Prior Authorization Review Panel
MCO Policy Submission

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Plan: Keystone First Community HealthChoices	**Submission Date**: 5/1/2024
Policy Number: ccp.1045	**Effective Date:** 12/2013 **Revision Date:** April 1, 2024
Policy Name: 65TGene expression profile testing for breast cancer	

Type of Submission – Check all that apply:

New Policy
X Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

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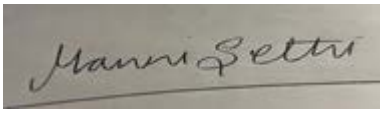
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

Gene expression profile testing for breast cancer

Clinical Policy ID: CCP.1045

Recent review date: 4/2024

Next review date: 8/2025

Policy contains: Breast cancer; Gene expression profile/assay/test; Endopredict; MammaPrint®; Oncotype DX®; Prosigna; RealTime PCR.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Gene expression profile testing in early-stage breast cancer is clinically proven and, therefore, may be medically necessary to support determination of adjuvant chemotherapy when all of the following criteria are met (Ontario Health [Quality], 2020):

- Breast cancer is non-metastatic, or with one to three involved ipsilateral axillary lymph nodes.
- Breast tumor is estrogen receptor positive.
- Breast tumor is human epidermal growth factor receptor 2 receptor negative or breast tumor is human epidermal growth factor receptor 2 receptor positive and less than 1 cm in diameter.
- Adjuvant chemotherapy is not contraindicated due to any other factor (e.g., advanced age or significant comorbidities).
- Member and physician (prior to testing) have discussed the potential results of the test and agreed to use the results to guide therapy.

The following gene expression assays are clinically proven and, therefore, may be medically necessary for consideration of adjuvant systemic therapy in members with breast cancer (National Comprehensive Cancer Network, 2023):

- Oncotype DX® (Exact Sciences Corp., Madison Wisconsin).
- Endopredict® (Myriad Genetics, Inc., Salt Lake City, Utah).
- Breast Cancer Index® (Biotheranostics, Inc., San Diego, California).
- MammaPrint® (Agendia Inc. USA, Irvine, California).

- Prosigna® (Veracyte, Inc., South San Francisco, California).

Limitations

All other uses of gene expression testing for breast cancer are not medically necessary.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Breast cancer is the most common cancer among women worldwide and the leading cause of premature mortality among women in the United States. In 2022, an estimated 287,850 American women were diagnosed with breast cancer and 43,250 women died from the disease (National Cancer Institute, 2022).

Traditional breast cancer risk classification includes tumor type (ductal or lobular infiltrating carcinoma), histological grade (I to III), steroid hormone receptor and human epidermal growth factor receptor 2 status (positive or negative), and cancer absence/presence in the lymph nodes and distant organs (American Cancer Society, 2021).

Gene expression profile testing is a microarray analysis of genetic variations between normal and malignant cells. Patterns in genes may help predict if early-stage estrogen receptor-positive lymph node negative breast cancer are likely to have a higher risk of recurrence (prognosis). The information is intended to identify which women will most likely benefit from post-surgical chemotherapy and from avoiding unnecessary administration of (and adverse side effects of) chemotherapy (American Cancer Society, 2021; Smith, 2019).

Commercially available tests include (American Cancer Society, 2021; Smith, 2019):

- Oncotype DX. This test is for stage I, II, or III, and detects hormone receptor-positive tumors that have not spread to >3 lymph nodes and are human epidermal growth factor receptor-2 negative; or for ductal carcinoma in situ breast cancer. The test assigns a recurrence score to patients; those with higher scores are most likely to benefit from adding chemotherapy to hormone therapy. Oncotype DX is the most commonly used of the tests. Oncotype DX is the only gene expression signature that can predict response to chemotherapy.
- Endopredict. This test is used for tumors that are node-negative or node-positive (1 – 3 nodes) tumors that are human epidermal growth factor receptor-2 negative, for pre- and post-menopausal women. It predicts high and low risk recurrence (within 10 years) status for breast cancers.
- MammaPrint. This test can determine high or low risk of recurrence (within 10 years) of distant breast cancers after treatment. Indications are for invasive breast cancers <5 cm spread to three or fewer lymph nodes, regardless of hormone and human epidermal growth factor receptor-2 status.
- Prosigna. This test predicts high, low, or intermediate risk of recurrence (within 10 years) in post-menopausal women with hormone receptor-positive breast cancer. It is used for stage I and II cancers that have not spread to lymph nodes, or stage II cancers with three or fewer positive lymph nodes.

Findings

The National Comprehensive Care Network published a set of specific guidelines governing use of gene expression assays for use in adjuvant chemotherapy for breast cancer. They constitute the basis for the coverage section of this policy. Oncotype Dx is the preferred gene panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information, but their ability to predict

chemotherapy benefit has not been validated. These assays complement the staging workup but are not required for staging (National Comprehensive Cancer Network, 2023).

The American Society of Clinical Oncology endorsed the Cancer Care Ontario guidelines on decision-making in adjuvant systemic therapy for early-stage operable breast cancer. The endorsement included nodal status, tumor size, estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 status, tumor grade, and lymphovascular invasion as relevant factors. It also recommended using Oncotype DX score and Adjuvant! Online® among risk stratification tools (Henry, 2016). The Society updated and refined the endorsement several years later (Henry, 2019).

The American Society of Clinical Oncology criteria governing whether or not adjuvant chemotherapy is indicated in these patients includes the following (Harris, 2016):

- Chemotherapy indicated/potentially beneficial. Patients with positive lymph nodes, estrogen receptor-negative disease, human epidermal growth factor receptor 2-positive disease, Adjuvant Online mortality greater than 10%, grade 3 lymph node-negative tumors (tumor >5 mm), triple-negative (estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2-negative) tumors, lymphovascular invasion positivity, or estimated distant relapse risk of greater than 15% at 10 years based on Oncotype DX recurrence risk score.
- Chemotherapy not indicated/not beneficial. Patients with small node-negative tumors (tumor <5 mm) without high-risk features or for patients with human epidermal growth factor receptor 2-negative, strongly estrogen receptor-positive, and progesterone receptor-positive cancer with micro-metastatic nodal disease, tumor less than 5 mm, or Oncotype DX recurrence risk score with an estimated distant relapse risk of less than 15% at 10 years.

The National Institute for Health and Care Excellence also issued test-specific recommendations for the use of tumor profiling tests to guide adjuvant chemotherapy in breast cancer (National Institute for Health and Care Excellence, 2018).

In 2024, clinical practice guidelines published by the European Society for Medical Oncology supported the use of gene expression assays and endocrine response assessment in cases of uncertainty about indications for adjuvant chemotherapy in hormone receptor-positive, HER2-negative early breast cancer (after consideration of all clinical and pathological factors). The guideline states that among postmenopausal women with node-negative disease or limited node involvement and low-risk assay scores/biology, adjuvant chemotherapy did not further reduce recurrence rates compared to endocrine therapy alone. Similarly, among premenopausal women with limited node involvement and low-risk scores, adjuvant chemotherapy reduced recurrence rates compared to endocrine therapy alone. The guideline recommends that in cases of uncertainty about chemotherapy indications after other factors are considered, gene expression assays and endocrine response assessment in the preoperative setting can be used to help guide adjuvant chemotherapy decisions (Loibl, 2024). No policy changes warranted.

A literature review of 50 studies backed the American Society of Clinical Oncology guideline on specific biomarkers guideline adjuvant treatment in breast cancer. The review identified relevant biomarkers including ones indicated for use (Harris, 2016).

A systematic review of 71 studies (n = 561,188) of women with hormone-sensitive breast cancer included 27,748 who were age 40 or younger. The younger cohort had a higher proportion of intermediate- to high-risk tumors when classified by EndoPredict ($P = .04$), MammaPrint ($P < .01$), and Oncotype DX ($P < .01$). In young women with low genomic risk, 6-year distant recurrence-free survival was 94%, while five-year overall survival was nearly 100%. Still, young low-risk patients were more likely to receive chemotherapy versus those older than 40, indicating genomic tests are helpful tools in reducing chemotherapy (Villareal-Garza, 2020).

A qualitative review of 11 publications on the experience of using gene expression profile testing to make decisions in breast cancer treatment found that (Smith, 2019):

- Patients and oncologists relied heavily on profile testing to make decisions.
- Oncologists were concerned about over-reliance on profile testing to make treatment decisions.
- Some patients might overlook testing's limitations.
- Need to explain the complexity of testing added time to oncologists' visits with patients.

A systematic literature review of 68 studies showed gene expression profiling test results caused changes in treatment decisions in 20% to 50% of cases, including both recommending and withholding chemotherapy. Tests can effectively prognosticate risk of distant recurrence for the estrogen receptor/progesterone receptor-positive, human epidermal growth factor receptor 2-negative, lymph node-negative breast cancer population, but to a lesser extent to lymph node-positive patients. Limited evidence is available to assess predictive ability (Ontario Health [Quality], 2020).

A systematic review of 153 European studies of women with breast cancer, only one of which was a randomized controlled trial, found tumor profiling tests resulted in up to a 64% decrease in patients with chemotherapy recommendations (Harnan, 2019).

A literature review of 147 articles showed that results from Oncotype DX had a superior record of avoiding unnecessary chemotherapy in women with early-stage breast cancer than did MammaPrint (Blok, 2018).

A systematic review of 37 studies (29 of which addressed breast cancer) evaluated efficacy of genomic classifiers. Authors note that several models are effective, but issues of data quality remain (Trifiletti, 2017).

A systematic review of 41 studies assessed efficacy of two gene expression profiling and two expanded immunohistochemistry tests in guiding use of adjuvant chemotherapy in patients with early breast cancer.

Oncotype DX demonstrated impact on decision-making, with some support for predicting chemotherapy benefit. The other tests (including MammaPrint) had lower levels of evidence (Scope, 2017).

A systematic review/meta-analysis of four studies (n = 1,802) analyzed the ability of gene panels to identify pathogenic variants, and variants of unknown significance, which cannot be used in decision-making, through simultaneous testing of multiple susceptibility genes, in patients at high risk of breast cancer. Probability per patient of pathogenic variants and variants of unknown significance were 8% and 23%, respectively (*P* = .0052) (van Marcke, 2018).

A systematic review/meta-analysis of 15 studies (n = 2,229) of women with early-stage breast cancer showed Oncotype DX results changed treatment in 29.5% of patients and reduced chemotherapy by 12% (Augustovski, 2015).

A systematic review of four studies (n = 3,128) of early-stage breast cancer (node-positive) cases revealed that 26% to 51% of cases had changes in planned treatment, two-thirds of which were elimination of chemotherapy) due to recurrence score results from the Oncotype DX test. Patients at low risk for distant recurrence, and thus not likely to benefit from chemotherapy, were helped (Brufsky, 2014).

A systematic review/meta-analysis of 23 studies of women with early stage breast cancer determined Oncotype DX changed the clinical-pathological adjuvant chemotherapy recommendation in 33.4% of patients. In addition, patients with low relative risk scores were significantly more likely to follow results of Oncotype DX tests, suggesting a tendency toward less aggressive treatment despite a high risk score (Carlson, 2013).

A systematic review of 30 studies concluded that Oncotype DX was most effective in predicting chemotherapy benefit in women with early breast cancer. MammaPrint had a good predictive value, but this finding was based on studies with small sample sizes (Ward, 2013).

A systematic review of 29 articles reported routine use of Oncotype DX and MammaPrint resulted in optimal allocation of adjuvant chemotherapy and reduced chemotherapy utilization (Rouzier, 2013).

A systematic review of 27 studies criticized the assessment of gene expression profiling test results. Authors point out that 15 of these studies received industry funding. In addition, 18 studies did not incorporate clinical characteristics such as tumor size and grade commonly used to make chemotherapy decisions, thus biasing results and not reflecting clinical practice (Wang, 2018).

A randomized, phase 3 study of 6,693 women with early-stage breast cancer found that, among 1,550 who were assessed as being at high clinical risk but low genomic risk after gene expression testing, the five-year rate of survival without distant metastasis was 94.7%, among those who did not receive chemotherapy, 1.5% higher among those who did. Authors calculate that 46% of women with breast cancer at high clinical risk do not require chemotherapy (Cardoso, 2016).

In 2022, we updated the references and added two systematic reviews examining the role of Oncotype DX in predicting response to neoadjuvant treatment in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (Boland, 2021; Davey, 2021). Both findings require further study to determine the impact of adding the Oncotype recurrence score on patient outcomes.

Results of a systematic review of seven studies (n = 1,744) found the pathological complete response rate was significantly higher in the group with a high recurrence score than in the group with a low-intermediate score (10.9% versus 1.1%, relative risk 4.47, 95% confidence interval 2.76 to 7.21, $P < .001$), along with a significant risk difference between the two groups ($P = .001$) (Boland, 2021). The clinical significance of these results requires further study as patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer tend to respond poorly to neoadjuvant chemotherapy. In the second systematic review of eight studies (n = 691 patients), those with low (< 25) to intermediate Oncotype DX recurrence scores (< 30) on core biopsy were four times more likely to achieve a partial response to neoadjuvant endocrine therapy than those with high-risk recurrence score ($P < .001$ each at a recurrence score level) (Davey, 2021).

In 2023, we updated the references and added four systematic reviews and meta-analyses that attempt to address key knowledge gaps regarding the role of gene expression profiling (primarily Oncotype DX) in older adults, in locoregional disease, and in males with early stage, estrogen receptor positive, human epidermal growth factor receptor-2 negative breast cancer. While promising, the results require validation in prospective, randomized studies. No policy changes are warranted.

For gene expression profiling in older patients with early hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer, two systematic reviews found that while its prognostic role is well established, its impact on chemotherapy-related survival is uncertain. The age cutoffs varied among included studies, but the majority of participants were age 65 or older, and Oncotype DX was the most studied panel. Gene expression profiling was offered less frequently to older versus younger patients. Additional validation in older patients with high-risk tumors is needed (Battisti, 2022, five observational studies, n = 445,323; Lemij, 2023; n = 15 observational studies).

A systematic review and network meta-analysis of 16 studies (n = 21,037, including 590 with locoregional recurrence) found a direct correlation between the Oncotype DX recurrence score and locoregional recurrence in estrogen receptor-positive breast cancer when applying traditional and TAILORx cut-offs (both $P < .050$). The mean follow-up was 66.4 months (range 27.0 to 120.0 months) (Davey, 2022a).

Results of a systematic review and meta-analysis of six observational studies (n = 176,338, including 1,826 males) suggest Oncotype DX recurrence scores were similar for female and male participants (recurrence scores < 18, odd ratio 1.04, 95% confidence interval .94 to 1.16, scores 18 to 30 (1.12, 1.00-1.26) and scores > 30 (.69, .45 to 1.07) (Davey, 2022b).

In 2024, we added guidelines from European Society for Medical Oncology, however no policy changes were warranted.

References

On February 23, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “breast neoplasm (MeSH)” and "gene expression test (MeSH).” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American Cancer Society. Breast cancer gene expression tests. https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-gene-expression.html. Last revised November 8, 2021.

Augustovski F, Soto N, Capirale J, Gonzalez L, Gibbons L, Ciapponi A. Decision-making impact on adjuvant chemotherapy allocation in early node-negative breast cancer with a 21-gene assay: Systematic review and meta-analysis. *Breast Cancer Res Treat*. 2015;152(3):611-625. Doi: 10.1007/s10549-015-3483-3.

Battisti NML, De Glas N, Soto-Perez-de-Celis E, et al. Chemotherapy and gene expression profiling in older early luminal breast cancer patients: An international society of geriatric oncology systematic review. *Eur J Cancer*. Sep 2022;172:158-170. Doi: 10.1016/j.ejca.2022.05.039.

Blok EJ, Bastiaannet E, van den Hout WB, et al. Systematic review of the clinical and economic value of gene expression profiles for invasive early breast cancer available in Europe. *Cancer Treat Rev.* 2018;62:74-90. Doi: 10.1016/j.ctrv.2017.10.012.

Boland MR, Al-Maksoud A, Ryan É J, et al. Value of a 21-gene expression assay on core biopsy to predict neoadjuvant chemotherapy response in breast cancer: Systematic review and meta-analysis. *Br J Surg.* 2021;108(1):24-31. Doi: 10.1093/bjs/znaa048.

Brufsky AM. Predictive and prognostic value of the 21-gene recurrence score in hormone receptor-positive, node-positive breast cancer. *Am J Clin Oncol*. 2014;37(4):404-410. Doi: 10.1097/COC.0000000000000086.

Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med.* 2016;375(8):717-729. Doi: 10.1056/NEJMoa1602253.

Carlson JJ, Roth JA. The impact of the Oncotype Dx breast cancer assay in clinical practice: A systematic review and meta-analysis. *Breast Cancer Res Treat*. 2013;141(1):13-22. Doi: 10.1007/s10549-013-2666-z.

Davey MG, Cleere EF, O'Donnell JP, Gaisor S, Lowery AJ, Kerin MJ. Value of the 21-gene expression assay in predicting locoregional recurrence rates in estrogen receptor-positive breast cancer: A systematic review and network meta-analysis. *Breast Cancer Res Treat*. Jun 2022;193(3):535-544. Doi: 10.1007/s10549-022-06580-w.(a)

Davey MG, Davey CM, Bouz L, et al. Relevance of the 21-gene expression assay in male breast cancer: A systematic review and meta-analysis. *Breast*. Aug 2022;64:41-46. Doi: 10.1016/j.breast.2022.04.009.(b)

Davey MG, Ryan É J, Boland MR, et al. Clinical utility of the 21-gene assay in predicting response to neoadjuvant endocrine therapy in breast cancer: A systematic review and meta-analysis. *Breast.* 2021;58:113-120. Doi: 10.1016/j.breast.2021.04.010.

Harnan S, Tappenden P, Cooper K, et al. Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer: A systematic review and economic analysis. *Health Technol Assess*. 2019 Jun;23(30):1-328. Doi: 10.3310/hta23300.

Harris LN, Ismaila N, McShane LM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016; 34(10):1134-1150. Doi: 10.1200/JCO.2015.65.2289.

Henry NL, Somerfield MR, Abramson VG, et al. Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: Update of the ASCO endorsement of the Cancer Care Ontario guidelines. *J Clin Oncol*. 2019;37(22):1965-1977. Doi: 10.1200/JCO.19.00948.

Henry NL, Somerfield MR, Abramson VG, et al: Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: American Society of Clinical Oncology endorsement of Cancer Care Ontario guideline recommendations. *J Clin Oncol.* 2016;34(19):2303-2311. Doi: 10.1200/JCO.2015.65.8609.

Lemij AA, Baltussen JC, de Glas NA, et al. Gene expression signatures in older patients with breast cancer: A systematic review. *Crit Rev Oncol Hematol*. Jan 2023;181:103884. Doi: 10.1016/j.critrevonc.2022.103884.

Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2024;35(2):159-182. Doi:10.1016/j.annonc.2023.11.016

National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER cancer stat facts: Female breast cancer. National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/statfacts/html/breast.html. Published 2022.

National Comprehensive Cancer Network®. Breast cancer. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Version 2.2023. www.nccn.org. Published February 7, 2023.

National Institute for Health and Clinical Excellence Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Diagnostics guidance [DG34]. https://www.nice.org.uk/guidance/dg34/chapter/1-Recommendations. Published December 19, 2018.

Ontario Health (Quality). Gene expression profiling tests for early-stage invasive breast cancer: A health technology assessment. *Ont Health Technol Assess Ser*. 2020;20(10):1-234. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7143374/. Published online March 6, 2020.

Rouzier R, Pronzato P, Chereau E, Carlson J, Hunt B, Valentine WJ. Multigene assays and molecular markers in breast cancer: Systematic review of health economic analyses. *Breast Cancer Res Treat*. 2013;139(3):621-637. Doi: 10.1007/s10549-013-2559-1.

Scope A, Essat M, Pandor A, et al. Gene expression profiling and expanded immunohistochemistry tests to guide selection of chemotherapy regimens in breast cancer management: A systematic review. *Int J Technol Assess Health Care*. 2017;33(1):32-45. Doi: 10.1017/S0266462317000034.

Smith A, Farrah K. Gene expression profiling tests for breast cancer: A rapid qualitative review. Canadian Agency for Drugs and Technologies in Health. https://www.ncbi.nlm.nih.gov/books/NBK545134/. Published April 18, 2019.

Trifiletti DM, Sturz VN, Showalter TN, Lobo JM. Towards decision-making using individualized risk estimates for personalized medicine: A systematic review of genomic classifiers of solid tumors. *PLoS One*. 2017;12(5):e0176388. Doi: 10.1371/journal.pone.0176388.

van Marcke C, Collard A, Vikkula M, Duhoux FP. Prevalence of pathogenic variants and variants of unknown significance in patients at high risk of breast cancer: A systematic review and meta-analysis of gene-panel data. *Crit Rev Oncol/Hematol.* 2018;132:138-144. Doi: 10.1016/j.critrevonc.2018.09.009.

Villareal-Garza C, Ferrigno AS, De la Garza-Ramos C, Barragan-Carrillo R, Lambertini M, Azim HA Jr. Clinical utility of genomic signatures in young breast cancer patients: A systematic review. *NPJ Breast Cancer*. 2020;6:46. Doi: 10.1038/s41523-020-00188-3.

Wang S-Y, Dang W, Richman I, Mougalian SS, Evans SB, Gross CP. Cost-effectiveness analyses of the 21-gene assay in breast cancer: Systematic review and critical appraisal. *J Clin Oncol*. 2018;36(16):1619-1627. Doi: 10.1200/JCO.2017.76.5941.

Ward S, Scope A, Rafia A, Pandor S, Harnan P, Evans L, Wyld L. Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: A systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2013;17(44):1-302. Doi: 10.3310/hta17440.

Policy updates

7/2013: initial review date and clinical policy effective date: 12/2013

7/2014: Policy references updated.

7/2015: Policy references updated.

7/2016: Policy references updated.

7/2017: Policy references updated.

7/2018: Policy references updated.

2/2019: Policy references updated. Policy ID changed to CCP.1045.

4/2020: Policy references updated.

4/2021: Policy references updated.

4/2022: Policy references updated.

4/2023: Policy references updated.

4/2024: Policy references updated.