FEP 2.04.76 Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers

Effective Date: April 15, 2018

Related Policies:
5.21.06 Herceptin (Trastuzumab)

Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers

Description

Novel assays that quantitatively measure total human epidermal growth factor receptor 2 (HER2) protein expression and homodimers have been developed to improve the accuracy and consistency of HER2 testing.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. HERmark® Breast Cancer Assay (Monogram Biosciences) is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

POLICY STATEMENT

The assessment of human epidermal growth factor receptor 2 (HER2) status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered **investigational**.

POLICY GUIDELINES

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

For individuals who have breast cancer and are undergoing assessment of HER2 status who receive quantitative total HER2 protein expression and HER2 homodimer measurement, the evidence includes validation studies and retrospective analysis of the association between levels and survival outcomes. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Retrospective analysis using HERmark have shown that the assay may predict a worse response to trastuzumab in certain populations. However, findings have been inconsistent, and no clear association with clinical outcomes has been shown. Additionally, cut points for defining patient groups varied across studies. Clinical utility of the HERmark assay has not been demonstrated, and clinical trials are needed to determine the impact on clinical outcomes of patients stratified by the HERmark assay. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on the treatment of breast cancer (v.2.2017) do not address the use of HERmark.[21]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada, Hawaii). Palmetto GBA's decisions apply for all molecular diagnostic tests for Medicare.

Palmetto GBA has assessed HERmark and determined that the test meets criteria for analytic and clinical validity and clinical utility as a reasonable and necessary Medicare benefit.[22] Effective December 9, 2011, Palmetto GBA will reimburse HERmark services for patients with breast cancer.

REFERENCES

1. Arteaga CL, O'Neill A, Moulder SL, et al. A phase I-II study of combined blockade of the ErbB receptor network with trastuzumab and gefitinib in patients with HER2 (ErbB2)-overexpressing metastatic breast cancer. *Clin Cancer Res.* Oct 01 2008;14(19):6277-6283. PMID 18829509
2. de Alava E, Ocana A, Abad M, et al. Neuregulin expression modulates clinical response to trastuzumab in patients with metastatic breast cancer. *J Clin Oncol.* Jul 01 2007;25(19):2656-2663. PMID 17602072

3. Piccart M, Lohrisch C, Di Leo A, et al. The predictive value of HER2 in breast cancer. *Oncology.* 2001;61 Suppl 2:73-82. PMID 11694791
4. Shi Y, Huang W, Tan Y, et al. A novel proximity assay for the detection of proteins and protein complexes: quantitation of HER1 and HER2 total protein expression and homodimerization in formalin-fixed, paraffin-embedded cell lines and breast cancer tissue. *Diagn Mol Pathol.* Mar 2009;18(1):11-21. PMID 19214113
5. Monogram Biosciences. HERmark Breast Cancer Assay. 2017; https://www.monogrambio.com/oncology-tests. Accessed October 24, 2017.
6. Larson JS, Goodman LJ, Tan Y, et al. Analytical validation of a highly quantitative, sensitive, accurate, and reproducible assay (HERmark) for the measurement of HER2 total protein and HER2 homodimers in FFPE breast cancer tumor specimens. *Patholog Res Int.* Jun 28 2010;2010:814176. PMID 21151530
7. Huang W, Reinholz M, Weidler J, et al. Comparison of central HER2 testing with quantitative total HER2 expression and HER2 homodimer measurements using a novel proximity-based assay. *Am J Clin Pathol.* Aug 2010;134(2):303-311. PMID 20660336
8. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med.* Jan 2007;131(1):18-43. PMID 19548375
9. Yardley DA, Kaufman PA, Huang W, et al. 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. *Breast Cancer Res.* Mar 18 2015;17:41. PMID 25886996
10. Bates M, Sperinde J, Kostler WJ, et al. Identification of a subpopulation of metastatic breast cancer patients with very high HER2 expression levels and possible resistance to trastuzumab. *Ann Oncol.* Sep 2011;22(9):2014-2020. PMID 21289364
11. Joensuu H, Sperinde J, Leinonen M, et al. Very high quantitative tumor HER2 content and outcome in early breast cancer. *Ann Oncol.* Sep 2011;22(9):2007-2013. PMID 21285132
12. Toi M, Sperinde J, Huang W, et al. Differential survival following trastuzumab treatment based on quantitative HER2 expression and HER2 homodimers in a clinic-based cohort of patients with metastatic breast cancer. *BMC Cancer.* Feb 23 2010;10:56. PMID 20178580
13. Lipton A, Kostler WJ, Leitzel K, et al. Quantitative HER2 protein levels predict outcome in fluorescence in situ hybridization-positive patients with metastatic breast cancer treated with trastuzumab. *Cancer.* Nov 15 2010;116(22):5168-5178. PMID 20661914
14. Lipton A, Goodman L, Leitzel K, et al. HER3, p95HER2, and HER2 protein expression levels define multiple subtypes of HER2-positive metastatic breast cancer. *Breast Cancer Res Treat.* Aug 2013;141(1):43-53. PMID 23959396
15. Han SW, Cha Y, Paquet A, et al. Correlation of HER2, p95HER2 and HER3 expression and treatment outcome of lapatinib plus capecitabine in her2-positive metastatic breast cancer. *PLoS One.* 2012;7(7):e39943. PMID 22848366
16. Duchnowska R, Biernat W, Szostakiewicz B, et al. Correlation between quantitative HER-2 protein expression and risk for brain metastases in HER-2+ advanced breast cancer patients receiving trastuzumab-containing therapy. *Oncologist.* Jan 2012;17(1):26-35. PMID 22234627
17. Barros FF, Abdel-Fatah TM, Moseley P, et al. Characterisation of HER heterodimers in breast cancer using in situ proximity ligation assay. *Breast Cancer Res Treat.* Apr 2014;144(2):273-285. PMID 24557338
18. Duchnowska R, Sperinde J, Chenna A, et al. Quantitative measurements of tumoral p95HER2 protein expression in metastatic breast cancer patients treated with trastuzumab: independent validation of the p95HER2 clinical cutoff. *Clin Cancer Res.* May 15 2014;20(10):2805-2813. PMID 24668646
19. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res.* Nov 1 2004;10(21):7252-7259. PMID 15534099
20. Green AR, Barros FF, Abdel-Fatah TM, et al. HER2/HER3 heterodimers and p21 expression are capable of predicting adjuvant trastuzumab response in HER2+ breast cancer. *Breast Cancer Res Treat.* May 2014;145(1):33-44. PMID 24706169
21. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: Breast cancer. Version 2.2017. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 31, 2017.
22. Palmetto GBA®. MolDX: HERmark Assay by Monogram Coding and Billing Guidelines (M00028, V10). 2017; http://www.palmettogba.com/palmetto/MolDX.nsf/DocsCat/MolDx%20Website~MolDx~Browse%20By%20Topic~Covered%20Tests~8TVSBJ3016?open&navmenu=Browse%5EBy%5ETopic%7C%7C%7C%7C. Accessed November 15, 2017.

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POLICY HISTORY

Date	Action	Description
March 2012	New Policy	
December 2012	Update Policy	Policy and references updated with literature search, no change in policy statement .
December 2013	Update Policy	Policy updated with a literature search with references added. No change in policy statement. Reference 14 updated.
December 2014	Update Policy	Policy updated with literature review. References 11, 14-16, and 18 added; references 3 and 17 updated. No change to policy statement.
March 2018	Update Policy	Policy updated with literature review through October 17, 2017; references 1-3, 5, 7, and 10 added; reference 22 updated. Policy statement unchanged.