# Significance of HER2 across solid tumors

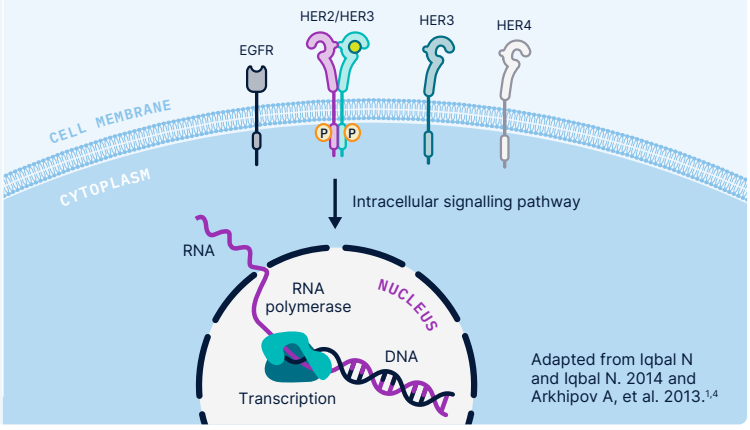
## Why test for HER2?

HER2 is a clinically significant biomarker, which may have predictive and prognostic implications.[1,2] Assessing HER2 status across solid tumors may inform clinical decisions.[2]

## The role of *HER2 (ERBB2)*

- The HER2 protein, encoded by the *HER2 (ERBB2)* gene, is a receptor tyrosine kinase and member of the EGFR family[3]
- In normal cells, expression of HER2 allows regular cell cycle progression,[1] while in cancer cells it promotes excessive cell growth[4]
- HER2 is activated through homodimerization and heterodimerization with members of the EGFR family,[4,5] mediating epithelial cell growth and differentiation via downstream signaling pathways[5]

## HER2 receptor




Adapted from Iqbal N and Iqbal N. 2014 and Arkhipov A, et al. 2013.[1,4]

| Alteration | HER2 overexpression | *HER2 (ERBB2)* amplification | *HER2 (ERBB2)* mutation |
|---|---|---|---|
| |  |  |  |
| **Definition** | Overabundance of HER2 protein on the surface of tumor cells[6] | Elevated number of *HER2 (ERBB2)* gene copies and/or RNA transcripts[7] | Activating mutation in the *HER2 (ERBB2)* gene[8] |
| **Consequence** | Upregulation of signaling pathways[9] | Increased number of transcripts → upregulation of signaling pathways[1] | Increased activation of receptor → upregulation of signaling pathways[8] |
| **Testing method** | IHC[10] | ISH or NGS[6,7]* | NGS[7]* |
| **Specimen type** | Tissue[10] | Tissue (ISH or NGS)<br>Plasma ctDNA (NGS)[7] | Tissue (NGS)<br>Plasma ctDNA (NGS)[7] |

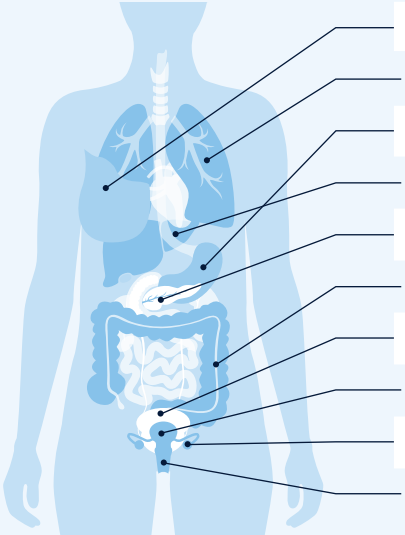
*ISH is a molecular testing method that detects *HER2 (ERBB2)* DNA copy number,[6] while NGS detects both *HER2 (ERBB2)* DNA copy number, RNA transcripts, and/or *HER2 (ERBB2)* mutations.[7]

## Alterations in *HER2 (ERBB2)*

- *HER2 (ERBB2)* is a known proto-oncogene first described in breast cancer[3]
- Alterations are implicated as a negative prognostic factor in multiple tumor types, including gastric, endometrial, and ovarian[1]
- Prevalence varies among tumor types but is associated with aggressive disease, poor outcomes, and increased recurrence risk[1,11,12]

## Prevalence of HER2 alterations across solid tumors

The prevalence of HER2 alterations varies in type of alteration and between tumor types.[5]



| | HER2 IHC 3+ (%) | HER2 IHC 2+ (%) | *HER2 (ERBB2)* amplification** (%) | *HER2 (ERBB2)* mutation† (%) |
|---|---|---|---|---|
| **Breast**[8,13-19] | 10-20 | 19-49 | 13-23 | 2-4 |
| **NSCLC**[8,10,13,20-26] | 1-5 | 1-19 | ~1 | 2-4 |
| **Gastric/EGJ**[8,13,16,19,27-31] | 3-14 | 5-14 | 9-20 | 1-9 |
| **Biliary tract**[8,10,13,32-38] | 5-10 | 12-24 | 5-7 | 6-10 |
| **Pancreas**[13,16,19,37,39-41] | 1-7 | 6-9 | 2-24 | 1-3 |
| **Colorectum**[8,10,13,19,37,42-49] | 1-4 | 2-9 | 3-6 | 3-6 |
| **Bladder**[8,10,13,19,37,50-53] | 4-13 | 5-52 | 2-8 | 6-13 |
| **Endometrium**[8,10,13,16,19,37,54-57] | 3-28 | 14-39 | 4-8 | 2-3 |
| **Ovary**[10,13,16,19,37,58-61] | 1-5 | 0-24 | 1-2 | 1-3 |
| **Cervix**[8,10,13,16,20,62,63] | 4-11 | 14-18 | 3-7 | 2-5 |

***HER2 (ERBB2)* amplification is measured using ISH techniques, including FISH, CISH and SISH, or by NGS.[6,24] †*HER2 (ERBB2)* mutations are detected through sequencing techniques, such as NGS or Sanger sequencing.[23,43]

## Summary of HER2 testing recommendations in ASCO-CAP guidelines and CAP reporting templates

| Oncology specialty | Tumor type | Scoring criteria published | HER2 tests included in tumor-specific CAP templates for reporting of biomarker testing results[69-74] | | |
|---|---|---|---|---|---|
| | | | HER2 overexpression | *HER2 (ERBB2)* amplification | *HER2 (ERBB2)* mutation |
| **Breast** | **Breast** | **ASCO-CAP guidelines[64]** | **IHC** | **ISH** | |
| **Gastrointestinal** | **Biliary tract** | *No universal guideline*[65]* | General IHC biomarker template available† | | |
| | **Gastric/EGJ** | **ASCO-ASCP-CAP guidelines[66]** | **IHC** | **ISH or Genomic test** | **Genomic test** |
| | **Pancreatic** | *No universal guideline*[65]* | General IHC biomarker template available† | | |
| | **Colorectal** | HERACLES trial scoring criteria[67]*,** | **IHC** | **ISH or Genomic test** | **Genomic test** |
| **Thoracic** | **NSCLC** | *No universal guideline*[65]* | **IHC** | **Genomic test** | **Genomic test** |
| **Genitourinary** | **Bladder** | *No universal guideline*[65]* | General IHC biomarker template available† | | |
| **Gynecologic** | **Endometrial** | Fader trial scoring criteria[68,69]* | **IHC** | **ISH** | |
| | **Ovarian** | *No universal guideline*[65]* | General IHC biomarker template available† | | |
| | **Cervical** | *No universal guideline*[65]* | General IHC biomarker template available† | | |

*Assay-scoring system combinations should be validated according to the intended clinical use of the test, and the validation cohort should consist of at least 20 positive and 20 negative tissues.[75] **Scoring criteria at discretion of laboratory director.[75] †Where specific templates are not available, the CAP template for Reporting Results of Quantitative IHC Biomarker Testing of Specimens from Patients With Carcinoma may be used.[74]

ASCO, American Society of Clinical Oncology; ASCP, American Society for Clinical Pathology; CAP, College of American Pathologists; CISH, chromogenic *in situ* hybridization; ctDNA, circulating tumor DNA; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; EGJ, esophagogastric junction; *ERBB2*, erythroblastic oncogene B-2; FISH, florescence *in situ* hybridization; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HER4, human epidermal growth factor receptor 4; IHC, immunohistochemistry; ISH, *in situ* hybridization; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; RNA, ribonucleic acid; SISH, silver *in situ* hybridization.

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