GENERAL

asco cap her2 test guideline recommendations

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Introduction

Herceptin (trastuzumab) and other HER2-targeted therapies have revolutionized the treatment of HER2-positive breast cancer. Accurate determination of HER2 status is therefore essential for selecting patients who will benefit from these agents. Over the past decade, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) have developed evidence-based guidelines to standardize HER2 testing. These **ASCO CAP HER2 test guideline recommendations** provide a framework that covers specimen handling, immunohistochemistry (IHC), in situ hybridization (ISH), reflex testing, quality control, and reporting. In this article, we walk through each component of the guidelines, explain the rationale behind key decisions, and offer practical tips for implementing them in a routine pathology laboratory.

Understanding HER2 in Breast Cancer

What is HER2?

HER2, or human epidermal growth factor receptor 2, is a transmembrane tyrosine kinase receptor that regulates cell proliferation, differentiation, and survival. In approximately 15–20% of invasive breast cancers, HER2 is overexpressed or amplified, driving aggressive tumor behavior. Because HER2 is a druggable target, determining its expression level is critical for therapeutic decision making.

Role of HER2 in Tumor Biology

HER2 overexpression leads to constitutive signaling through the PI3K/AKT and MAPK pathways, promoting rapid cell growth and resistance to apoptosis. Tumors that are HER2-positive often display higher rates of recurrence and poorer overall survival compared with HER2-negative disease. However, the advent of HER2-directed agents has dramatically improved outcomes, making precise testing a cornerstone of personalized oncology care.

ASCO CAP HER2 Testing Guidelines

History and Evolution

In 2001, ASCO and CAP first published a joint statement on HER2 testing. Since then, the guidelines have been periodically updated to reflect advances in assay technology, emerging evidence, and regulatory changes. The most recent revision (2018) emphasizes a reflex testing strategy that integrates IHC and ISH, and introduces stringent quality control requirements for laboratories worldwide.

Core Recommendations

- Dual modality testing: IHC is the initial screening method; ISH is used for equivocal IHC results.
- Standardized scoring: IHC scores range from 0 to 3+, while ISH results are reported as amplified or non amplified based on HER2/CEP17 ratio or copy number.
- Reflex testing thresholds: IHC 0 or 1+ !’ HER2-negative; IHC 2+ !’ reflex to ISH; IHC 3+ !’ HER2-positive.
- Quality assurance: Laboratories must participate in CAP proficiency testing and maintain internal QC metrics.
- Reporting: Results should include the testing methodology, score, and interpretation in the context of clinical management.

Specimen Collection and Handling

Tissue Types

HER2 testing can be performed on formalin fixed, paraffin embedded (FFPE) tissue obtained via core needle biopsy, excisional biopsy, or surgical resection. Fresh or frozen tissue is not recommended because fixation preserves antigenicity and nucleic acid integrity.

Fixation Protocols

- Formalin fixation must be 10% neutral buffered formalin (NBF) for a minimum of 6 hours and a maximum of 72 hours to avoid over fixation.
- Transport to the laboratory should be within 24 hours of excision; prolonged cold storage (>48 hours) can degrade HER2 epitopes.
- Documentation of fixation time and conditions is essential for reproducibility and quality audit.

In Situ Hybridization (ISH) Testing

FISH vs CISH

Two ISH modalities are endorsed by the guidelines:

- Fluorescence in situ hybridization (FISH) uses fluorescent probes to detect HER2 gene amplification. It is considered the gold standard for confirming equivocal IHC results.
- Chromogenic in situ hybridization (CISH) employs chromogenic probes that can be visualized under a standard bright field microscope, allowing simultaneous assessment of HER2 protein and gene status.

Both methods require a HER2/CEP17 ratio "e2.0 or a HER2 copy number "e6.0 per cell as criteria for amplification.

Interpretation Criteria

1. Amplification: HER2/CEP17 ratio "e2.0 or average HER2 copy number "e6.0 per cell.
2. Non amplification: HER2/CEP17 ratio
3. Equivocal: Rare cases may present with mixed signals; these require expert review and potential repeat testing.

Immunohistochemistry (IHC) Testing

Antibody Selection

The ASCO CAP guidelines recommend the use of FDA approved HER2 antibodies (e.g., 4B5, SP3, or 4A4). Antibody selection should be validated for each laboratory’s platform, and cross reactivity with other HER family members must be excluded.

Scoring System

IHC results are scored as follows:

- 0: No staining or membrane staining in
- 1+: Faint/barely perceptible membrane staining in >10% of tumor cells.
- 2+: Weak to moderate complete membrane staining in >10% of tumor cells.
- 3+: Strong complete membrane staining in >10% of tumor cells.

Only a score of 3+ is considered HER2-positive; 0 or 1+ is negative; 2+ is equivocal and triggers reflex ISH testing.

Reflex Testing Strategies

When to Reflex IHC to ISH

Any sample with an IHC score of 2+ requires reflex ISH testing according to the ASCO CAP recommendations. This approach minimizes false negative results and ensures that patients receive accurate HER2 status for therapy selection.

When to Reflex ISH to IHC

In rare instances where an ISH test indicates amplification but the corresponding IHC is 0 or 1+, a second IHC evaluation may be warranted to rule out pre analytical errors or intratumoral heterogeneity. The guidelines advise repeating the IHC on a fresh section or a different tumor block.

Quality Assurance and Accreditation

CAP Participation

Participation in the CAP HER2 Proficiency Testing program is mandatory for laboratories performing HER2 testing. The program includes blinded test cases, scoring rubrics, and detailed feedback reports. Laboratories must achieve a minimum score of 90% to maintain accreditation.

External Quality Assessment

In addition to CAP, laboratories should consider external quality assessment schemes such as the College of American Pathologists External Quality Assurance (CAP EQA) or the International Organization for Standardization (ISO) 15189. These initiatives help identify systematic errors and benchmark performance against global standards.

Practical Implementation in the Pathology Lab

Workflow Integration

To streamline HER2 testing:

- Implement a “HER2 reflex order” in the laboratory information system (LIS) that automatically triggers ISH when IHC is 2+.
- Allocate dedicated IHC and ISH technicians to ensure timely processing.
- Use barcoded slide identifiers to prevent mix ups.

Documentation and Reporting

Reports should include:

- Methodology (IHC or ISH) and antibody/probe details.
- Scoring and interpretation (e.g., “HER2 2+ (equivocal); ISH amplification confirmed (HER2/CEP17 ratio 3.2) – HER2-positive”).
- Quality control metrics (e.g., internal positive/negative controls).
- Recommendations for clinical management (e.g., eligibility for trastuzumab).

Emerging Technologies and Future Directions

Digital Pathology and AI

Artificial intelligence (AI) algorithms are being developed to automate HER2 scoring on digital slides. Early studies demonstrate high concordance with pathologist assessments, offering the potential to reduce turnaround time and inter observer variability. However, AI tools must undergo rigorous validation and regulatory approval before clinical deployment.

Next Generation Sequencing (NGS)

NGS panels that include HER2 gene amplification metrics are gaining traction, especially in cases where tissue is limited. While NGS provides comprehensive genomic profiling, it currently complements rather than replaces traditional IHC/ISH testing due to cost, turnaround time, and the need for robust bioinformatic pipelines.

Frequently Asked Questions (FAQ)

Yes. Core needle biopsies provide sufficient tissue for both IHC and ISH, provided the sample is adequately fixed and representative of the tumor.

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