

is a reasonable concern with the reliability of HER2 IHC assays, especially when it is negative. FISH therefore emerges as the most reliable testing method for HER2.⁹ According to ASCO/CAP 2013, all newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available.

1. HER2 test result should be reported as positive for HER2 if:
 - IHC 3+ based on circumferential membrane staining that is complete, intense
 - ISH positivity is based on:
 - Single-probe average HER2 copy number ≥ 6.0 signals/cell
 - Dual-probe HER2/CEP17 ratio ≥ 2.0 ; with an average HER2 copy number ≥ 4.0 signals/cell
 - Dual-probe HER2/CEP17 ratio ≥ 2.0 ; with an average HER2 copy number < 4.0 signals/cell
 - Dual-probe HER2/CEP17 ratio < 2.0 ; with an average HER2 copy number ≥ 6.0 signals/cell
2. HER2 test result should be reported as equivocal and reflex test should be ordered (same specimen using the alternative test) or a new test (new specimen, if available, using same or alternative test) if:
 - IHC is 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate and within $> 10\%$ of the invasive tumor cells; or complete and circumferential membrane staining that is intense and within $\leq 10\%$ of the invasive tumor cells
 - ISH is equivocal based on:
 - Single-probe ISH average HER2 copy number ≥ 4.0 and < 6.0 signals/cell
 - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number ≥ 4.0 and < 6.0 signals/cell
3. HER2 test result should be reported as negative if a single test (or both tests) performed show:
 - IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within $> 10\%$ of the invasive tumor cells
 - IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within $\leq 10\%$ of the invasive tumor cells
 - ISH negative based on:
 - Single-probe average HER2 copy number < 4.0 signals/cell
 - Dual-probe HER2/CEP17 ratio < 2.0 with an average HER2 copy number < 4.0 signals/cell