HHS Public Access

Author manuscript

Clin Lab Med. Author manuscript; available in PMC 2018 December 04.

Published in final edited form as:

Clin Lab Med. 2018 March ; 38(1): 161–173. doi:10.1016/j.cll.2017.10.013.

Breast Cancer in Low- and Middle-Income Countries:

Why We Need Pathology Capability to Solve This Challenge

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Keywords

Breast cancer; Pathology; Sub-Saharan Africa; Low- and middle-income countries; Cancer control

INTRODUCTION

The global burden of cancer is increasing worldwide, with most new cancer cases and cancer-related mortality occurring in low- and middle-income countries (LMIC).[1] It is estimated that by 2035, two-thirds of new cancer diagnoses will occur in developing countries.[2] Breast cancer remains the leading cancer diagnosis and cause of cancer-related deaths among women globally.[1] In most LMIC, breast cancer is either the leading or the second most common cause of cancer deaths among women. Although early-stage breast cancer is potentially curable, mortality-to-incidence ratios for breast cancer are significantly worse in LMIC than in countries of high income.[3] The high mortality-to-incidence ratio means patients diagnosed with breast cancer are more likely to die from their cancer in LMIC. Some of the mortality-to-incidence ratios reported in Middle, Eastern, and West Africa are as high as 0.55, compared with 0.16 in North America.[3] These alarming figures have drawn global attention to this cancer epidemic and the socially and economically devastating consequences of breast cancer among women in the world's poorest settings.

A country's strategy for national cancer planning requires knowledge of the disease burden in the country, information that is obtained when it is possible to make an accurate cancer diagnosis and document all relevant prognostic factors for a tumor. With this information, it is then possible to allocate available resources for patient care. Accurate diagnoses require timely and adequate pathology support.[4] Current reports show a significant deficiency in both professional and technical pathology services in LMIC, with some of the lowest

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numbers of pathologist-to-population ratios documented in sub-Saharan Africa.[5] Ratios in sub-Saharan Africa vary from that in Mauritius, where there is approximately 1 pathologist for every 84,133 persons, to Niger where there is one pathologist to 9,264,500 persons.[5] Moreover, countries like Somalia, Benin, Eritrea, and Burundi have only one or no pathologist in-country.[6] By comparison, the pathologist-to-population ratio in North America is 1 to 17,544 persons.[7]

Most patients in sub-Saharan Africa present with advanced stage disease: stage III and IV.[8–15] Despite the advanced stage of their disease, many of these patients can benefit from surgery, chemotherapy, targeted therapies, and endocrine therapy, depending on tumor biology, with treatments aimed at improving quality of life, and in some cases, significantly prolonging life. Even advanced disease requires confirmation of the presence of breast carcinoma by pathologic diagnosis, because other benign or malignant tumors can mimic breast cancer, for example, lymphoma, phyllodes tumor, or untreated infection, and all of these merit different treatment approaches.[16] A significant proportion of breast biopsies for palpable masses in a large cohort of breast cases in Ghana and a retrospective analysis of breast presentations in Rwanda was benign.[9,16] Thus, it is unethical and unsafe to offer mastectomy, cytotoxic chemotherapy, or other systemic therapy to a woman without having a pathologically confirmed diagnosis of breast cancer at the onset, and optimal treatment depends on the elucidation of both the stage of disease and the biologic markers, hormone receptors, and Human epidermal growth factor receptor 2 (HER2).

Prognostic factors, including tumor size, grade, estrogen receptor (ER) status, and nodal involvement, drive treatment choices. These prognostic factors are obtained from gross examination of a surgical specimen and subsequent histopathological review under a microscope. Tissue samples obtained by fine-needle aspirate (FNA), core-needle biopsy, or excision biopsy can all be adequate specimens for diagnostic purposes. In the United States, initial diagnosis with core-needle biopsy is recommended. It is more likely to yield adequate tissue to assess invasive versus in situ status and hormone receptors and HER2 than FNA and is less invasive than excisional biopsy. For patients who ultimately have a benign diagnosis, it avoids surgery altogether. Obtaining a complete and timely histopathological review is a tremendous challenge in LMIC given the lack of access to high-quality tissue processing facilities and prognostic marker evaluation. Innovative approaches to breast cancer diagnostics are needed to more rapidly satisfy the demand for accurate diagnoses at the point of care in the absence of adequate tissue processing facilities, trained technicians to run those facilities, and pathologists in LMIC. The goal is to demonstrate the extent to which timely and accurate histopathological diagnoses of breast cancer are critical to delivering high-quality breast cancer care to patients in LMIC.

BREAST CANCER HISTOPATHOLOGIC FEATURES AND RELEVANCE IN CLINICAL MANAGEMENT

Tumor, Nodal Status, and Histologic Grade

Population-based cancer registries in most LMICs do not contain a high percentage of anatomically staged cancers and detailed breast cancer prognostic features, which impairs

the ability to prognosticate and treat patients adequately. The most important prognostic factors in breast cancer along with tumor size and nodal status are tumor grade and ER status. HER2 status is important in countries where specific targeted therapies are available. The prognostic and predictive significance of these features have been demonstrated and validated in multiple studies. Tables 1 and 2 summarize current American Joint Commission on Cancer staging for breast cancer, 7th edition. In the National Surgical Adjuvant Breast and Bowel Project B-06 trial, an increase in the number of positive lymph nodes was associated with a worse prognosis.[17,18] Tumor size, perimenopausal status, number of axillary lymph node metastases, poorly differentiated grade, and presence of lymphatic invasion were also identified as negative independent predictors of prognosis.[19] In a long-term follow-up of patients with breast cancer with stage I and II disease followed for a median of 18.2 years, the risk of local recurrence at 20 years for T1N0 and T1N1 (1–3 positive nodes at diagnosis) disease was estimated at 2.8% and 6.5%, respectively.[19] Tumor biology heavily influences the time course for local recurrence, with most recurrences in ER-negative tumors being within 8 years of diagnosis, and risk of recurrence in ER-positive tumors increasing annually for the lifetime of the patient. Annual recurrence risk is 1% to 2% in N1 disease and 3% to 4% annually in N2 disease (≥4 positive nodes).[20] In addition, recent studies have shown that in multivariate analyses of patients with operable breast cancer treated according to standard protocol, histologic grade remains an independent predictor of breast cancer–specific survival and disease-free survival when analyzed as a whole and within stage subsets.[21–23]

Histologic Subtypes of Breast Cancer and Their Clinical Importance

Histologic subtype can also be important in determining therapy and is an important prognostic factor. Although the most common histologic subtypes are invasive ductal carcinoma of no special type (~60%), and invasive lobular carcinoma (~15%), more than 20 different subtypes of breast carcinoma exist, each with different risk factors, patterns of spread, and response to therapy.[24] Tumor subtypes with a better prognosis include tubular and cribriform, which are always ER positive, but also mucinous carcinoma and some other rare subtypes, such as secretory carcinoma and adenoid cystic carcinoma, which have a good prognosis despite their ER-negative status.[25–27] ER-negative breast cancers typically have a worse prognosis with an early risk of recurrence compared with ER-positive tumors, and when feasible, chemotherapy is offered to improve survival and decrease risk of recurrence if the tumors are greater than 1 cm in size. It is important to be able to recognize rare subtypes of ER-negative cancer like adenoid cystic carcinoma and secretory carcinoma to prevent overtreatment with chemotherapy when it is not indicated.

ASCERTAINMENT OF MOLECULAR PATHOLOGY AND CLINICAL RELEVANCE

Hormone Receptor Status

Thirty percent of women with ER-positive early breast cancer will eventually present with recurrent disease. All women with ER-positive disease should be offered endocrine therapy to reduce this risk. Tamoxifen is the least expensive endocrine therapy available and acts as

an anti-estrogen, binding the estrogen receptor. It reduces the risk of recurrence by half and slows tumor growth in sensitive tumors, but there is no benefit from endocrine therapy in tumors not expressing ER, and therapy should be avoided in these patients given the potential side effects of hormonal therapy, which include menopausal symptoms, thrombosis, osteoporosis, and very rarely, endometrial carcinomas.[28,29] Endocrine therapy with tamoxifen is affordable and widely available in most LMIC. Furthermore, it is less toxic than intravenous and oral systemic chemotherapy and requires less frequent visits and monitoring. It is therefore critical for basic pathology evaluations to include an assessment of ER status by immunohistochemistry to identify those women who could benefit from endocrine therapy. Seventy percent of tumors in developed countries overexpress ER. The proportion of women in LMIC that have ER expression is less, around 60%, primarily because of different population demographics. The proportion of the population that is postmenopausal and/or obese is lower in LMIC compared with high-income countries, and these are clinical factors associated with hormone receptor positivity.

Accurate determination of ER status requires access to high-quality histology and immunohistochemistry facilities as part of a pathologic review. A major quality control issue in LMICs is appropriate handling of biopsy or excision specimens. Frequently, there is little control over cold ischemic time of the tissue specimen, which is often prolonged because of limited access to pathology processing facilities and even physician ignorance in handling the tissue specimen. It is also common to have a pathology specimen fixed in formalin that is either diluted and is a suboptimal volume for adequate rapid fixation, or specimens are overfixed by sitting in formalin for weeks before being processed. All of these factors influence ER evaluation and can increase the false negative rates of ER status. For many years, it was thought that African women had much higher rates of ER-negative breast carcinoma, an erroneous assumption based on poor tissue handling and poor-quality histopathology and immunohistochemical evaluation of specimens. To reduce the impact of poor tissue processing on evaluation of ER status in high-income countries, tissue handling guidelines have been issued by the American Society of Clinical Oncology and the College of American Pathologists (CAP).[30–32] Cold ischemia time, which is the time from loss of vascular blood supply to tissue to the time it is exposed to fixative such as formalin, should be less than 60 minutes.[32] Longer times lead to degradation of critical biomarker proteins and false negative results. Tissue fixation time is also critical, with an optimal time defined as a minimum of 6 hours of fixation for core biopsies, and a maximum of 72 hours for optimal hormone receptor assessment. Shorter and longer times have been linked to false negative and false positive results, although it takes several weeks of prolonged fixation for a strongly ER-positive tumor to become completely ER negative, rather than hours or days of prolonged fixation.[33,34]

In addition to guiding patient care, high-quality immunohistochemistry will permit better understanding of potential ethnic variation in the expression of breast tumor hormonal markers in sub-Saharan Africa.[35–40] The reported range in expression of ER in breast tumors ranges from 24% to 71% among black women in West Africa compared with 63% in South Africa.[41–43] Data from Rwanda and Kenya also suggest that East Africa may have higher rates of ER-positive disease and closer to that of Europe and North America at 60% to 70%, especially in places like Rwanda, where the cold ischemic time for most samples is known.

[44–47] The heterogeneity of these data is more likely to be a phenomenon of tissue handling procedures and quality of histopathology and immunohistochemistry review than a significant ethnic difference, but in the absence of knowledge about tissue handling and access to quality pathology, it is not possible to know this for certain. Increasing access to high-quality immunohistochemistry will better delineate the molecular heterogeneity of breast cancer subtypes in sub-Saharan Africa and other LMICs. In addition, it will expand access to quality immunohistochemistry for use in other cancer types and subtypes.

Human Epidermal Growth Factor Receptor 2 Receptor Status

Breast cancers that overexpress HER2 are aggressive tumors with a high risk of early recurrence and death. The use of HER2-targeted therapy has greatly improved outcomes for these patients and is standard therapy in high-income countries, but HER2 therapies are costly, and are rarely available in LMIC. The most recent update of the World Health Organization's model list of essential medicines in 2015 included the HER2-targeted medicine, trastuzumab, because of its significant positive impact on survival.[48] In the absence of available therapy, HER2 testing by immunohistochemistry or fluorescence in situ hybridization is not merited. As trastuzumab goes off patent soon and biosimilars become available, this is projected to halve the cost of HER2-targeted therapy in Europe, India, and North America, and more affordable HER2-targeted therapy options can be expected, which may increase availability in LMICs.[49,50]

PATHOLOGY EVALUATION OF SURGICAL SPECIMENS AFTER PREOPERATIVE THERAPY

In LMICs where a significant majority of patients with breast cancer present with advanced stage disease, preoperative chemotherapy or endocrine therapy may be appropriate for improving surgical resectability in inoperable tumors and not just offered in the palliative setting. Preoperative (or neoadjuvant) chemotherapy does not adversely affect survival outcomes compared with adjuvant therapy.[51,52] Pathologic assessment of a completely resected tumor bed and appropriate node sampling following preoperative chemotherapy provide useful prognostic information for a patient. Patients with no residual invasive carcinoma in the breast and axillary lymph nodes after preoperative chemotherapy (called a pathologic complete response) have a superior recurrence-free survival, particularly if they are ER negative.[53] Those with residual disease after neoadjuvant chemotherapy have a higher risk of distant recurrence and a worse prognosis.[54]

PATHOLOGY TURNAROUND TIME

In addition to accurate histopathological diagnosis and biomarker assessments, it is critical to improve the timeliness of pathology results in LMIC. With current challenges in pathology services in most LMIC, the turnaround time (TAT) for pathology results is on the order of weeks to months in some countries. Because initial therapy is determined by pathologic evaluation of tumor size, nodal status, grade, ER/progesterone receptor (PR), and HER2 status, prolonged TAT can lead to either needing to choose a therapy without this critical information, which may result in inappropriate therapy, or waiting for results, which

could allow disease to progress, consequently worsening prognosis. A historical analysis identified that delays in excess of 3 months before initiating therapy led to stage migration in patients with breast cancer.[55] In some cases, even more timely pathology is needed to identify patients who might benefit from more surgery, such as re-resection of positive margins and residual disease, or complete axillary lymph node dissection for patients wherein positive sentinel lymph nodes have been identified. A retrospective review of TAT from Butaro Cancer Center in Rwanda reported a median TAT from specimen receipt to reporting of 32 days.[56] Another retrospective analysis from Malawi identified median TAT for cancer specimens paid out of pocket as 43 days, and 101 days for nonpaid for specimens, which rely on state funds.[57] The CAP recommends a TAT of 2 business days for biopsy specimens.[58] Two days is likely not an attainable goal currently in most LMIC. A realistic goal of maximum TAT of 1 week will still be timely to aid in most of the clinical prognostication and management choices discussed in this article.

PATHOLOGY AND NATIONAL BREAST CANCER CONTROL

LMIC nearly alway lack detailed and complete cancer registry data, impairing ability to assess a country's disease burden and specific patient population needs to guide disease prioritization and allocation of resources for breast cancer treatment. Without adequate pathology, resources for breast cancer may be misguided and may not translate into improved survival outcomes for patients. For instance, it is imperative both in the clinical management of patients and from the national medicines procurement level to be able to ascertain the proportion and projected number of patients with breast cancer that are and will be ER positive and will benefit from endocrine therapy. Knowing the proportions of specific molecular subtypes and specifically ER positive breast cancers ultimately facilitates the procurement of adequate quantities of endocrine therapy, a medicine that can be prescribed daily for 5 years in the adjuvant setting and daily until time of tumor progression in the metastatic and palliative setting.[59,60] In addition, as HER2 biosimilars become available, there might be utility in assessing HER2 status and determining whether this is a cost-effective therapy that can be financed by LMIC governments. Breast cancer is commonly managed by a multimodality specialty team, involving surgery and radiation oncology. In countries where this is outsourced to specific public surgical centers or private radiation facilities, quality pathologic evaluation is needed to predict the utilization of these modalities and to guide future resource allocation to the different arms of breast cancer control. The elements of a pathology evaluation, including tissue handling, tissue histology, and immunohistochemical evaluations of the key prognostic factors described above, inform key holders about the distribution of disease. Quality pathology evaluation is a key factor along with access to medical and surgical therapies and interventions to increase earlier detection, with the goal of improving outcomes for women with breast cancer in LMICs.

BREAST CANCER PATHOLOGY IN LOW- AND MIDDLE-INCOME COUNTRIES: INNOVATION AND RESEARCH

Given the histopathologic and molecular heterogeneity of breast cancer, especially within sub-Saharan Africa, complete and timely pathology is needed to accurately assess the

variations in disease burden and molecular subtypes. These efforts are severely impaired by the deficit of pathologists in LMIC. Innovations in leapfrog technology have been used in various LMIC by partnering with other institutions in developed countries to assist with pathology reporting. One such example is the collaboration between Ministry of Health in Rwanda, Partners in Health, and the Dana-Farber Cancer Institute in providing remote pathology assessment via telepathology to assist with breast cancer and other pathology diagnoses. The setup of whole slide image scanning and the automation of processing have helped with the provision of timely and complete pathology services for patients with cancer in Rwanda.[61] In Kenya, task shifting is being used to increase pathology capacity in-country by training pathologists to teach medical officers, who then teach other medical officers, to perform biopsies, FNAs, and bone marrow biopsies.[62]

High-quality immunohistochemistry is a challenge in LMIC hospitals, even for those hospitals that have adequate histology resources to provide quality hematoxylin and eosin stain diagnoses from pathology specimens. Inadequate IHC capacity limits the ability to provide the prognostic marker ER status for women with a cancer diagnosis. One solution is to use molecular pathology to solve this problem. Although molecular pathology remains a challenge even in countries where pathologists are able to perform histopathologic assessments, point-of-care testing could be a reality. The GeneXpert technology is a platform for performing quantitative reverse transcription polymerase chain reaction that is already widely distributed in LMIC for a variety of tests, including rapid diagnosis of tuberculosis using a simple dedicated cartridge. A dedicated cartridge that can perform messenger RNA amplification of ER, PR, HER2, and Ki-67 and give breast cancer biomarker results from formalin-fixed paraffin-embedded is anticipated to soon be available, which can be used to provide prognostic markers in the absence of access to ER immunohistochemistry.[63]

A future need in LMIC is to have low-cost point-of-care tests for molecular evaluations like OncotypeDX, but it is not an urgent need right now because very few women present with early breast cancer (tumors <5 cm and axillary node negative), and there is less of a dilemma in most of the breast cancer population as to whether to offer chemotherapy or not. In high-income countries, additional molecular testing, such as OncotypeDX, provides prognostic information on the risk of recurrence at 10 years in ER-positive tumors that are either node negative (N0) or node positive (1–3 positive nodes). It is frequently used in a predictive manner to help in the decision-making process whether to withhold chemotherapy and offer only endocrine therapy. Tumors with low recurrence scores (RS <11) do not need chemotherapy, and those with inter-mediate scores (RS 11–25) are likely to have minimal benefit from chemotherapy.[64–68]

Improving clinical research and pathology capacity in LMIC will enrich the knowledge of unique variations in the molecular and genomic landscape of breast cancer among different racial and geographic populations. A recent study of the genomic alterations in breast tumors from Nigeria, West Africa compared with African American women and women of European ancestry, analysis on structural variants (SV) showed genome-wide SV counts among the 3 populations are comparable in ER-negative cancers; however, among ER-positive cancers, Nigerians had significantly more SV counts compared with African

Americans or European Americans in ER-positive cancers, suggestive of a more aggressive ER-positive phenotype.[69] These data emphasize the heterogeneity of genomic landscape for breast cancer and the need to improve quality pathology, which would inform accurate prognostic risk assessment and choice of targeted therapy to specific diverse populations.

Finally, in areas where there are high burdens of infectious comorbidities, such as HIV, quality pathology reviews of tissue specimens and clinical research will help to better understand whether worse outcomes reported in HIV-positive patients with breast cancer are due to treatment-related toxicity or to interaction with the biology of their disease. In addition, there is significant potential for research to help to identify breast cancer risk factors and employ the right tools to mitigate the high cancer burden. Ultimately, increased pathology capacity will help provide timely information to guide clinical care and help narrow the survival gap between patients with breast cancer in developed and developing countries.

Acknowledgments

Disclosure Statement: J.E. Brock received research funding from Cepheid. Y.M. Martei, L.E. Pace, and L.N. Shulman have nothing to disclose.

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KEY POINTS

- Breast cancer is the leading cause of cancer mortality among women in low- and middle-income countries (LMIC). Timely and accurate histopathological diagnoses of breast cancer are critical to delivering high-quality breast cancer care to patients in LMIC.
- The most important prognostic factors in breast cancer along with tumor size and nodal status are tumor grade and estrogen receptor status. Human epidermal growth factor receptor 2 status is important in countries where specific targeted therapies are available.
- Endocrine therapy with tamoxifen is affordable and widely available in most LMIC. It is therefore critical for basic pathology evaluations to include an assessment of estrogen receptor status by immunohistochemistry to identify those women who could benefit from endocrine therapy.
- Detailed and complete cancer registry data are needed to assess a country's disease burden and specific patient population needs to guide disease prioritization and allocation of resources for breast cancer treatment.
- Innovations in leapfrog technology and low-cost point-of-care tests for molecular evaluations are needed to provide accurate and timely pathology, with the ultimate goal of improving survival outcomes for patients with breast cancer in LMIC.

Table 1

American Joint Committee on Cancer TNM summary staging system for breast cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	**Carcinoma in situ**
T1	**Tumor ≤20 mm in greatest dimension**
T2	**Tumor >20 mm but ≤50 mm in greatest dimension**
T3	**Tumor >50 mm in greatest dimension**
T4	Tumor of any size with direct extension to the chest wall and/or the skin (ulceration or skin nodules)
Regional lymph nodes (N): Clinical	
NX	Regional lymph nodes cannot be assessed
N0	**No regional lymph node metastasis**
N1	**Metastases to movable ipsilateral I, II axillary lymph nodes**
N2	**Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases**
N3	**Metastases in ipsilateral infraclavicular (level III) axillary lymph node(s) with or without level I or II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular node(s) with or without axillary or internal mammary lymph node involvement**
Pathologic (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	**No regional lymph node metastases histologically**
pN1	**Micrometastases; metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected**
pN2	**Metastases in 4–9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes detected in the absence of axillary lymph node metastases**
pN3	**Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary level I, II lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes**
Distant metastasis (M)	
M0	No clinical or radiographic evidence of distant metastasis
cM0(1+)	**No clinical or radiographic evidence of distant metastasis, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases**
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Staging in boldface represents staging information that can only be obtained via pathologic assessment. Metastatic disease at the time of initial presentation will also require pathologic assessment to confirm diagnosis.

Data from American Joint Committee on Cancer. Breast cancer staging. 7th edition. Available at: https://cancerstaging.org/references-tools/quickreferences/Documents/BreastSmall.pdf. Accessed October 19, 2017.

Table 2

Anatomic stage/prognostic groups and summary of recommended systemic therapies

						Receptor Status		
						ER and/or PR Positive	**HER2 Positive**	**Triple-Negative Breast Cancers**
Stage 0	Tis	N0	M0					
Stage IA	T1	N0	M0	Stage 1	Endocrine therapy	YES	NO	NO
Stage IB	T0	N1mi	M0		HER2-directed therapy	NO	YES	NO
	T1	N1mi	M0		Chemotherapy	+/−[a]	YES	YES
Stage IIA	T0	N1	M0	Stage 2				
	T1	N1	M0		Endocrine therapy	YES	NO	NO
	T2	N0	M0		HER2-directed therapy	NO	YES	NO
Stage IIB	T2	N1	M0		Chemotherapy	+/−[a]	YES	YES
	T3	N0	M0					
Stage IIIA	T0	N2	M0	Stage 3				
	T1	N2	M0					
	T2	N2	M0					
	T3	N1	M0		Endocrine therapy	YES	NO	NO
	T3	N2	M0		HER2-directed therapy	NO	YES	NO
Stage IIIB	T4	N0	M0		Chemotherapy	YES	YES	YES
	T4	N1	M0					
	T4	N2	M0					
Stage IIIC	Any	T N3	M0					
Stage IV	Any T	Any N	M1	Stage IV	Endocrine therapy	YES	NO	NO
					HER2-directed therapy	NO	YES	NO
					Chemotherapy	+/−[b]	YES	YES

[a] +/− is indicated for subsets for which genomic assays assist with clinical decision regarding the additional benefit of chemotherapy versus not.

[b] In the metastatic setting, chemotherapy for ER/PR-positive tumors is recommended only for patients with visceral crisis or those who have failed multiple lines of endocrine therapy.