Prior Authorization Review Panel
MCO Policy Submission

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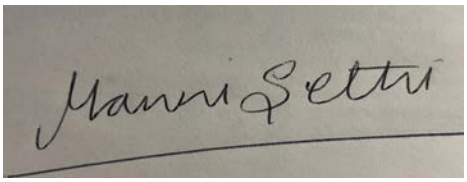
Plan: Keystone First	**Submission Date**: 1/1/2023
Policy Number: ccp.1437	**Effective Date:** 1/2020 **Revision Date:** December 1, 2023
Policy Name: Molecular analysis for targeted therapy for breast cancer	
Type of Submission – Check all that apply: **New Policy** **x Revised Policy*** **Annual Review – 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:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Family of Health Plans

Molecular analysis for targeted therapy for breast cancer

Clinical Policy ID: CCP.1437

Recent review date: 12/2023

Next review date: 4/2025

Policy contains: Breast cancer; immunohistochemistry; in situ hybridization; next-generation sequencing.

Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First's 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 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's 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's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First's clinical policies are not guarantees of payment.

Coverage policy

As the landscape of targeted therapies is rapidly evolving, molecular analysis for targeted therapy for breast cancer is clinically proven and, therefore, may be medically necessary for indications specified in National Comprehensive Cancer Network clinical practice guidelines, other cancer care guidelines (where indicated), and U.S. Food and Drug Administration-approved package labeling for indication and usage.

Molecular analyses of the following genetic predictors of response to targeted gene therapy in breast cancer management are clinically proven and, therefore, may be medically necessary, when using validated tests performed in Clinical Laboratory Improvement Amendment-certified laboratories, and when the test results will influence treatment planning (National Comprehensive Cancer Network, 2023; U.S. Food and Drug Administration, 2023a; see appendix):

- Human epidermal growth factor receptor 2 (*HER2*) protein overexpression or *HER2* gene amplification in tumor specimens in members with new primary or metastatic breast cancer, using a validated immunohistochemistry or *in situ* hybridization assay performed in a *HER2*-accredited laboratory.
- *HER2* protein overexpression* or *HER2* gene amplification* for members considered for trastuzumab, pertuzumab, ado-trastuzumab emtansine, or fam-trastuzumab deruxtecan-nxkie therapy.
- Reflex testing may be medically necessary on an alternative tumor specimen or on the same specimen using an alternative test if the initial *HER2* test result is equivocal.
- Germline breast cancer (*BRCA1/2)* mutations* (when previous germline testing did not include large re-arrangement analysis) in members considered for olaparib or talazoparib therapy.
- Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutation status* in members considered for alpelisib therapy.

- Reflex testing in tumor tissue may be medically necessary to confirm undetected circulating tumor deoxyribonucleic acid assay (i.e., negative) results (Merker, 2018).
- Programmed cell death ligand-1 (*PD-L1*) expression* (gene CD274) in tumor or circulating plasma cells (liquid biopsy) in members considered for atezolizumab therapy.
- *PD-L1* expression* in tumor or circulating plasma cells, microsatellite instability or mismatch repair status (*MLH1*, *MSH2*, *MSH6* or *PMS2* protein expression), or tumor mutational burden status* in members considered for pembrolizumab.
- Neurotrophic receptor tyrosine kinase (*NTRK* 1/2/3) gene fusion testing in members considered for entrectinib or larotrectinib* therapy.
- *ESR1* mutation* in members considered for elacestrant therapy.
- Mismatch repair deficiency* in members considered for dostarlimab-gxly therapy.
- *Ki-67* protein expression* in members considered for abemaciclib therapy.
- *RET* gene fusion in members considered for selpercatinib therapy.

*Denotes using only a U.S. Food and Drug Administration–approved companion diagnostic test listed in the appendix.

Refer to **CCP.1012 Genetic testing for breast and ovarian cancer** for a list of medically necessary molecular testing panels with demonstrated clinical utility for hereditary breast cancer risk assessment.

Refer to **CCP.1045 Gene expression profile testing for breast cancer** for a list of medically necessary tumor gene expression signatures with demonstrated clinical utility.

For any determinations of medical necessity for medications, refer to the applicable state approved pharmacy policy.

Limitations

Molecular testing for all other somatic and germline mutations as predictors of response to targeted gene therapies in breast cancer is investigational/not clinically proven and, therefore, not medically necessary, including but not limited to (National Comprehensive Cancer Network, 2023):

- Routine *CYP2D6* testing to direct optimal adjuvant endocrine therapy with tamoxifen.
- Circulating tumor cell counts.
- Circulating tumor deoxyribonucleic acid assays that measure genomic variants other than *PIK3CA*.

Repeat testing using any of the molecular analyses listed in the Coverage section above is investigational/not clinically proven and, therefore, not medically necessary except for molecular assays measuring *HER2* status in the presence of recurrence, when the results will impact treatment planning (National Comprehensive Cancer Network, 2023).

Alternative covered services

Guideline-directed treatment for breast cancer.

Background

Tumor molecular markers are important adjuncts in cancer care for diagnosis, prognosis, and prediction of treatment response. The efficacy of a growing number of approved, molecularly selective anticancer agents depends on matching patients to beneficial treatment on the basis of actionable molecular markers, i.e., the molecular features of their tumors that are predictive of treatment response (Schwartzberg, 2017). The goals of

predictive molecular profiling are to avoid underuse of well-documented variant target-drug pairs and overuse of variant-drug therapy without proven benefit.

Tests of these molecular markers encompass a variety of platforms and analytic approaches, including immunohistochemistry, *in situ* hybridization, and next-generation deoxyribonucleic acid sequencing and targeted ribonucleic acid sequencing. Somatic (tumor) and germline (inherited) testing may be used to help select treatment options. Germline testing is usually performed on blood or saliva samples, whereas somatic testing is performed on tumor tissue samples or circulating tumor cells in blood (Litton, 2019).

The term “liquid biopsy” encompasses measurement of soluble factors, such as proteins, tumor markers, circulating tumor cells, and circulating cell-free nucleic acids, in blood components to provide similar diagnostic information to that obtained from a tumor biopsy (Merker, 2018). Potential advantages over tumor biopsy are convenience, minimal procedural risk, lower cost, ability to perform serial measurement, and more complete information.

Regulation

The U.S. Food and Drug Administration regulatory structure classifies molecular tests based on test complexity and risk of an incorrect result to the patient. Molecular tests may be exempt from review (Class I tests), cleared under the 510(k) process (Class II tests), or approved under a premarket approval process (Class III tests). All U.S. Food and Drug Administration-approved tests have been validated, but laboratory-developed tests, or the reagents used in the test, may not always be uniformly validated. The Centers for Medicare & Medicaid Services administers additional regulations for clinical laboratories that are certified through the Clinical Laboratory Improvement Amendment of 1988 (Javitt, 2022).

The U.S. Food and Drug Administration (2023a; see appendix) lists several companion diagnostic tests that provide essential information for the safe and effective use of a corresponding therapeutic product in breast cancer care.

Findings

For this policy, molecular testing is confined to those tests that demonstrate clinical utility by accurately identifying genetic or genomic variants, predict response to specific targeted breast cancer therapies, and ultimately affect outcome. The National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend measuring estrogen and progesterone receptor status by immunohistochemistry on all tumor samples of invasive breast cancer. For all ductal carcinoma *in situ*, estrogen receptor status is recommended, and progesterone receptor status is considered optional. Both organizations recommend *HER2* status to direct therapy in all patients diagnosed with breast cancer, and additional *HER2* testing of the metastatic site, if tissue sample is available (Allison, 2020; National Comprehensive Cancer Network, 2023; Wolff, 2023).

Hormone receptor status is also indicated in the presence of cancer recurrence or metastasis. For patients with advanced metastatic breast cancer and known hormone receptor and *HER2* status, the evidence supports a limited number of molecular tests that can accurately predict therapy response and effect patient outcome, as follows.

Somatic (tumor) mutation testing

The *ERBB2* gene, commonly known as *HER2* or *HER2/neu*, is a member of the transmembrane tyrosine kinase receptors that regulate important cellular processes such as cell growth, survival, and differentiation (Dean, 2021). When mutated or overexpressed, this gene can lead to abnormal cell growth and more aggressive clinical behavior. The *HER2* gene is overexpressed in 15% to 20% of breast cancers. Inhibitors of *HER2* gene overexpression are tyrosine kinase inhibitors or monoclonal antibodies that slow down or stop cell growth.

HER2 gene amplification measured by *in situ* hybridization or *HER2* protein overexpression measured by immunohistochemistry remain the primary predictors of responsiveness to *HER2*-targeted therapies in breast cancer. Several approved testing methods exists for detecting *HER2* protein overexpression or the presence of *HER2* gene amplification, but there remains a lack of standardization across trials in assay use and interpretation that hinders comparison of tests. Moreover, for metastatic disease in patients without *HER2* overexpression or gene amplification, an immunohistochemistry 11 or 21 result may make patients eligible for certain recently available targeted treatment (Wolff, 2023).

Potential candidates for pertuzumab, trastuzumab, and ado-trastuzumab emtansine require assessment of *HER2* status by an accurate and validated U.S. Food and Drug Administration-approved companion diagnostic assay (see appendix). If there is discordance between histopathology and *HER2* test results or there are equivocal *HER2* test results, additional *HER2* testing is indicated to adequately inform the treatment decision. Reflex testing should be performed on an alternative specimen or on the same specimen using an alternative test if the initial *HER2* test result is equivocal. Since *HER2* status may change over time or with treatment, repeat testing may be indicated (Wolff, 2023).

Several circulating tumor deoxyribonucleic acid assays (liquid biopsies) have been assessed for detection of potentially targetable somatic variants primarily in patients with advanced cancers, but few have demonstrated clinical utility in terms of accurately predicting treatment response (Merker, 2018). Available liquid biopsy assays have suboptimal sensitivity and significant discordance with tumor tissue genotyping, and a diagnostic approach relying only on circulating tumor deoxyribonucleic acid analysis in plasma could fail to identify relevant information. Only one circulating tumor deoxyribonucleic acid assay has demonstrated clinical validity and utility in predicting treatment response in breast cancer: *PIK3CA* mutation testing.

In advanced, estrogen receptor-positive breast cancer, the most common somatic mutation is *PIK3CA*, which occurs in 20 percent to 40 percent of breast cancers and is an independent negative prognostic factor (hazard ratio = 1.67, 95% confidence interval 1.15-2.43, *P* = .007) (Sobhani, 2018). The *PIK3CA* gene encodes a lipid kinase involved in multiple signaling pathways related to cell growth. Results of the Phase 3 SOLAR-1 trial demonstrated that cancers with mutations in *PIK3CA* show substantial sensitivity to the alpha-selective PI3 kinase inhibitor alpelisib in combination with fulvestrant (hazard ratio 0.65, 95% confidence interval 0.50 to 0.85, *P* = .00065) (Andre, 2019).

The National Comprehensive Cancer Network (2019a) recommends alpelisib in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, *HER2*-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen (National Comprehensive Cancer Network, 2019a; see appendix). *PIK3CA* mutation testing may be assessed on tumor biopsy or circulating tumor deoxyribonucleic acid in peripheral blood using only a U.S. Food and Drug Administration-approved companion diagnostic test (see appendix). Both the National Comprehensive Cancer Network (2019a) and the American Society of Clinical Oncology and College of American Pathologists (Merker, 2018) recommend reflex testing in tumor tissue to confirm negative liquid biopsy results.

In patients with metastatic breast cancer, a prospective, randomized phase 3 trial failed to demonstrate the clinical utility of a circulating tumor cell count as a predictor of treatment response (Smerage, 2014). The National Comprehensive Cancer Network (2019a) guideline has not addressed the clinical role of circulating tumor cells for predicting treatment response in breast cancer.

Approximately 2% of all breast cancers harbor microsatellite instability, reflecting underlying defects in mismatch deoxyribonucleic acid repair that may impact tumor sensitivity to immunotherapy. However, routine use of tumor-sequencing panels that report microsatellite instability as a marker of mismatch repair deficiency has not been established, because the specificity of microsatellite instability testing and potential for false positive results requires clarification (Litton, 2019).

The immune pathway involving *PD-L1* expressed on tumor cells and its receptor PD-1 on the surface of T cells is a major target for new immunosuppressive therapies in several cancers, as a large number of somatic mutations due to mismatch-repair defects may be susceptible to immunotherapy with anti-*PD-L1*-positive antibody (Litton, 2019). A meta-analysis of 19 studies (n = 12,505 participants with breast cancer) found that over-expression of *PD-L1* may indicate a poor prognosis and suggests the potential benefit of a therapeutic blockade of the *PD-L1*/PD-1 pathway (Li, 2019). In a phase 3 trial of 902 participants, atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer (Schmid, 2018). For this cohort, the National Comprehensive Cancer Network (2019a) recommends testing *PD-L1* biomarker status on tumor-infiltrating immune cells to identify patients most likely to benefit from atezolizumab plus albumin-bound paclitaxel combination therapy.

Germline (inherited) deoxyribonucleic acid testing

Germline deoxyribonucleic acid testing may be conducted through sequencing of the tumor biopsy, sequencing of circulating tumor deoxyribonucleic acid in blood, or potentially both (Litton, 2019). Testing for germline mutations is established in risk assessment for hereditary breast cancer syndromes, as genes associated with high risk of breast cancer (e.g., *BRCA1/2*, *p53*, *PTEN*, *CDH1*, and *PALB2*) may direct patients toward high-risk surveillance and prophylactic surgeries. Refer to **CCP.1012 Genetic testing for breast and ovarian cancer** — for a list of medically necessary molecular testing panels with demonstrated clinical utility for hereditary breast cancer risk assessment.

With the emergence of poly ADP ribose polymerase (PARP) inhibitors as a treatment option in breast cancer, the role for germline *BRCA1/2* molecular testing in predicting treatment response in patients already diagnosed with breast cancer is evolving. The rationale for PARP inhibitors in breast cancer is that breast cancer cells with mutated *BRCA1/2* genes have higher levels of PARP expression than noncancerous cells and, therefore, are more susceptible to PARP inhibition. PARP inhibitors enhance the effects of deoxyribonucleic acid-damaging chemotherapies and radiation therapies, but their effectiveness have not been addressed in people with somatic *BRCA* mutations (Litton, 2019).

The National Comprehensive Cancer Network (2023) recommends germline *BRCA 1/2* testing in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. Somatic testing alone may be inadequate, as a small percentage of *BRCA*-related cancers contain purely somatic mutations, and current somatic sequencing approaches of tumor specimens may miss some types of germline mutations in *BRCA1/2.* These mutations include notably large structural variants such as substitutions, insertion and deletion alterations, copy number alterations in large numbers of genes, and select gene rearrangements.

Tumor ribonucleic acid-expression signatures

For early-stage breast cancer, current molecular assays developed to guide therapy rely on quantitative analyses of ribonucleic acid (transcriptome) expression for multiple genes commonly expressed in estrogen receptor-positive tumors. Early-stage breast cancers with higher-risk genomic signatures carry a greater risk for recurrence and may benefit from extended antiestrogen adjuvant therapy or adjuvant chemotherapy. Refer to **CCP.1045 Gene expression profile testing for breast cancer** for a list of medically necessary tumor gene expression signatures with demonstrated clinical utility.

In 2020, the U.S Food. and Drug Administration (2020a) expanded the approval of the immunotherapy pembrolizumab to target solid tumors with a specific genetic mutation regardless of cancer type. We modified the coverage section to reflect these changes. We updated the references, the National Comprehensive Cancer Network (2020) breast cancer guideline, and the list of U.S. Food and Drug Administration-approved companion diagnostic tests and corresponding therapeutic products (see appendix), as follows:

We added molecular testing for pembrolizumab to the coverage section. Its indications now include:

- Treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥ 10 mutations per megabase) solid tumors, as determined by an approved companion diagnostic test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. Tumor mutational burden is a measure of the total number of mutations found in the deoxyribonucleic acid of cancer cells. Tumors that have a high number of mutations may be more likely to be recognized as abnormal and attacked by the body's immune system, and, therefore, respond to certain types of immunotherapy, such as pembrolizumab. The Foundation One CDx test (Foundation Medicine Inc., Cambridge, Massachusetts) has been approved for determining candidacy for this indication (see appendix).
- Treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Microsatellite instability and mismatch repair deficiency are types of genetic changes to a cell that interfere with its ability to self-repair. Sequencing, immunohistochemical staining, and polymerase chain reaction testing of tumor tissue are used to measure these genetic changes (National Comprehensive Cancer Network, 2020).
- We added *NTRK* 1//2/3 gene fusion testing using next generation sequencing, fluorescence in situ hybridization, immunohistochemistry, polymerase chain reaction to determine candidacy for larotrectinib or entrectinib. Both drugs are indicated for the treatment of solid tumors that have an *NTRK* gene fusion without a known required resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment (National Comprehensive Cancer Network, 2020; U.S. Food and Drug Administration, 2022, 2019).
- We added the INFORM *HER2* Dual ISH deoxyribonucleic acid Probe Cocktail (Ventana Medical Systems Inc., Harvard, Massachusetts) to the list of approved companion diagnostic tests for determining candidacy for ado-trastuzumab emtansine targeted therapy (see appendix). This addition does not require a coverage change.

In 2021, we updated the references, the National Comprehensive Cancer Network (2021) breast cancer guideline, and the list of U.S. Food and Drug Administration-approved companion diagnostic tests and corresponding therapeutic products for breast cancer (see appendix), with the following changes to the policy:

- We added *PD-L1* expression in tumor or circulating plasma cells to determine candidacy for pembrolizumab, using only a U.S. Food and Drug Administration–approved or –cleared companion test listed in the appendix. The PD-L1 IHC 22C3 pharmDx test (Dako North America, Inc.) has been approved for this indication.
- We expanded the indications for the FoundationOne CDx test to include candidacy for larotrectinib.
- We added two new companion diagnostic tests to the appendix — FoundationOne Liquid CDx (Foundation Medicine, Inc.) to assess candidacy for alpelisib and Ventana HER2 Dual ISH DNA Probe Cocktail (Ventana Medical Systems, Inc.), to assess candidacy for trastuzumab.

In 2023, we updated the policy coverage according to changes in the list of U.S. Food and Drug Administration-approved companion diagnostic tests (2023a; appendix) and National Comprehensive Cancer Network (2023) recommendations for new targeted therapies approved for use in breast cancer treatment, as follows:

- Atezolizumab had been approved for use in combination with albumin-bound paclitaxel for advanced triple negative breast cancer with *PD-L1* expression in at least 1% tumor-infiltrating immune cells. The approval for this indication was removed in October 2021 (U.S. Food and Drug Administration, 2023c), and the Ventana PD-L1 assay was removed from the list of companion diagnostic tests (appendix). The National Comprehensive Cancer Network (2023) continues to recommend atezolizumab for this indication as an off-label use.

- For olaparib or talazoparib therapy, we clarified that the sample type to be used with the BRACAnalysis CDx companion diagnostic was whole blood (see appendix).

The following molecular tests and, where indicated, companion diagnostic tests were added to the coverage section and appendix:

- *ESR1* mutation in a plasma specimen detected by the Guardant360 CDx companion diagnostic test to select patients for elacestrant therapy.
- Mismatch repair deficiency detected by the Ventana MMR RxDx Panel companion diagnostic test to select patients for dostarlimab-gxly therapy.
- *Ki-67* protein expression detected using the Ki-67 IHC MIB-1 pharmDx companion diagnostic test to select patients for abemaciclib.
- *HER2*-low (immunohistochemistry 1+ or 2+/*in situ* hybridization negative) detected by the PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody companion diagnostic test to select patients for fam-trastuzumab deruxtecan-nxki therapy.
- *RET* gene fusion to select patients for selpercatinib therapy. There is no companion diagnostic for this therapy.

References

On October 3, 2023, 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 “molecular therapy” (MeSH), “breast neoplasm” (MeSH), and “genomic testing.” "HER2 genetic testing." 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.

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U.S. Food and Drug Administration. ROZLYTREK® (entrectinib). Initial approval: 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212725s008lbl.pdf. Updated August 2023. (b)

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Policy updates

11/2019: initial review date and clinical policy effective date: 1/2020

12/2020: Policy references updated. Coverage modified.

12/2021: Policy references updated. Coverage modified.

12/2022: Policy references updated.

12/2023: Policy references updated. Coverage modified.

Appendix

Table 1. U.S. Food and Drug Administration cleared or approved companion diagnostic devices in breast cancer care (in vitro tools only)

A companion diagnostic device provides information that is essential for the safe and effective use of a corresponding therapeutic product. The instructions for use are stipulated in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product. The table lists devices in alphabetical order.

Diagnostic name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Generic name - NDA/BLA
Bond Oracle *HER2* IHC System	P090015	Leica Biosystems	Trastuzumab - BLA 103792
BRACAnalysis CDx	P140020/S012, S0152	Myriad Genetic Laboratories, Inc.	Whole blood samples Olaparib - NDA 208558 Talazoparib - NDA 211651
FoundationOne CDx	P170019 P170019/S004 P170019/S008	Foundation Medicine, Inc.	Trastuzumab - BLA 103792 Pertuzumab - BLA 125409 Ado-trastuzumab emtansine - BLA 125427 Alpelisib - NDA 212526 Pembrolizumab - BLA 125514 for solid tumors (tumor mutational burden ≥ 10 mutations per megabase) Larotrectinib - NDA 210861, 211710 for solid tumors (NTRK1/2/3 fusions)
FoundationOne Liquid CDx	P200016	Foundation Medicine, Inc.	Alpelisib - NDA 212526
Guardant360 CDx	P200010/	Guardant Health, Inc.	Elacestrant - NDA 217639 (plasma)
HER2 CISH pharmDx Kit	P100024	Dako Denmark A/S	Trastuzumab - BLA 103792
HER2 FISH pharmDx Kit	P040005/S009	Dako Denmark A/S	Trastuzumab - BLA 103792 Pertuzumab - BLA 125409 Ado-trastuzumab emtansine - BLA 125427
HercepTest	P980018/S018	Dako Denmark A/S	Trastuzumab - BLA 103792 Pertuzumab - BLA 125409 Ado-trastuzumab emtansine - BLA 125427
INFORM HER2 Dual ISH deoxyribonucleic acid Probe Cocktail	P100027 P100027/S030	Ventana Medical Systems, Inc.	Trastuzumab - BLA 103792 Ado-trastuzumab emtansine - BLA 125427
INFORM HER-2/neu	P940004	Ventana Medical Systems, Inc.	Trastuzumab - BLA 103792
InSite Her-2/neu KIT	P040030	Biogenex Laboratories, Inc.	Trastuzumab - BLA 103792
Ki-67 IHC MIB-1 pharmDx (Dako Omnis)	P210026	Agilent Technologies	Abemaciclib - NDA 208716

Diagnostic name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Generic name - NDA/BLA
PathVysion HER-2 DNA Probe Kit	P980024	Abbott Molecular Inc.	Trastuzumab - BLA 103792
PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody	P990081/S001-S028, S039, S047	Ventana Medical Systems, Inc.	Trastuzumab - BLA 103792 Ado-trastuzumab emtansine - BLA 125427 Fam-trastuzumab deruxtecan-nxki - BLA 761139
PD-L1 IHC 22C3 pharmDx	P150013/S020	Dako North America, Inc.	Pembrolizumab – BLA 125514
SPOT-LIGHT HER2 CISH Kit	P050040	Life Technologies Corporation	Trastuzumab - BLA 103792
therascreen PIK3CA RGQ PCR Kit	P190001 P190004	QIAGEN GmbH	Alpelisib - NDA 212526 (tissue and plasma)
Ventana HER2 Dual ISH DNA Probe Cocktail	P190031	Ventana Medical Systems, Inc.	Trastuzumab - BLA 103792
Ventana MMR RxDx Panel	P210001	Ventana Medical Systems, Inc.	Dostarlimag-gxly - NDA 761174 -for advanced solid tumors

Source: U.S. Food and Drug Administration (2023a). Current as of August 21, 2023.