HER2Know | By pathologists, for pathologists

Significance of HER2 across solid tumors

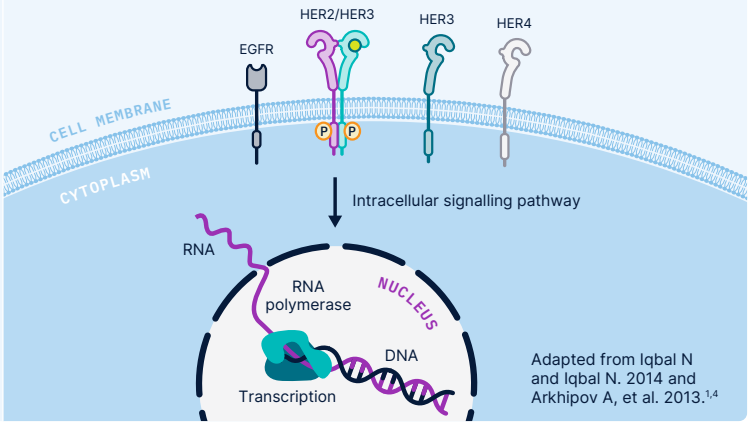
Why test for HER2?

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) Plasma ctDNA (NGS)[7]	Tissue (NGS) Plasma ctDNA (NGS)[7]

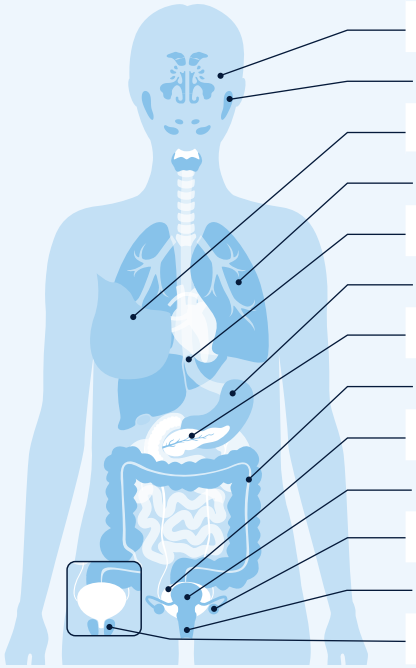
*ISH is a molecular testing method that detects *HER2 (ERBB2)* DNA copy number,[6] while NGS detects both *HER2 (ERBB2)* DNA copy number, RNA transcripts, and/or *HER2 (ERBB2)* mutations.[7]

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§ (%)
Head and neck[2,10,13-18]	1-11	4-15	1-10	2-3
Salivary gland[13,16,19-25]	13-37	3-21	4-8	1-11
Breast[8,13,26-31]	10-20	19-49	13-23	2-4
NSCLC[8,13,32-38]	1-5	1-19	~1	2-4
Biliary tract[8,13,16,39-43]	4-13	12-24	5-7	6-10
Gastric/EGJ[8,13,28,31,44-48]	3-14	5-14	9-20	1-9
Pancreas[13,16,28,32,49-51]	1-7	6-9	2-24	1-3
Colorectum[8,13,16,31,52-57]	1-3	2-9	3-6	3-6
Bladder[8,13,16,31,58-61]	4-31	5-52	2-8	6-13
Endometrium[8,13,16,28,31,62-65]	4-28	14-44	4-8	2-3
Ovary[13,16,28,31,66-69]	1-5	0-24	1-2	1-3
Cervix[8,13,28,70,71]	8-14	14-18	3-7	2-5
Prostate[13,16,31,72-75]	0-5	0-18	1-59	~1

†Individual tumor prevalence numbers reflect US and ex-US populations. Due to limited testing data for particular tumor types in the US, data from global populations has been included. ‡*HER2 (ERBB2)* amplification is measured using ISH techniques, including FISH, CISH and SISH, or by NGS.[6,36] §*HER2 (ERBB2)* mutations are detected through sequencing techniques, such as NGS or Sanger sequencing.[35,55]

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; P, phosphate; RNA, ribonucleic acid; SISH, silver *in situ* hybridization.

Summary of HER2 testing recommendations in guidelines

(ASCO-CAP, NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®)) and CAP reporting templates

Oncology specialty	Tumor type	Scoring criteria guidance	HER2 testing recommendations in the NCCN Guidelines®	HER2 tests included in tumor-specific CAP templates for reporting of biomarker testing results[80,96-101]		
				HER2 overexpression	*HER2 (ERBB2)* amplification	*HER2 (ERBB2)* mutation
Breast	**Breast**	**ASCO-CAP guidelines for breast cancer[76]**	IHC, ISH[82]	**IHC**	**ISH**	
Gastrointestinal	**Biliary tract**	*No universal guideline*[77†]	IHC, FISH, NGS[83]	General IHC biomarker template available[§]		
	Colorectal	HERACLES trial scoring criteria[78†,‡]	IHC, FISH, NGS[84,85]	**IHC**	**ISH or Genomic test**	**Genomic test**
	Gastric/EGJ	**ASCO-ASCP-CAP guidelines for GEA[79]**	IHC, ISH, NGS[86,87]	**IHC**	**ISH or Genomic test**	**Genomic test**
	Pancreatic	*No universal guideline*[77†]	IHC, FISH, NGS (amplification)[88]	General IHC biomarker template available[§]		
Thoracic	**NSCLC**	*No universal guideline*[77†]	IHC, NGS (mutation), PCR (mutation)[89]	**IHC**	**Genomic test**	**Genomic test**
Head and neck	**Salivary gland**	*No universal guideline*[77†]	NGS[90]	**IHC**	**ISH**	
	Other*		NGS[90]	General IHC biomarker template available[§]		
Genitourinary	**Bladder**	*No universal guideline*[77†]	IHC[91]	General IHC biomarker template available[§]		
	Prostate		*None*[92]	General IHC biomarker template available[§]		
Gynecologic	**Endometrial**	ASCO-ASCP-CAP guidelines for GEA or Fader trial scoring criteria[80,81†]	IHC, FISH[93]	**IHC**	**ISH**	
	Cervical	ASCO-ASCP-CAP guidelines for GEA[81†]	IHC, FISH[94]	**IHC**	**ISH**	
	Ovarian		IHC[95]	**IHC**	**ISH**	

*Including oral cavity (including mucosal lip), oropharynx, hypopharynx, glottic larynx, supraglottic larynx, ethmoid sinus, maxillary sinus, and occult primary.[90] †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.[102] ‡Scoring criteria at discretion of laboratory director.[102] §Where specific templates are not available, the CAP template for Reporting Results for Quantitative IHC Biomarker Testing of Specimens from Patients with Carcinoma may be used.[101]

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ASCO, American Society of Clinical Oncology; ASCP, American Society for Clinical Pathology; CAP, College of American Pathologists; *ERBB2*, erythroblastic oncogene B-2; EGJ, esophagogastric junction; FISH, florescence *in situ* hybridization; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

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