The Update Committee recommends that HER2 status (HER2 negative or positive) be determined in all patients with invasive (early stage or recurrence) breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive).
REAL WORLD in Literature

Breast Cancer Research and Treatment
June 2016, Volume 157, Issue 2, pp 385–394

Real-world outcomes in young women with breast cancer treated with neoadjuvant chemotherapy

The real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu-positive early breast cancer in Taiwan.
Lang HC1, Chen HW2, Chiou TJ3, Chan AL4.

A method for using real world data in breast cancer modeling.
Pobiruchin M1, Bochum S2, Martens UM3, Kieser M4, Schramm W5.

Eribulin monotherapy improved survivals in patients with ER-positive HER2-negative metastatic breast cancer in the real world: a single institutional review.
Watanabe J1.
“Would you really make a decision about something as important as this with a single data point—just one reading of one slide?” This is the issue at hand today, with the publication of two extremely important papers on testing for HER2 (3,4).

Recognizing both the importance of accurately detecting HER2 overexpression in evaluating the worth of trastuzumab in the adjuvant setting and the imprecise science of clinical laboratory testing, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Breast Intergroup Trial both required central laboratories to test for HER2. The decision to “build quality in” by requiring more than one data point was wise.

In the study by Roche et al. (4), 26% of the tests that were found positive in the community could not be confirmed in central laboratory testing. The results by Paik et al. (3) were similar; 18% of the tests that were found positive in the community could not be confirmed in central laboratory testing.


REAL WORLD in Literature

Paik et al. attempt to understand the reasons for the false testing results, and clues may be found in the volume of laboratory tests performed or the ability to confirm test results using a second methodology.

The increased costs for added quality measures at the local level should translate to lower costs at a societal level.

Accurate measurement of HER2 in individual patients means smaller sample size for clinical trials, fewer inconclusive or erroneous clinical trial results, and avoidance of costs associated with administering therapies to patients unlikely to benefit.

The avoidance of costs on a human level is even harder to measure, but includes a lower risk of side effects in individuals receiving therapy from which they are not likely to benefit, less confusion on the part of our patients who need to know if a particular therapy is of potential benefit when making personal health-care decisions, and avoiding the loss of public trust that can occur with the dissemination of conflicting medical information.
......, we propose that the best way (in a multicenter study) to improve the accuracy of IHC for HER2 is to calibrate it against a gold standard such as fluorescence in situ hybridization (FISH).

The calibration process consisted of the introduction of heat-induced epitope retrieval and an increase in the dilutions of the primary antibodies.

Forty-four of 116 cancers (37.9%) showed HER2 gene amplification. Before calibration, the accuracy of IHC was 89.6% (95% confidence interval [CI] 84.1% to 95.1%) at the 10% cutoff value and 93.0% (95% CI 88.3% to 97.7%) at the 60% cutoff value. After calibration, the accuracy of the IHC was 93.0% (95% CI 88.3% to 97.7%) at the 10% cutoff value and 95.0% (95% CI 91.1% to 98.9%) at the 60% cutoff value, which corresponded to HER2 overexpression in 47 (39.5%) and 45 (37.8%) of 119 cancers, respectively.
Real World in Literature

Quantitative measurement of HER2 expression in breast cancers: comparison with ‘real-world’ routine HER2 testing in a multicenter Collaborative Biomarker Study and correlation with overall survival


Abstract

Introduction: **Accurate assessment of HER2 status is critical in determining appropriate therapy for breast cancer patients, but the best HER2 testing methodology has yet to be defined.** In this study, we compared quantitative HER2 expression by the HERmark™ Breast Cancer Assay (HERmark) with routine HER2 testing by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), and correlated HER2 results with overall survival (OS) of breast cancer patients in a multicenter Collaborative Biomarker Study (CBS).
The neoadjuvant GeparQuattro trial reported a rather high rate of discordance of 27% between central and local evaluation of HER2 status, which is similar to previous reports of inaccurate local HER2 results in the NSABP B-31 and the NCCTG N9831 studies.

Interesting data from the NSABP B31 study suggest that HER2 non-overexpressing breast cancer may benefit from targeted HER2 therapy [21].

For HER2 expression that does not meet the threshold for HER2-positive disease, enrollment into prospective clinical trials is encouraged, such as NCY01275677 (NSABP B47) that aims to address the benefit of adjuvant HER2-targeted therapies in tumors with a lower level of HER2 expression.

More accurate and quantitative measurement of lower HER2 expression levels may also be helpful for ongoing and planned trials of new anti-HER2 therapies, such as investigational anti-HER2 monoclonal antibodies such as margetuximab and anti-HER2 vaccines targeting HER2 non-overexpressing breast cancer patients [22-24].

Recently published reports continue to show lack of concordance for HER2 results between laboratories despite significant emphasis and progress made to standardize routine HER2 testing post publication of the ASCO/CAP guidelines for HER2 testing in 2007 [11-13]. Since then, clarifications and updates to the ASCO/CAP HER2 testing guidelines have been issued, and ASCO and CAP convened to conduct a formal and comprehensive review and revised the guidelines in 2013. The main objective of HER2 testing remains to accurately determine which patients may benefit from HER2-based targeted therapies.

ASCO-CAP2013, IHC in invasive component

HER2 negativi (0): positività di membrana assente oppure appena percettibile in ≤10% delle cellule

HER2 negativi (1+): positività di membrana incompleta, appena percettibile in >10% delle cellule

HER2 positivi (score 3+): positività forte e completa in > 10% delle cellule

Casi 2+: modificati rispetto allo score FDA e ASCO-CAP 2007

a) positività debole/moderata anche se incompleta in>10%
b) positività forte e completa in≤10% delle cellule

Testing criteria define HER2-positive status when (on observing within an area of tumor that amounts to > 10% of contiguous and homogeneous tumor cells) there is evidence of protein overexpression (IHC) or gene amplification (HER2 copy number or HER2/CEP17 ratio by ISH based on counting at least 20 cells within the area)
HER2 testing (invasive component) by validated single-probe ISH assay

Batch controls and on-slide controls show appropriate hybridization

Average HER2 copy number ≥ 6.0 signals/cell*

ISH positive

Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell*

ISH equivocal

Average HER2 copy number < 4.0 signals/cell

ISH negative

Must order a reflex test (same specimen using dual-probe ISH or using IHC) or order a new test (new specimen if available, using ISH or IHC)
HER2 testing (invasive component) by validated dual-probe ISH assay

Batch controls and on-slide controls show appropriate hybridization

**HER2/CEP17**
- ratio ≥ 2.0*
  - Average HER2 copy number ≥ 4.0 signals/cell*
    - ISH positive
  - Average HER2 copy number < 4.0 signals/cell*
    - ISH positive

**HER2/CEP17**
- ratio < 2.0
  - Average HER2 copy number ≥ 6.0 signals/cell*
    - ISH positive
  - Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell*
    - ISH equivocal
  - Average HER2 copy number < 4.0 signals/cell
    - ISH negative

Must order a reflex test (same specimen using IHC), test with alternative ISH chromosome 17 probe, or order a new test (new specimen if available, ISH or IHC).
Why were changes made to the ASCO/CAP HER2 guideline?

In the intervening years, numerous papers were published and issues raised by individuals and organizations about the original guideline recommendations. The update was created to address concerns, analyze and include the evidence and harmonize the recommendations with those of the ASCO – CAP Guideline Recommendations for Immunohistochemistry Testing of Estrogen and Progesterone Receptors in Breast Cancer (ER/PgR guideline) published in 2010.
What are the changes?

1. Cold ischemic time – For both HER2 and ER/PgR, follow the ER/PgR recommendation that time from tissue removal to initiation of fixation be less than or equal to one hour. Document this time on the accession slip or in the report or both.

2. Handling of specimens obtained remotely – For both HER2 and ER/PgR, follow the ER/PgR recommendation that specimens obtained remotely using non-biopsy procedures be bisected through the tumor on removal. Record on the accession slip the time of removal, fixative type and time placed in fixative.

3. Fixation duration in neutral buffered formalin should be 6-72 hours and conformance to these guidelines should be documented in the report or on the accession slip.

4. All breast cancer metastases or recurrences should also be tested for HER2.

5. Core samples, preferred for ER and PgR testing, are now acceptable for HER2 testing as well. In situations where the core shows artifacts or the results are negative in a patient with a high grade tumor, the test should be repeated on a resection specimen.

http://www.cap.org/apps/docs/committees/immunohistochemistry/her2_faqs.pdf
What are the changes?

6. Algorithms for defining what should be called HER2 positive, HER2 equivocal, HER2 negative and indeterminate have been refined and clarified for both IHC and ISH. Testing by analytically validated (hopefully also FDA-approved) brightfield in situ hybridization methods are now acceptable.

7. Interpretation guidelines for both IHC and ISH have been clarified.

8. Concordance requirements for IHC and ISH have been changed. Concordance between these assay types should be 95% but it is the responsibility of the laboratory director of each lab to define the level of concordance in his/her laboratory and monitor it in order to provide accurate testing.

9. Validation for both new HER2 tests and modified HER2 testing has been changed to agree with published validation requirements for ER and PgR testing.

Why were the HER2 and ER/PgR testing guidelines produced?

Laboratory assays for HER2 and Estrogen Receptor (ER) and Progesterone Receptor (PgR) are essential in selecting patients for anti-HER2 and hormonal therapy, yet inaccuracies in testing pose a significant problem in ensuring that patients are treated appropriately. The CAP and the American Society of Clinical Oncology (ASCO) collaborated in producing guidelines to improve testing accuracy and reduce the substantial risks associated with false positive and false negative results.
How long should breast specimens be fixed before tissue processing begins?

Breast specimens that will be subject to ER/PgR and HER2 testing should be fixed in neutral buffered formalin for a minimum of six hours and a maximum of 72 hours... For specimens fixed longer than 72 hours for HER2 or ER and PgR in which negative test results are obtained, **the report should state that prolonged fixation could be a possible cause for the negative result**, and alternative testing methods should be considered (e.g. FISH for HER2; gene expression assay for ER). For HER2 testing, labs should also consider confirming by FISH any specimen fixed longer than 72 hours that is not Score 3 by IHC.
Do I need to include the actual fixation time on the report?

No. For all cases in which the fixation time is within the recommended interval specified in the ASCO/CAP guidelines for HER2 and ER/PgR testing (6 to 72 hours for ER and PgR and HER2), laboratories can append a standard statement to their reports that fixation time was in compliance with ASCO/CAP guidelines.

However, laboratories will be required to put a disclaimer in any report in which the fixation time is outside those parameters. In addition, for cases with fixation times outside the recommended intervals in which a negative test result is obtained, the report should state that prolonged fixation could be a possible cause for the negative result and alternative testing methods should be considered (e.g. FISH for HER2; gene expression assay for ER).

For HER2 testing, labs should also consider confirming by FISH any specimen fixed longer than 72 hours that is not Score 3 by IHC. It is also acceptable to test another sample from the same patient for these factors in these situations rather than using alternative testing methods on the same sample.
The guidelines recommend slicing breast specimens at 5 to 10 mm intervals before fixing in formalin. Should specimens be refrigerated without fixative until this can be done?

No. Refrigeration delays fixation, which has a detrimental effect on immunostaining. The testing guidelines require that specimens that will be subject to HER2, ER, or PgR testing be placed in formalin less than one hour after the tumor is removed from the patient; any further delay in fixation is now considered unacceptable.

In addition to placing in fixative as soon as possible, the guidelines also recommend slicing the specimen at regular intervals to ensure adequate fixation throughout. Since most cases also require assessment of specimen margins, institutions must develop procedures to ensure proper handling of breast excision specimens.

As with any other intraoperative consultation, a pathologist (or other appropriately trained person under the direct supervision of a pathologist) must be available to handle these specimens.
Is shorter fixation (i.e. less than 6 hours) acceptable for needle biopsies due to their smaller size?

No. The original HER2 Testing Guidelines specified a minimum one-hour formalin fixation time for needle biopsies, but included a caveat that longer fixation is strongly recommended for these specimens. While formalin penetrates tissues at the rate of about 1mm/hour, penetration is not the same as fixation and the biochemical cross-linking that represents formalin fixation requires more time.

Published studies have documented that a minimum of 6-8 hours formalin fixation is needed to obtain consistent IHC assay results for ER; fixation for less than this time has been shown to cause false negative ER staining.

Because of the adverse effects of underfixation, which cannot be overcome by antigen retrieval, testing on specimens fixed for less than 6 hours is no longer acceptable. Cases in which tissues have been fixed less than 6 hours should be reported as ‘Estrogen Receptor Uninterpretable’ with an explanatory comment.
Do the guidelines exclude testing of cytology specimens (fluids and aspirates) that have been fixed in 95% ethanol rather than formalin?

No. Fixatives other than formalin are not precluded by the guidelines. For tissue specimens, laboratories that choose to use a fixative other than neutral buffered formalin must validate that fixative’s performance against the results of testing of the same samples fixed in neutral buffered formalin and tested with the identical assay. Since cytology specimens are not ordinarily fixed in formalin such concordance studies are not practical, but labs performing testing on such specimens must document that they validated their methods and achieved acceptable concordance, perhaps by comparing staining of alcohol fixed cytology specimens with subsequently excised routinely processed, formalin-fixed, surgical pathology specimens.
Would using a rapid processor be acceptable?

The effect of rapid tissue processing protocols on predictive marker testing is unknown. Before offering such testing using any alternative method, the lab must validate that method by comparing it with testing done by standard methods (i.e. the lab must test the same samples processed routinely and processed by the alternative method, and demonstrate 95% concordance for positive and negative results).
Validation of reagents or equipment by vendors or manufacturers does not represent an acceptable substitute for validation done by each laboratory.
The guidelines state that sections should not be used for IHC testing if cut more than 6 weeks earlier. Does this mean that stains should be done within 6 weeks of paraffin embedding or within 6 weeks of sectioning onto glass slides?

The latter is correct. There is no requirement that HER2 stains be done within 6 weeks of embedding, but labs should avoid doing HER2 stains on sections that were cut more than 6 weeks earlier. This also applies to positive control sections; labs should avoid using control slides that have been stored for prolonged periods after sectioning.
The guidelines state “Must report HER2 test result as indeterminate if technical issues prevent one or both tests (IHC and ISH) from being reported as positive, negative, or equivocal. Conditions may include: Inadequate specimen handling”. Does this mean that fixation <6 hours or >72 hours is a technical issue that prevents the tests from being reported as positive or negative and therefore must be called Indeterminate?

No. “Indeterminate” is to be reported if technical issues prevent one or both tests (IHC and ISH) performed in a tumor specimen from being reported as positive, negative, or equivocal. This may occur if specimen handling was inadequate, if artifacts (crush or edge artifacts) make interpretation difficult, or if the analytic testing failed. Another specimen should be requested for testing, if possible, and a comment should be included in the pathology report documenting intended action.

"It is at the pathologist's discretion to define inadequate specimen handling".
Does the CAP address HER2 and ER/PgR testing in the Laboratory Accreditation Program (LAP) checklists?

Yes, checklist requirements regarding HER2 assay validation, specimen fixation, proficiency testing, and use of the ASCO/CAP scoring criteria for reporting results are included in the Anatomic Pathology (ANP), Cytogenetics (CYG), and Molecular Pathology (MOL) checklists. These checklists are available to CAP accredited laboratories through e-LAB Solutions or can be purchased by non-CAP accredited laboratories.
Is participation in proficiency testing (PT) required for all sites that do HER2 testing?

Yes. In order to be compliant with the ASCO/CAP HER2 guidelines, any laboratory that reports results of such testing must participate in an accepted PT program (see exception below). The CAP Accreditation Program requires participation in a CAP-accepted PT program.

"The ASCO/CAP guidelines for HER2 testing apply only to breast carcinoma. HER2 testing on other tumor types (e.g. gastric carcinoma) is not covered by these guidelines at the current time."
Laboratory Accreditation and Proficiency Testing Questions

What PT material does the CAP offer?

*HER2 by Immunohistochemistry (IHC) Survey (HER2)*
The HER2 Survey is an IHC Survey that provides 28 challenges, two tissue microarray slides consisting of 14 cores each, twice per year. Enrollment in the HER2 Survey will satisfy LAP requirements for participation in a CAP-accepted PT program for HER2 by IHC.

*HER2 by Fluorescence in situ Hybridization (FISH) Survey (CYH)*
CYH is a FISH Survey that provides 10 challenges, twice per year. Enrollment in the CYH will satisfy the LAP requirement for participation in a CAP-accepted PT program for HER2 by FISH, interpretation and hybridization onsite activity. Laboratories that do interpretation only must perform alternative assessment.

*HER2 by Brightfield in situ Hybridization Survey (ISH2)*
The ISH2 Survey is a CISH (chromogenic in situ hybridization) and SISH (silver in situ hybridization) Survey that provides 10 challenges, twice a year. Enrollment in the ISH2 Survey will satisfy alternative assessment requirements for ISH.
We report HER2, ER and PgR using an automated image analysis system. What requirements apply to us?

Image analysis can be an effective tool for improving interpretation consistency; however, the pathologist is responsible for ensuring that the result provided by image analysis reflects measurement of invasive carcinoma only. The pathologist must document that he or she has reviewed either the stained patient test slides or the images and ensured that the appropriate area was scored.

Image analysis equipment, just as other laboratory equipment, must be calibrated and subjected to regular maintenance and internal quality control evaluation. Image analysis procedures must be validated before implementation.
F. Visinoni
Comprendere il presente per navigare il futuro

1) Insoddisfacente accuratezza


Risultato – Circa il 20% degli attuali test HER2 possono essere inaccurati.
While distribution of H2T (total Her 2 protein expression) values correlated significantly with all routine HER2 testing methods, higher concordance was observed between HERmark and central IHC retest as compared to local HER2 tests..... Thus, the HERmark assay may supplement existing routine HER2 testing in the ‘real-world’ setting as an accurate central HER2 test alternative, particularly for those cases with uncertainty in routine HER2 results, for example, HER2 equivocal cases and HER2 results that show inconsistencies with other clinical and pathological parameters.
REAL WORLD in Literature

Conclusions

The novel HERmark assay offers highly sensitive and accurate quantification of HER2 protein expression that has demonstrated excellent concordance with central HER2 testing and better correlation as a prognostic factor in OS as compared with ‘real-world’ local HER2 status in a multicenter clinical cohort of breast cancer patients.

The HERmark assay may reclassify 10% of false-negative patients by conventional tests as truly positive and 10% who are currently testing false positive by conventional tests as negative.

Thus, a resultant change in therapy for 20% of patients may improve the outcomes for both HER2-negative and -positive cohorts.

Further clinical studies are warranted to confirm these findings within well-controlled clinical cohorts and clinical trials.
Criticità

Nel valutare il risultato di HER2, bisogna sempre tenere in mente il quadro clinico generale p.es:

- fare attenzione al tumore G1, positivo per recettori ormonali, basso ki67 ma HER2+
- tumore G3, negativo per recettori recettori ormonali, alto Ki67 ma HER2-
- Falsi positivi.... Pp.es: CDI diagnosticato come HER2 3+ su core biopsy nel 2008 MTS epatica HER2 negativa dopo 2 anni→ aspecificità
- ampia area centrale HER2 neg, ma Linfonodo HER2 3+
- Carcinoma lobulare infiltrante (G3) metastatico al linfonodo sentinella Ma HER2-; Dopo 6 anni metastasi cutanea addominale HER2 =3+→ ripetendo Her2 sul tumore primitivo: rare cellule 3+
Criticità
Possibili variazioni di HER2 tra metastasi e tumore primitivo (5-15% dei casi).

Ipotesi:

a) Vero cambiamento della biologia del tumore?
b) Eterogeneità tumorale?
c) Cause tecniche: Casi 1+ con fattori di rischio ma non testati all’ISH?
d) Diverse modalità di esecuzione di HER2 nel corso degli anni?
e) Diversi criteri di lettura con le nuove linee guida ASCO-CAP 2013

Testare HER2 anche nelle recidive e nelle metastasi, specie se il tumore primitivo era negativo (ESMO), (ASCO), (NCCN)

La re-biopsia ha portato ad un cambiamento della terapia nel 14% delle pazienti
Efficacia della “targeted” terapia adiuvante per Her2 anche nei tumori B neg. (positivi per estrogeni e negativi per HER2)

-->blocca la piccola popolazione di stem cells, HER2+ che pur costituendo solo 1-5% del HER2+ del tessuto tumorale, potrebbe essere responsabile della crescita tumorale e delle metastasi!

Hasan Korkaya, Max S. Wicha, Cancer Research 2013
REAL WORLD experience, WEB content

HER2-negative (1+) breast cancer with unfavorable prognostic features: to FISH or not to FISH? (Iorfida et al. Ann.Oncol. 2012)

Il 13% dei casi 1+ ma che presentano almeno un ulteriore fattore di rischio risultano amplificati in ISH

Fattori di rischio
alto grado, alto Ki 67,
invasione vascolare estesa, invasione vascolare estesa,
LN+,
rec.ormonali assenti
REAL WORLD---- CRO series

Di questi, 1218 sono di prelievo tumorale primario, 53 di metastasi a distanza, 226 di metastasi linfonodali e 158 di tessuto sano.

<table>
<thead>
<tr>
<th>HER2 IHC</th>
<th>Pri T 1138</th>
<th>%</th>
<th>MD 53</th>
<th>%</th>
<th>ML 226</th>
<th>%</th>
<th>TS 158</th>
</tr>
</thead>
<tbody>
<tr>
<td>0+</td>
<td>406</td>
<td>35,67</td>
<td>19</td>
<td>35,84</td>
<td>74</td>
<td>32,74</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>434</td>
<td>37,91</td>
<td>21</td>
<td>39,62</td>
<td>76</td>
<td>33,62</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>164</td>
<td>14,41</td>
<td>6</td>
<td>11,32</td>
<td>42</td>
<td>18,58</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>134</td>
<td>11,77</td>
<td>7</td>
<td>13,20</td>
<td>34</td>
<td>15,04</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Apsys CRO AP 3276 casi dal 2012 al 2016
NORDICQ per SISH

Analizzando i dati forniti dal gestore si nota:
- variabilità nei risultati ottenuti da laboratori diversi che utilizzano stessa strumentazione e stessi protocolli
- maggiore correlazione FISH/FISH piuttosto che FISH/altra metodica
46 labs correlazione 85% ..... 77% tra BRISH e FISH centrale, SOLO AMPLIFICATO

46 labs correlazione 85% ..... 77% tra BRISH e FISH centrale, SOLO AMPLIFICATO

CRO series: su 700 tests Her2, 61 sono stati analizzati con SISH = 8,7%. Ci sono anche casi esterni
NORDIQC per IHC

Analizzando i dati forniti dal gestore si nota che:

c’è una maggior corrispondenza tra i laboratori per quanto riguarda IHC piuttosto che ISH, nonostante l’utilizzo di test di varie ditte.
Maria C. 25/03/1930

2013
B236843 BIO Mab HER-2/4B5* positiva (>10%) con colorazione di membrana incompleta ed appena percettibile (Score 1+).

B237032 PO, Mab HER-2/4B5* positiva (> 10%) con colorazione di membrana incompleta ed intensità debole (Score 2+). SISH/HER2: la cellularità neoplastica contiene 4 copie del gene per nucleo; il rapporto c-erbB-2/HER2/Chr17 è pari a 2, pertanto c-erbB-2/HER2 risulta amplificato.

2015
B 249248 ML Mab HER-2/4B5* positiva (> 10%) con colorazione di membrana incompleta ed intensità debole (Score 2+). SISH RIPETUTA 3 VOLTE MA ASSENZA DI SEGNALE !!!
REAL WORLD---- CRO series

Maria Grazia V., 30/01/1961

2012
B221911 Bio (Mab HER-2/4B5* positiva (>10%) con colorazione di membrana incompleta ed appena percettibile (Score 1+). Si segnala un gruppo di cellule neoplastiche (< al 5%), con colorazione di membrana completa ed intensità moderata.)-- → nulla

B223115 PO (Mab HER-2/4B5* positiva (>10%) con pattern di colorazione di membrana completo ed intensità moderata (Score 2+), SISH: c-erbB-2/HER2 non amplificato.

2016
B263288 Metastasi Flessura colica. (Mab HER-2/4B5* positiva (>10%), con colorazione di membrana incompleta ed appena percettibile (Score 1+).
Filippa V., 13/06/1959

2004
B149849 Pab c-erbB-2*: positiva (con intensità forte).

2010
B201847 Ca mammella con metastasi ossee Mab HER-2/4B5* positiva con colorazione di membrana incompleta in circa il 40% ed intensità appena percettibile (1+).

2012
B224156 Recidiva cutanea 2012 Mab HER-2/4B5* positiva (>10%) con pattern di colorazione di membrana incompleto ed appena percettibile (Score 1+).

2014
B246044 Mab HER-2/4B5* negativa (score 0)
Maria Pia A., 29/06/1940

2015
B253396 Bio Neoplasia maligna epiteliomorfa (reperto patologico molto limitato).
Immunoistologicamente la cellularità neoplastica risulta: Pancheratina +, ECaderina +, Ki67 + (~ 5%), Vimentina -, S100 -, Recettori degli Estrogeni, Recettori del Progesterone, GCDfp-15 +.
HER 2 non valutabile per assenza di colorazione citoplasmatica.

Conclusioni
Carcinoma infiltrante (regione retroareolare), della mammella (dx).
B5b sec. FONCAM.

2015
B254023 PO
Immunoistologicamente la cellularità neoplastica risulta inoltre Mab HER-2/4B5*: anomalo staining citoplasmatico.
In data 01.09.2015; SISH: le cellule tumorali contengono 2-3 copie del gene per nucleo quindi il rapporto c-erbB-2/HER2/Chr17 è circa 1,25, pertanto c-erbB-2/HER2 risulta non amplificato.

In data 08.09.2015; La rideterminazione dei recettori ormonali, Ki67 ed HER2 su altro frammento neoplastico (repere 1/I) ha confermato la valutazione precedente sul repere 1/RI.
REAL WORLD---- CRO series