laboratories testing HER2 for GEA. In particular:**
 - **GEA specimens used for positive quality control**
 - **Participation in proficiency testing**
 - **GEA HER2 testing methods must be validated, if possible, HER2 GEA specimens are preferred to use as positive control.**
 - **The use of checklists for documentation**
 - **Continuing education**

Guideline statement 11

There is insufficient evidence to recommend for or against genomic testing in GEA patients at this time.

Rationale:

- **Currently, the genomic testing is used to help classify cases that are uninterpretable with standard IHC or ISH technology (eg, borderline amplification with or without extra centromere 17 signals by ISH.**

Guideline statement 11, continued

Rationale:

- **There is insufficient evidence to provide recommendations for or against the routine use of genomic technologies for purposes of qualifying for HER2-targeted therapy**

Pitfalls in IHC Assessment

- **Gastric intestinal metaplasia and epithelium next to ulcers**
- **Edge effect**
- **Non-specific granular and pericellular staining**
- **Diffuse cytoplasmic and/or nuclear staining**

Comparison of HER2 Scoring in GEA and Breast Carcinoma

		Esophagogastric	Breast
IHC	Extent	Biopsy ≥ 5 cells; resection $\geq 10\%$	$\geq 30\%$
	Circumferential	Mostly missing	Required for IHC2+/3+
ISH	Cell number	20 cohesive tumor cells showing highest gene count	Same
	Amplification	<i>HER2/CEP17</i> ≥ 2.0 is positive	<i>HER2/CEP17</i> ≥ 2.2 is positive
HER2 +	Tumor type	~ 30% intestinal type, 15% mixed type, 5% diffuse type	15-25% G2/G3 ductal type; special types rarely +
	Tumor location	~ 30% of GEJ, 15% gastric	No correlation

Polysomy scoring in ISH

- **>6 copies of *HER2* = positive**
- **<4 copies of *HER2* = negative**
- **4 to ≤ 6 copies of *HER2* = count an additional 20 cells**
 - **May use ancillary techniques:**
 - **Multiplex ligation-dependent probe amplification**

Additional Options For Indeterminate Scoring

- **Consultation between scorer and pathologist**
- **Using an alternate probe for chromosome 17**
- **Select a different tumor block**
- **Use genomics or alternate method**

Quality Assurance

- **Assure adequate staining without:**
 - **Background interference**
 - **Overdigestion**
 - **Other artifacts**
- **Failure to detect probe signals in non-malignant cells can indicate poor quality hybridization**

Other techniques used to determine *HER2* status

- **Polymerase chain reaction (PCR)**
- **Single nucleotide polymorphism (SNP) chip**
- **Comparative genomic hybridization (CGH) array**
- **Gene expression profiling by RNAseq or microarray**
- **Targeted/exome/whole genome sequencing**

Conclusions

- **HER2 testing is appropriate for advanced or metastatic GEA**
- **Guidelines recommend use of IHC first, followed by ISH for 2+ cases**
- **Use the Ruschoff/Hoffman scoring system**
- **Scoring systems for HER2 in breast cancer are not appropriate for GEA**

Link to Guideline

<http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2016-0331-CP>



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