



Genetics In Breast Cancer

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About 5% to 10% of breast cancers are related to specific inherited mutations



BRC A1 and BRC A2 which are mutated in familial breast cancers are involved in DNA repair.



**A. BRCA1 is located on chromosome
17q 21.3**

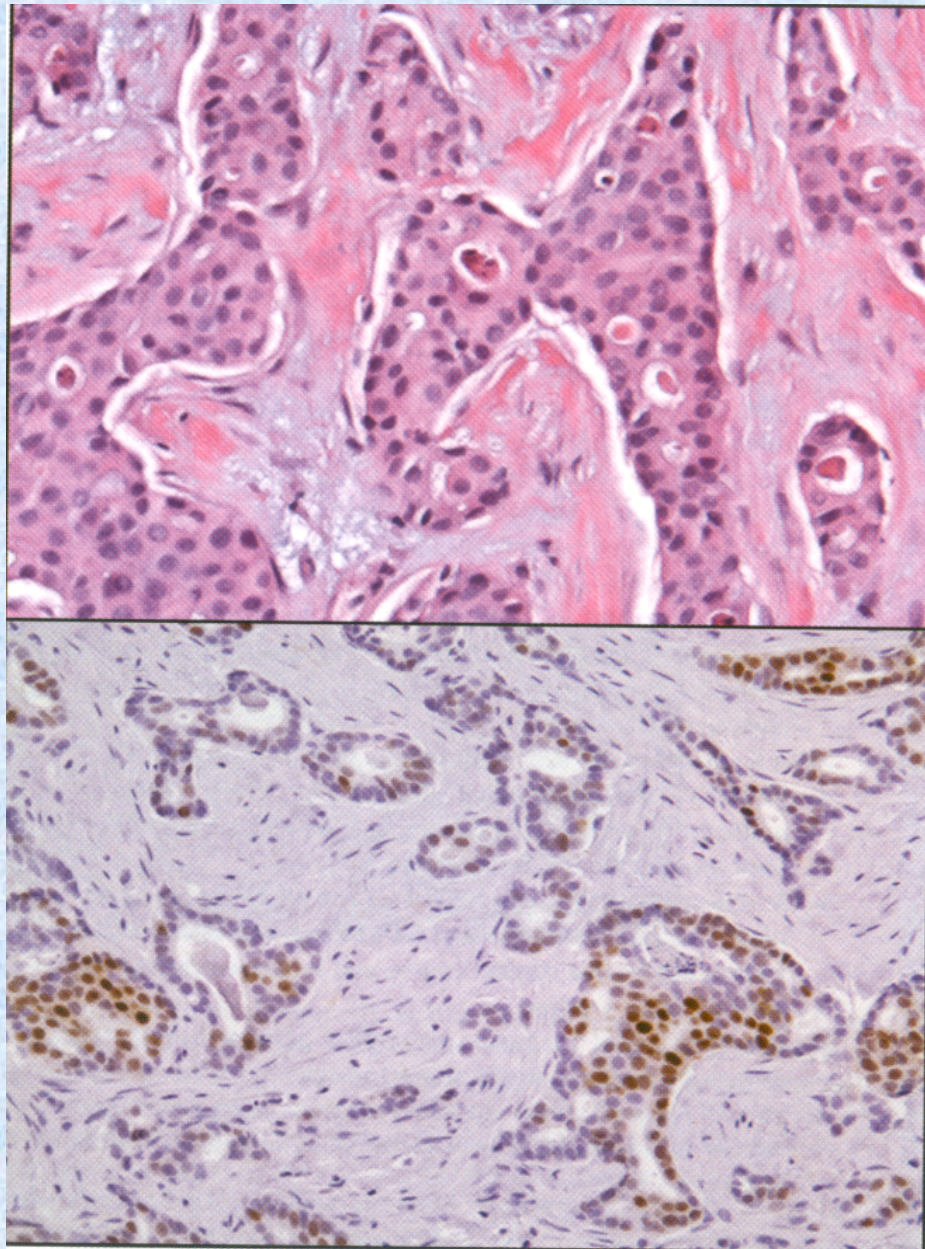
**B. BRCA2 is located on chromosome
13q 12-13.**



Most carriers of those mutant genes will develop breast cancer by the age of 70 years, as compared with only 7% of women who do not carry a mutation.



60% to 70% of breast carcinomas express estrogen receptors (ERs) and progesterone receptors (PRs).



Immunohistochemistry for the evaluation of estrogen receptor (ER)



The presence of ERS in breast cancer is a weak prognostic factor, however, it is optimally useful as a predictive factor for the benefit of adjuvant tamoxifen or aromatase inhibitor therapy.



Normal cells have one copy of the HER 2 gene on each chromosome 17 (CHR17) and when this gene is expressed in normal epithelial cells, it transmits signals regulating cell growth and survival.



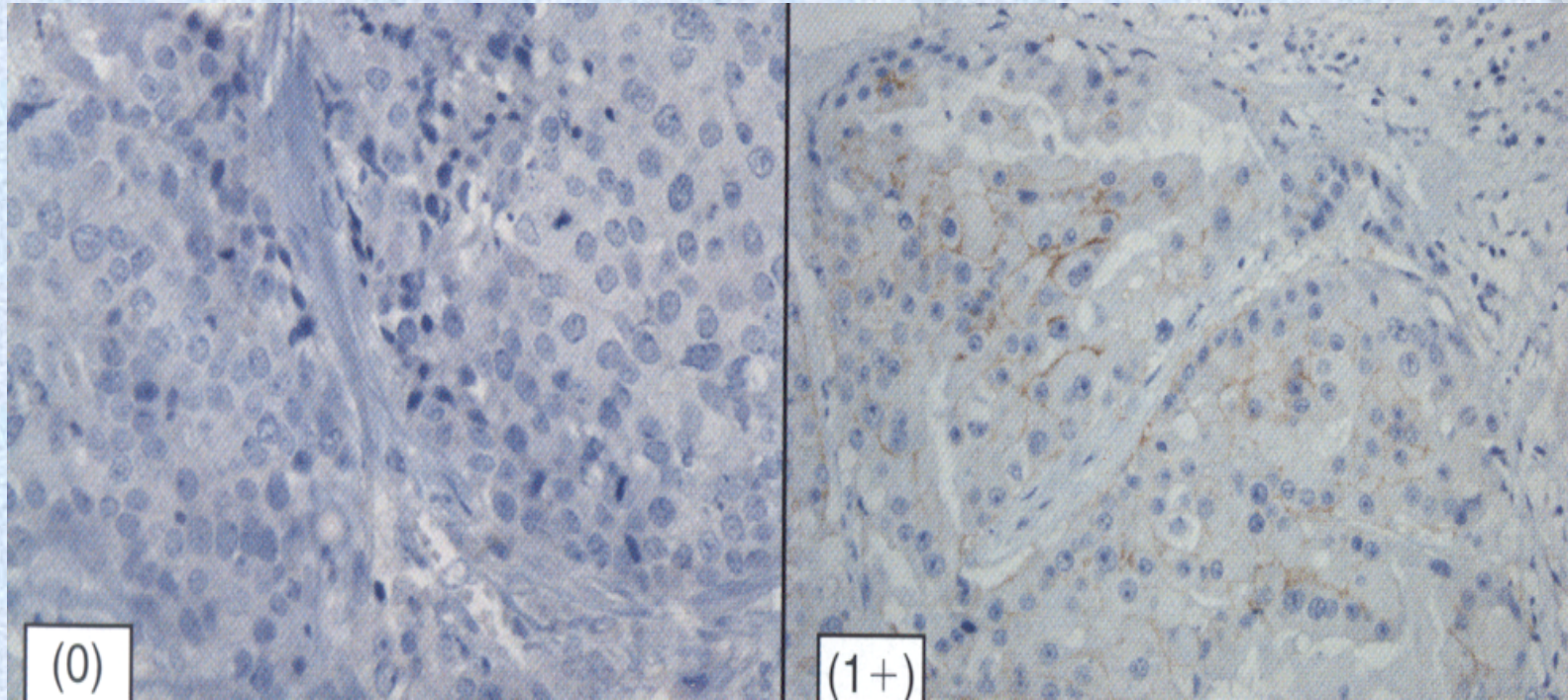
In approximately 15% to 25% of breast cancer, the HER2 gene is found to be amplified 2 fold to greater than 20 folds in each tumour cell nucleus.



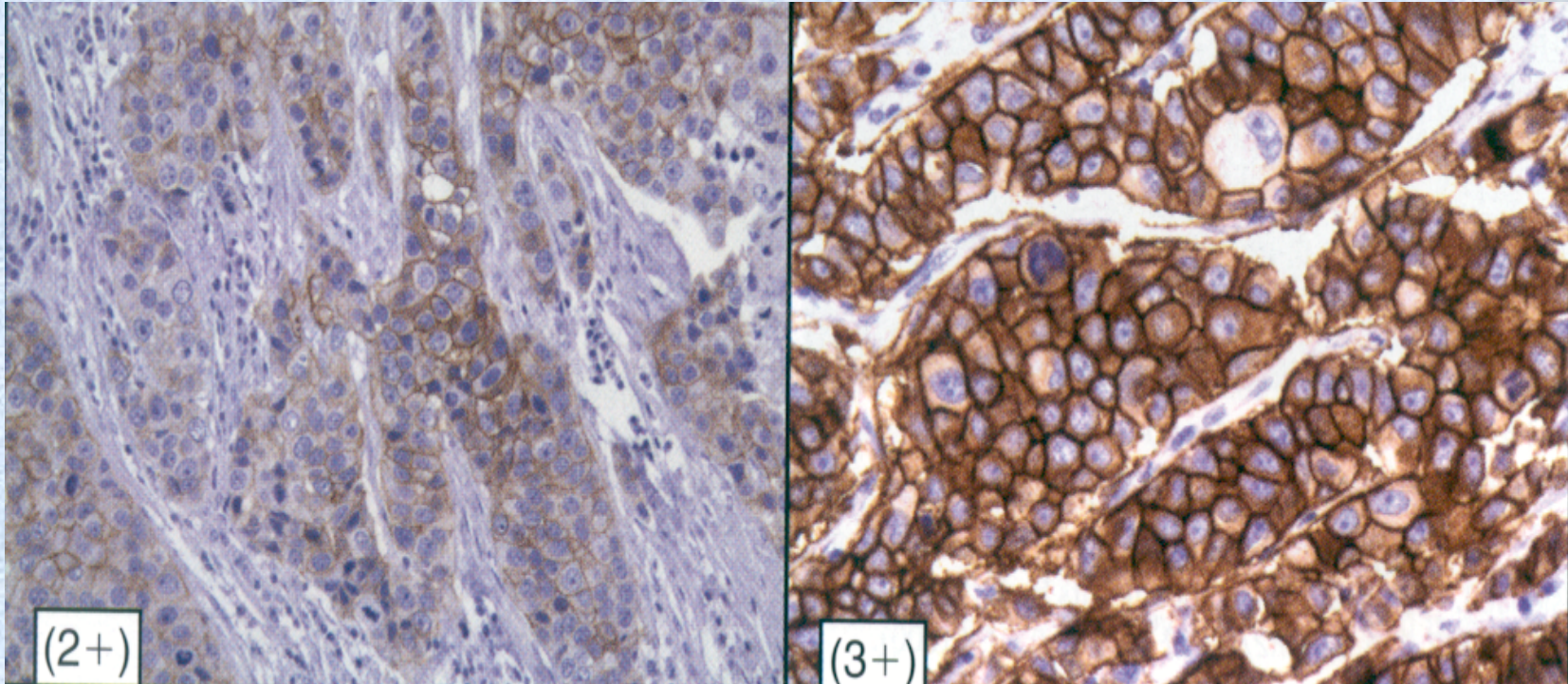
As a result, HER2 positive breast cancers tend to be aggressive.



The herceptin molecule (Trastuzumab) has been shown to demonstrate a high specificity and affinity for the HER2 receptor and also acts as a biologic targeted therapeutic agent against HER2 receptors.

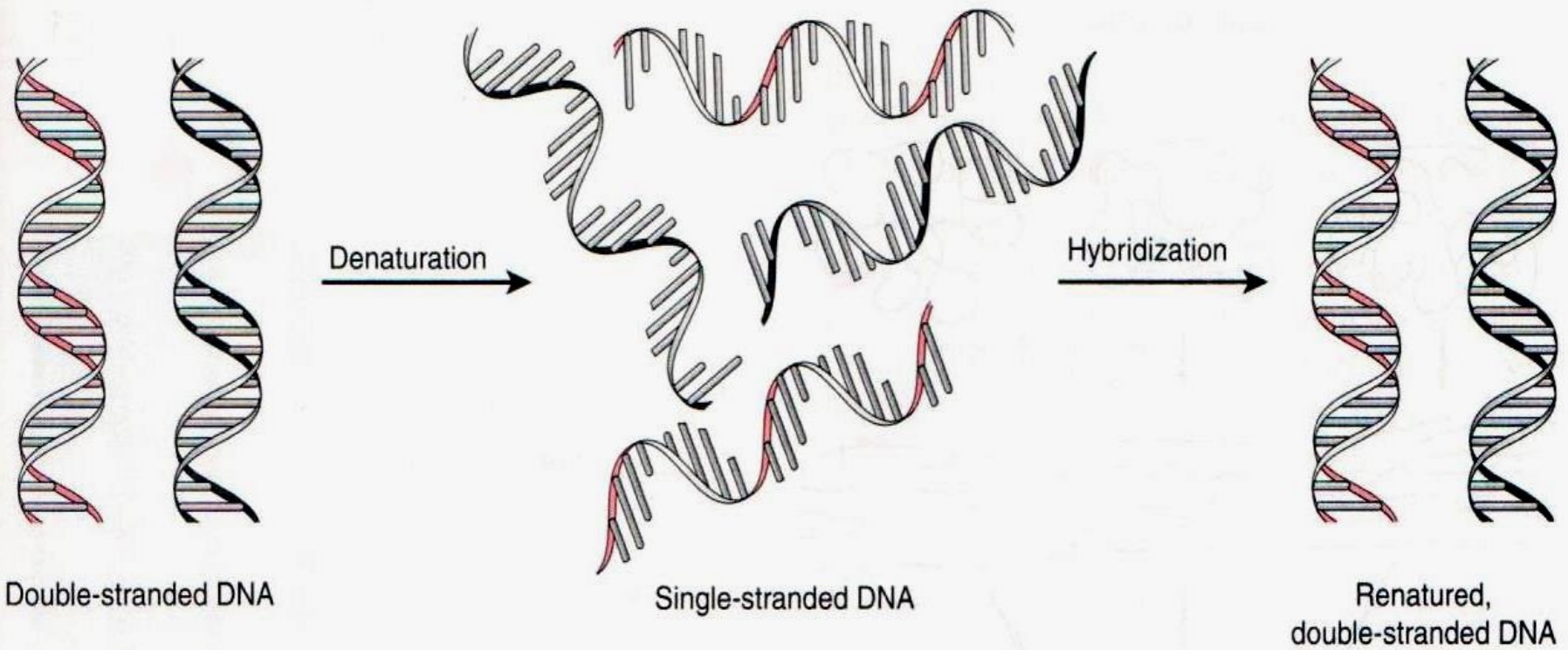


Immunohistochemistry (IHC) for the assessment of the level of HER2 protein expression at the tumor cell membrane.

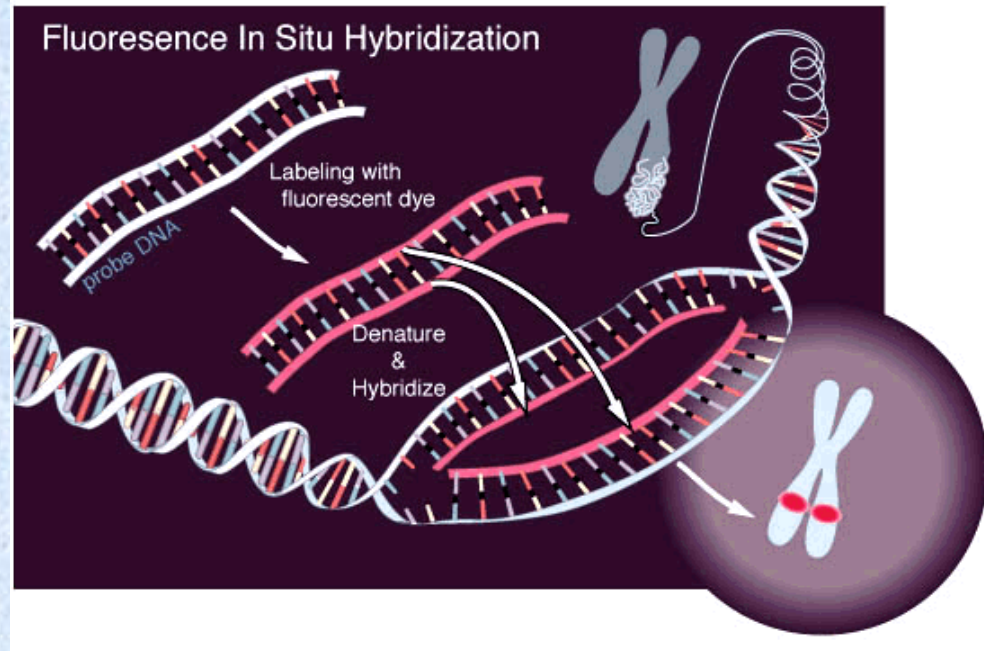
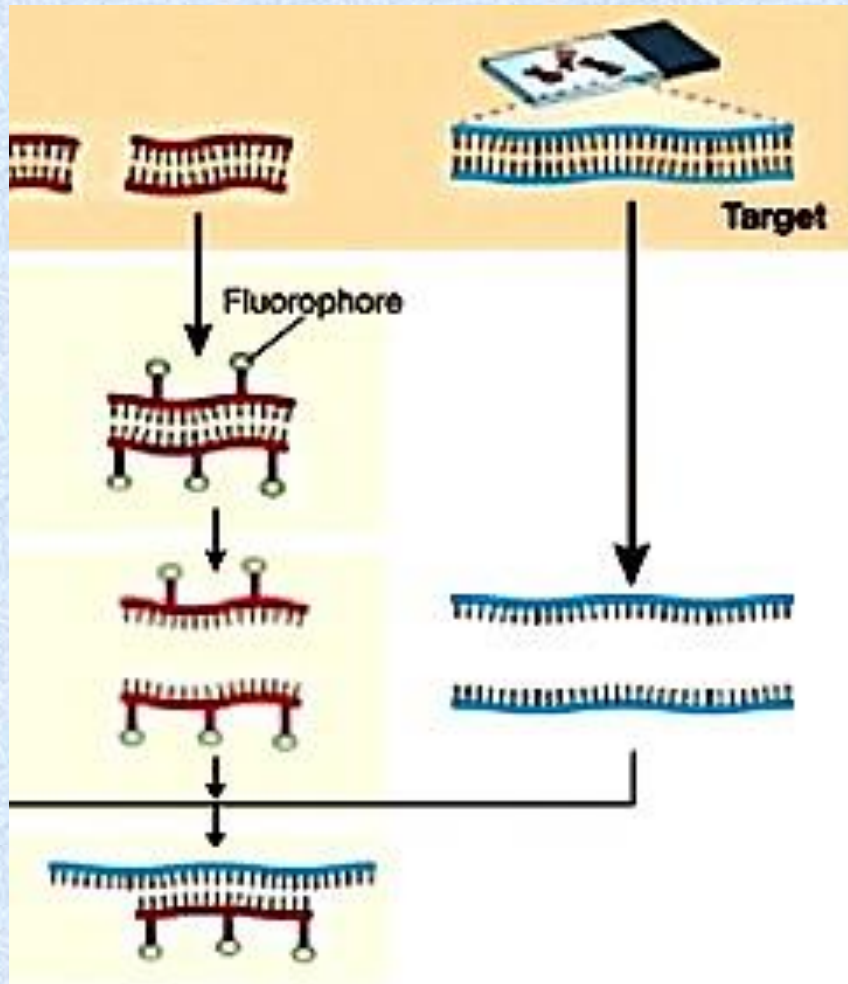


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The principle of nucleic acid hybridization. The two complementary strands of a Watson-Crick double helix can be “denatured” by a variety of treatments (such as high temperature, high pH, or very low salt conditions) to yield a collection of single-stranded DNA molecules. Under conditions that favor formation of renatured double-stranded DNA, complementary strands will “hybridize” to each other, but not to other fragments of DNA that have a different nucleotide sequence.



Schematic illustration of FISH technique

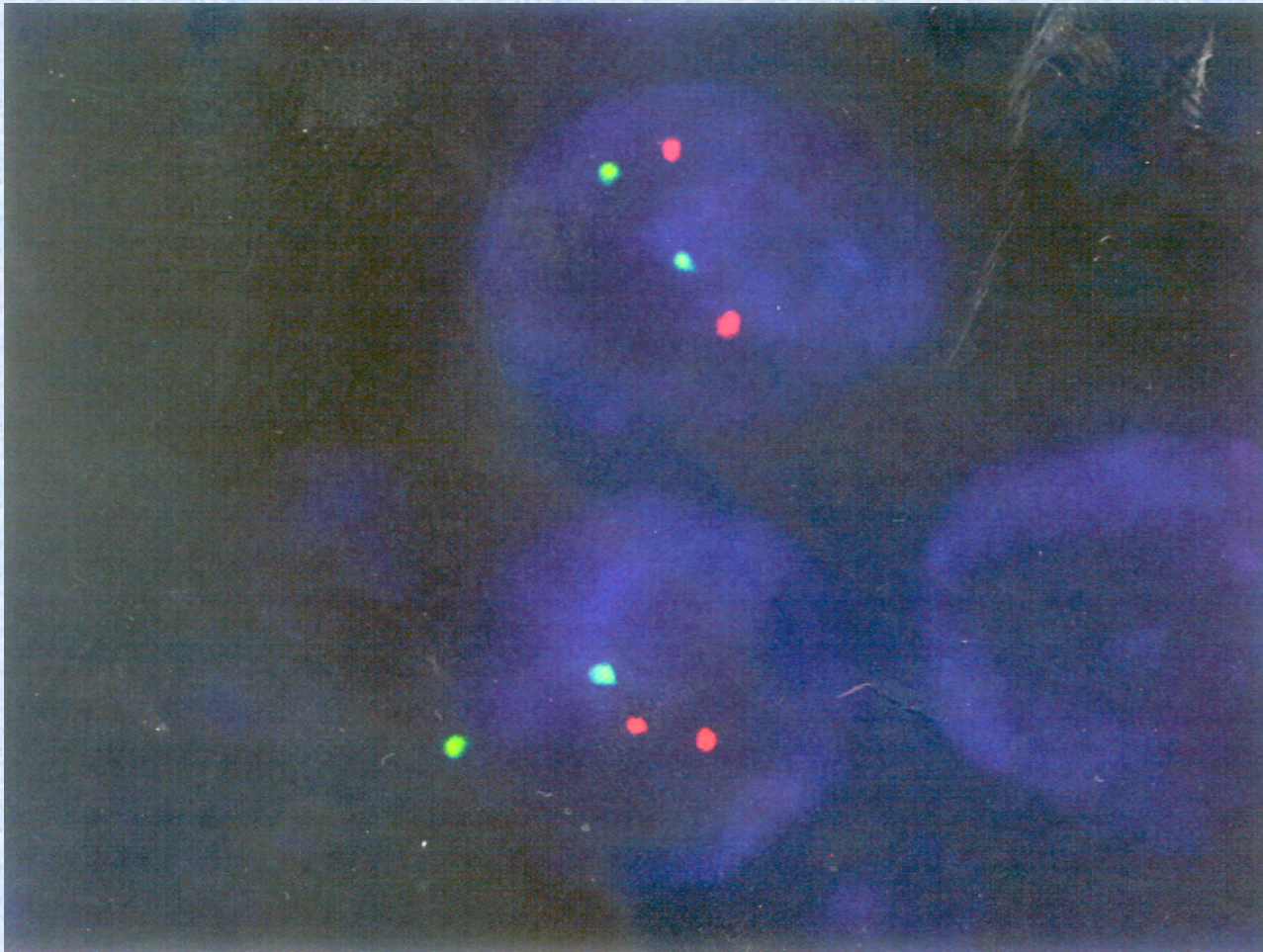
Principles of hybridisation

- * DNA is double stranded.
- * Bonds between complementary bases hold strands together (Cytosine ↔ Guanine; Adenine ↔ thymine).
- * Heat/alkalinise DNA – separation of strands ('denaturation') occurs.
- * Cool separated strands – *complementary* double strands re-form.
- * Labelled complementary single-strand DNA can identify a DNA sequence (e.g. a gene) in intact cells or disrupted cell preparations.

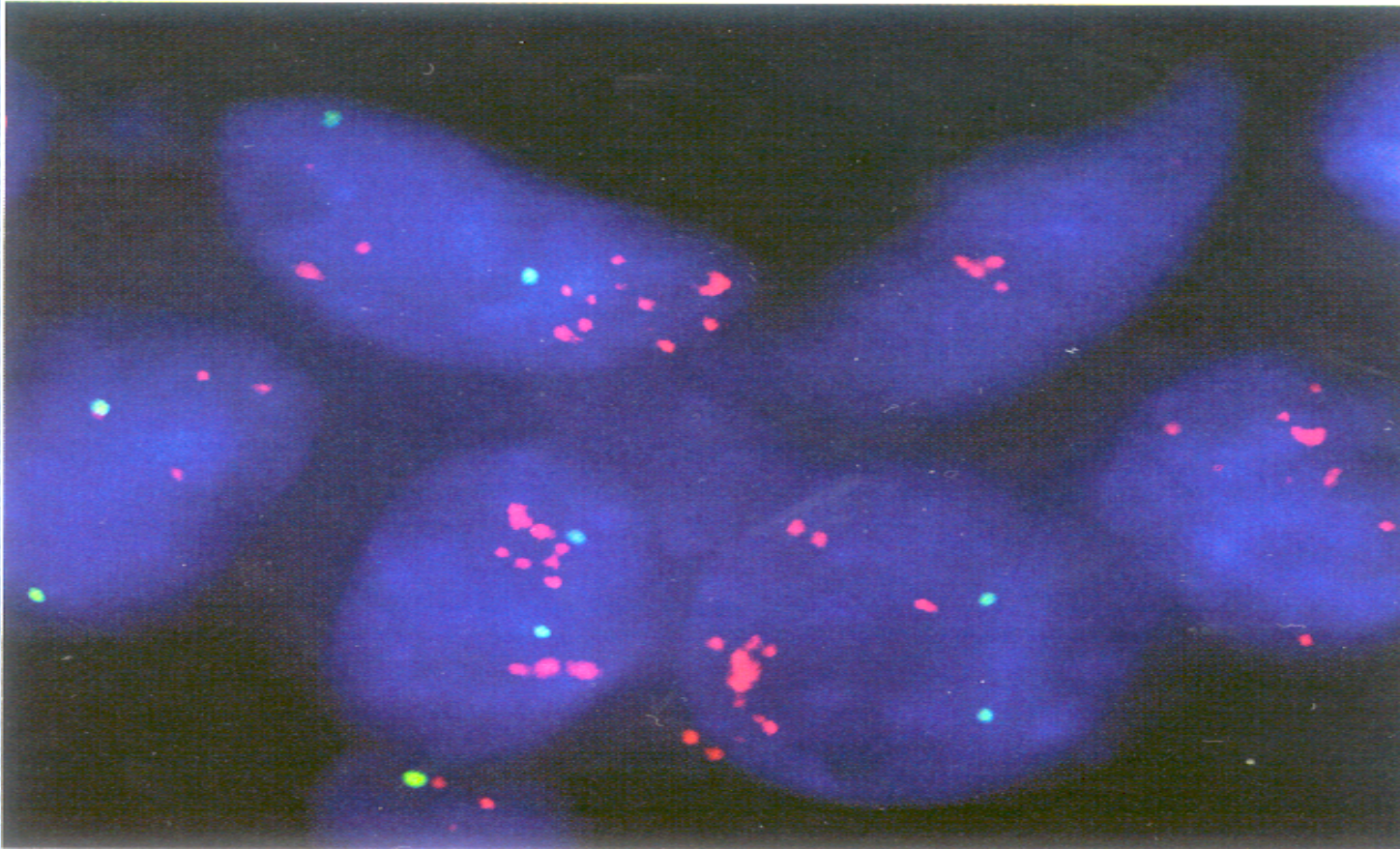
Immunophenotyping as a Surrogate for Molecular Category Using Estrogen Receptor, Progesterone Receptor and HER2 Status

Molecular Category

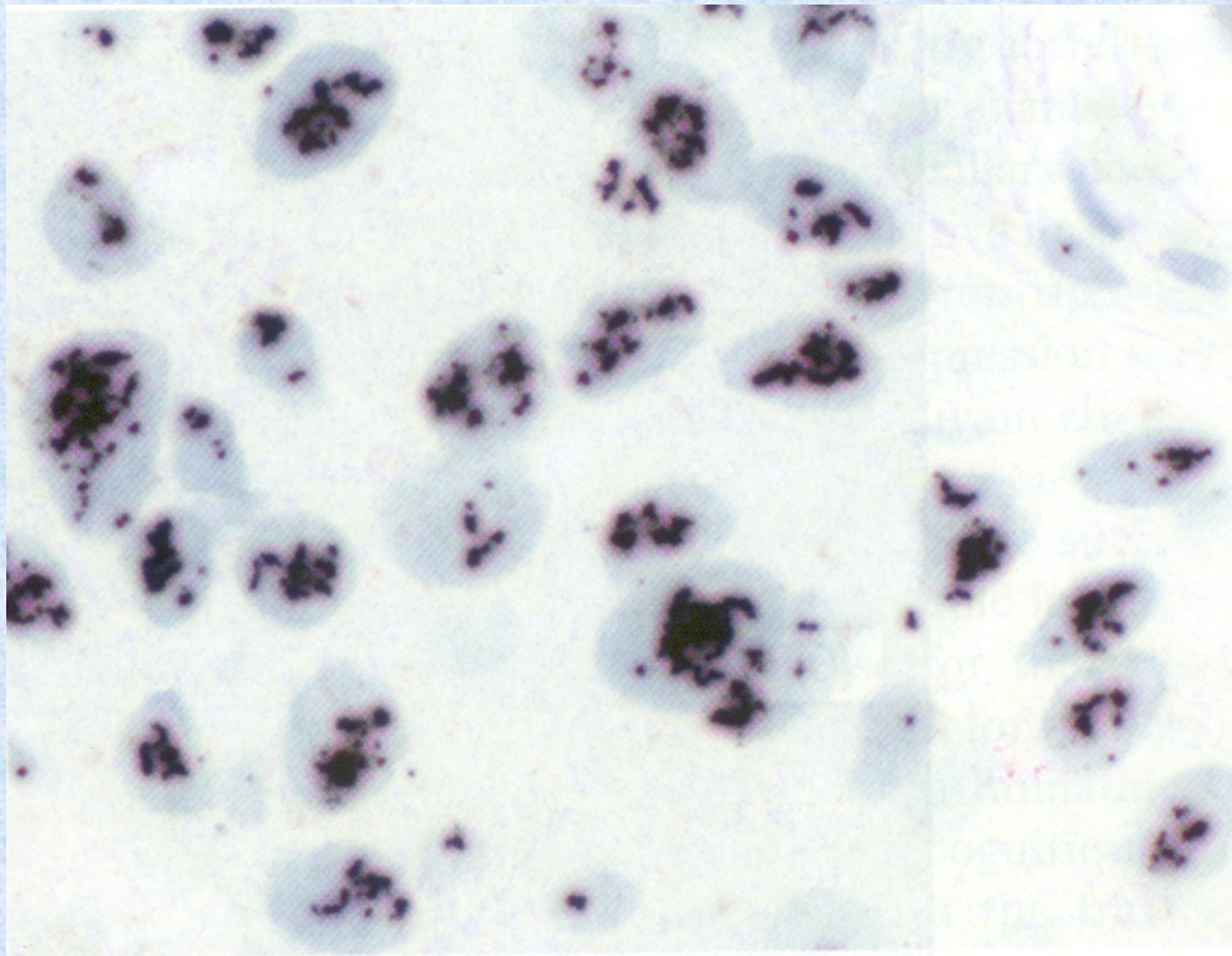
	Luminal A	Luminal B	HER2	Basal-like*
ER	+	+	-	-
PR	+	+	-	-
HER2	-	+	+	-



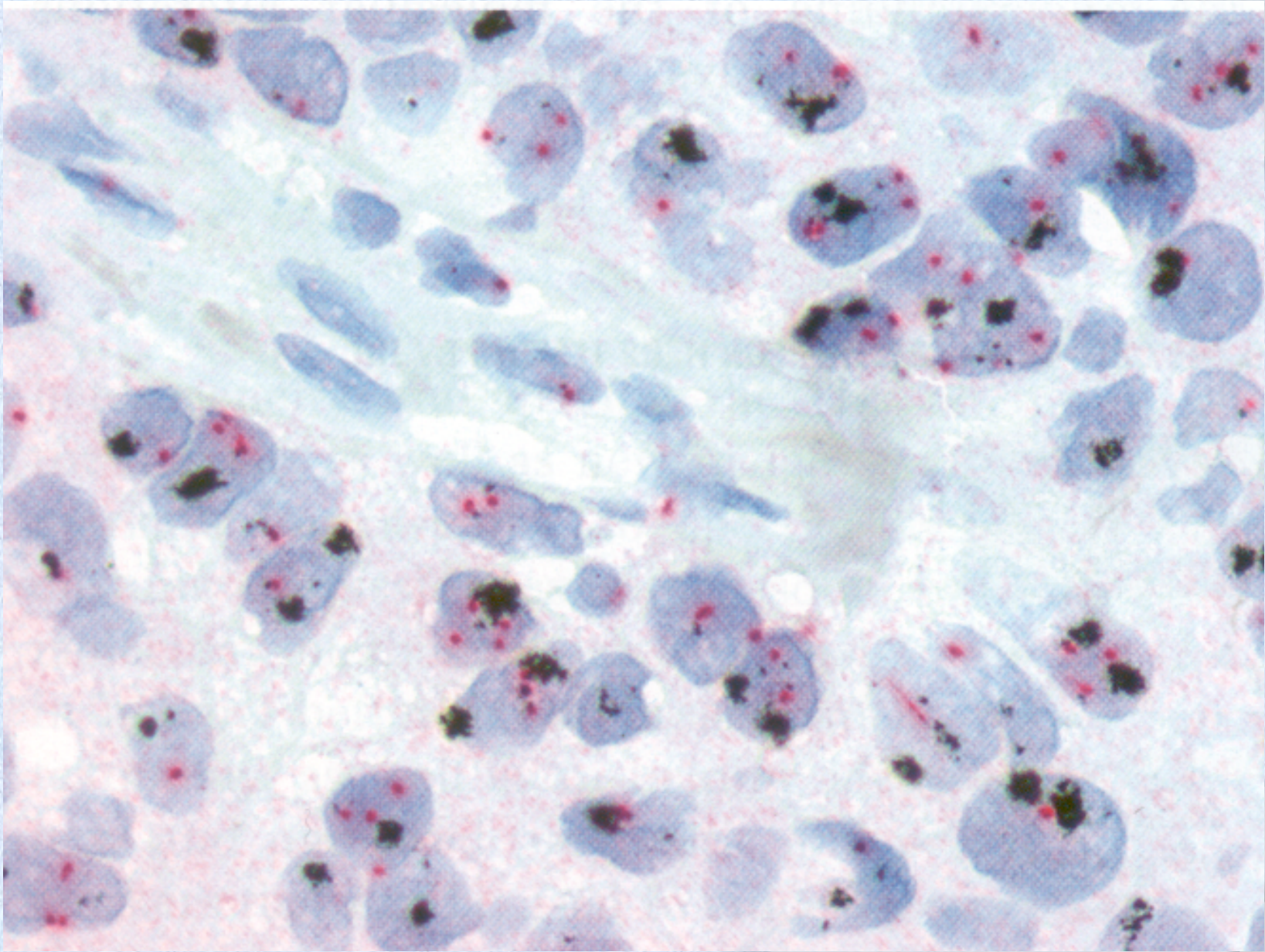
Fluorescence in situ hybridization image.



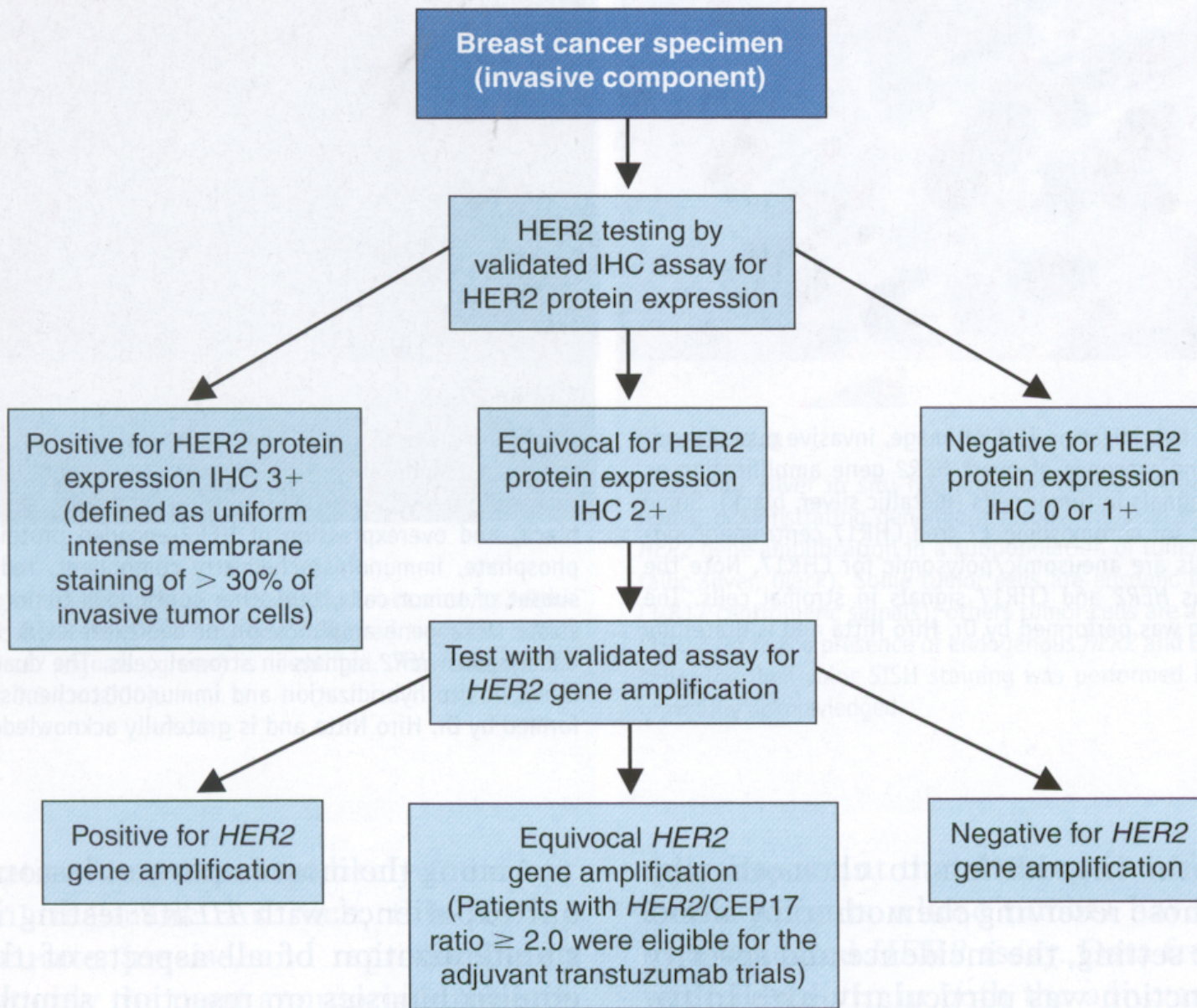
Fluorescence in situ hybridization image.



Silver in situ hybridization image.



Dual-color silver in situ hybridization (SISH) image.



ASCO/CAP guideline recommendations for the optimal algorithm for HER2 testing by IHC