

CAP Foundation Career Development Award in HER2

Three Priority Areas

Colorectal Cancer ^{27 28 29}

Accurate colorectal cancer (CRC) HER2 assessment is crucial for guiding treatment decisions and enrolling patients in appropriate clinical trials evaluating HER2-targeted regimens. Current barriers and gaps hindering the establishment of a standardized scoring criteria, needing further research, include the lack of uniformity of CRC cells types and staining patterns; use of varied HER2 IHC scoring criteria leading to inconsistencies in assessing HER2 status resulting in the misclassification of patients; and further study on CRC's unique HER2 expression to establish reliable guidelines aiding in the identification of CRC HER-2 positive cases.

Head and Neck Squamous Cell Carcinoma ^{30 31}

Despite the potential for targeted therapies against HER2 in Head and Neck Squamous Cell Carcinoma (HNSCC), a significant gap remains in the optimization and validation of HER2 IHC assays specifically for this cancer type. As no standardized evaluation methods for HER2 testing in HNSCC currently exist, guidelines and scoring systems developed for breast cancer are often applied and potentially lead to inaccurate results. Optimized and validated HER2 IHC assays are crucial to reliably identify patients who might benefit from HER2-targeted therapies. Further research is needed to determine the exact relationship between HER2 expression, patient outcome, and response to treatment regimens in different HNSCC subtypes.

Non-Small Cell Lung Cancer ^{32 33 34 35 36 37 38}

While HER2 is an increasingly important therapeutic target in non-small cell lung cancer (NSCLC), especially for patients with HER2 mutations, the role of IHC-based HER2 testing remains limited due to several unresolved challenges. Current scoring systems are adapted from breast or gastric cancer guidelines, which do not account for the biological and staining differences inherent to lung tumors. This often results in poor correlation with molecular alterations and misinterpretation of HER2 status. In NSCLC, HER2 expression tends to be heterogeneous, with weak and variable membranous staining patterns that complicate pathologic assessment. Moreover, HER2 overexpression by IHC does not consistently align with gene amplification (assessed via FISH) or activating mutations (detected by NGS), which are more predictive of response to HER2-targeted therapies. Prevalence reporting varies widely due to inconsistencies in antibodies, scoring thresholds, and assay interpretation, and the clinical significance of IHC positivity in the absence of molecular alterations remains

uncertain. Without standardized NSCLC-specific IHC scoring criteria and validated correlation with genomic drivers, patients may be incorrectly included in or excluded from HER2-targeted treatment. Addressing these diagnostic gaps through rigorous lung-specific IHC assay validation and integrated biomarker strategies is essential to improve patient selection, optimize therapeutic benefit, and advance the implementation of precision oncology in lung cancer.

Projects' primary objectives will be to optimize and validate HER2 IHC assays across the selected solid tumor type(s) using tumor-specific criteria and rigorous analytic validation methods. Additional objectives may relate to assessing inter- and intra-tumoral HER2 expression patterns and their correlation with other diagnostic modalities (e.g., ISH, NGS) or to develop evidence-based recommendations that can inform potential future CAP guidelines for HER2 testing in these tumor types. Scientific validity will be assessed based on significance of the proposed aims, innovative approach, scientifically sound approach with appropriate statistical methods, and clinical relevance. All proposals should be accompanied by mentored research experience and skills development for the early-career pathologist.

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<https://www.medpagetoday.com/resource-centers/metastatic-colorectal-cancer-focus/assessing-colorectal-cancer-path-improvement/5744> Accessed August 1, 2025.

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²⁹ Know Your Biomarker: Biomarkers HER2. *Global Colon Cancer Association*. 2022.

<https://www.knowyourbiomarker.org/biomarkers/her2#:~:text=Fast%20facts:,also%20cause%20HER2%20protein%20overexpression>. Accessed July 30, 2025.

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³² Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998-2006.

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³⁴ Pillai RN, Behera M, Berry LD, et al. HER2 mutations in lung adenocarcinomas: A report from the Lung Cancer Mutation Consortium. *Cancer*. 2017;123(21):4099-4105.

³⁵ Ricciardi GR, Russo A, Franchina T, et al. NSCLC and HER2: between lights and shadows. *J Thorac Oncol*. 2014;9(12):1750-1762.

³⁶ Li BT, Ross DS, Aisner DL, et al. HER2 Amplification and HER2 Mutation Are Distinct Molecular Targets in Lung Cancers. *J Thorac Oncol*. 2016;11(3):414-419.

³⁷ Li BT, Smit EF, Goto Y, et al. Trastuzumab Deruxtecan in *HER2*-Mutant Non-Small-Cell Lung Cancer. *N Engl J Med*. 2022;386(3):241-251.

³⁸ Nützinger J, Bum Lee J, Li Low J, et al. Management of HER2 alterations in non-small cell lung cancer - The past, present, and future. *Lung Cancer*. 2023;186:107385.