Dear Contractor Medical Director(s),

We are requesting reconsideration and revision of the following excerpted text from the LCD for Lab: Special Histochemical Stains and Immunohistochemical Stains (L35922) based on the recent expanded FDA label for abemaciclib, updated ASCO guidelines and updated NCCN Guidelines for Breast Cancer that all support the use of Ki-67 testing for certain breast cancer patients:

> ***IHC for Breast Pathology***
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> *The clinical care of patients with breast cancer depends upon the accurate diagnosis and the assessment of biomarkers. Hormone receptor assays and Her2 testing are recommended on all primary invasive breast cancers, and on recurrent or metastatic cancers. At the current time, there is no recommendation for Her2 testing on in situ breast lesions outside of a clinical trial. While there are a number of promising additional biomarkers, such as Ki-67, PI3K and gene expression assays, the College of American Pathologists (CAP), the American Society of Clinical Oncologists (ASCO) and the National Comprehensive Cancer Network (NCCN) have not recognized these markers in patient treatment pathways.*
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> *Estrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor 2 (Her2) are well-established prognostic markers in invasive breast cancer management. The triple negative breast carcinoma subtype (ER-/PR-/Her2-) has been associated with worse overall prognosis in comparison with other subtypes in study populations consisting of ethnic minorities and young women.*
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> *Ki-67 expression is a biomarker for proliferation and has been associated with response to therapy, but methods of measurement are controversial. In December, 2013, the CAP reported that there is "a lack of consensus on scoring, definition of low versus high expression, an appropriate cut point for positivity, or which part of the tumor should be scored (e.g., leading edge, hot spots, overall average). There is also paucity of data on the effects of pre-analytical variables (e.g., ischemic time, length of fixation, antigen retrieval) on Ki-67 staining. For these reasons, routine testing of breast cancers for Ki-67 expression is not currently recommended by either ASCO or the NCCN." Consequently, Ki-67 is not reasonable and necessary for breast cancer and will not be covered by Medicare.*
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> *The clinical utility of testing for hormone receptors in in-situ breast cancer differs from those of invasive disease. Guidelines and the peer reviewed literature support the use of ER testing for in-situ breast neoplasia and PR testing only when the ER status is negative (Lester, personal communication). Clinical guidelines have not been established for the use of Her2 or other biomarkers in patients with non-invasive breast neoplasia.*
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> ***In the absence of professional guidelines based on proven scientific literature, standing orders from clinicians for such tests as Ki-67 and EGFR on every breast cancer are not reasonable and necessary, and are not a covered Medicine service.***
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> *In addition, basal phenotype markers (e.g., IHC for CK5) are not routinely necessary. Neither are IHC stains such as E-cadherin, p27, or high molecular weight cytokeratin to distinguish ductal from lobular differentiation necessary on every breast case, nor are myoepithelial cell markers such as p63 or smooth muscle myosin heavy chain necessary on every case."*

Recent changes in the FDA indication and the societal guidelines materially affect the current determination that Ki-67 tests are not reasonable and necessary for breast cancer patients. We are requesting your review and revision based on the following justifications:

1. On 10/12/2021 the FDA expanded the label for VERZENIO® (abemaciclib) tablets, for oral use to include the following language:
    a. VERZENIO® is a kinase inhibitor indicated in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA approved test. Link: VERZENIO Label
2. On 11/15/2021 the ASCO guidelines "Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer" were updated to include abemaciclib + endocrine therapy for patients with high-risk HR+, HER2- early breast cancer. Link: Breast Cancer | ASCO
    a. Based on the monarchE analysis from the AFU1 datacut, ASCO recommends the following:
        i. "Two years of abemaciclib (150 mg twice daily) plus ET may be offered to patients with HR-positive, HER2-negative, node-positive early breast cancer with a high risk of recurrence and a Ki-67 score of ≥20% as determined by an FDA-approved test."
            1. Type: evidence-based, benefits outweigh harms
            2. Evidence quality: moderate
            3. Strength of recommendation: strong
        ii. The Panel also recommends "abemaciclib for two years plus ET for ≥5 years may be offered to the broader intent-to-treat population of patients with resected, HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence, defined as having > 4 positive axillary lymph nodes, or as having 1-3 positive axillary lymph nodes and one or more of the following features: histologic grade 3 disease, tumor size > 5 cm, or Ki-67 index > 20%."
            1. Type: evidence-based, benefits outweigh harms
            2. Evidence quality: moderate
            3. Strength of recommendation: strong
    b. Qualifying statements: "Although exploratory analyses suggested similar HRs in favor of abemaciclib regardless of Ki-67 status, there were relatively few Ki-67 low tumors in monarchE. When discussing treatment options with patients, the potential benefits (improved IDFS) should be weighed against the potential harms (treatment toxicity, financial cost)."
3. On 11/24/2021 the NCCN Guidelines for Breast Cancer were updated to include abemaciclib + endocrine therapy for patients with high-risk HR+, HER2- early breast cancer. Link: breast.pdf (nccn.org)
    a. Based on the monarchE analysis from the AFU1 datacut, NCCN recommends the following:
        i. For patients receiving adjuvant endocrine therapy: "In patients with HR-positive/HER2-negative high-risk breast cancer (ie, those with ≥4 positive lymph nodes, or 1-3 positive lymph nodes with one or more of the following: Grade 3 disease, tumor size ≥5cm, or a Ki-67 score of ≥20%) 2 years of adjuvant abemaciclib can be considered." (see BINV-K: Adjuvant Endocrine Therapy)

ii. For workup of patients with non-metastatic invasive breast cancer: "**Ki-67 test if considering adjuvant abemaciclib**." (see BINV-1: Clinical Stage, Workup)

We thank you for your time and consideration. We are happy to address any questions you may have.

Best,
Kristin

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