





# Breast Cancer Treatment: A Phased Approach to Implementation

Miriam Mutebi, MD<sup>1</sup>; Benjamin O. Anderson, MD<sup>2,3</sup>; Catherine Duggan, PhD <sup>2</sup>; Clement Adebamowo, MD, ScD<sup>4,5,6,7</sup>; Gaurav Agarwal, MS<sup>8</sup>; Zipporah Ali, MD, MPH, MPC<sup>9</sup>; Peter Bird, MD<sup>10</sup>; Jean-Marc Bourque, MD, MScPH<sup>11,12</sup>; Rebecca DeBoer, MD, MA<sup>13</sup>; Luiz Henrique Gebrim, MD, PhD<sup>14,15</sup>; Riccardo Masetti, MD<sup>16</sup>; Shahla Masood, MD<sup>17</sup>; Manoj Menon, MD<sup>2</sup>; Gertrude Nakigudde<sup>18</sup>; Anne Ng'ang'a, BDS<sup>19</sup>; Nixon Niyonzima, MD, PhD<sup>2,20</sup>; Anne F. Rositch, PhD, MSPH<sup>21</sup>; Karla Unger-Saldaña, MD, DSc<sup>22</sup>; Cynthia Villarreal-Garza, MD, DSc <sup>23</sup>; Allison Dvaladze, MPH<sup>3</sup>; Nagi S. El Saghir, MD <sup>24</sup>; Julie R. Gralow, MD<sup>3</sup>; and Alexandru Eniu, MD, PhD <sup>25</sup>

Optimal treatment outcomes for breast cancer are dependent on a timely diagnosis followed by an organized, multidisciplinary approach to care. However, in many low- and middle-income countries, effective care management pathways can be difficult to follow because of financial constraints, a lack of resources, an insufficiently trained workforce, and/or poor infrastructure. On the basis of prior work by the Breast Health Global Initiative, this article proposes a phased implementation strategy for developing sustainable approaches to enhancing patient care in limited-resource settings by creating roadmaps that are individualized and adapted to the baseline environment. This strategy proposes that, after a situational analysis, implementation phases begin with bolstering palliative care capacity, especially in settings where a late-stage diagnosis is common. This is followed by strengthening the patient pathway, with consideration given to a dynamic balance between centralization of services into centers of excellence to achieve better quality and decentralization of services to increase patient access. The use of resource checklists ensures that comprehensive therapy or palliative care can be delivered safely and effectively. Episodic or continuous monitoring with established process and quality metrics facilitates ongoing assessment, which should drive continual process improvements. A series of case studies provides a snapshot of country experiences with enhancing patient care, including the implementation of national cancer control plans in Kenya, palliative care in Romania, the introduction of a 1-stop clinic for diagnosis in Brazil, the surgical management of breast cancer in India, and the establishment of a women's cancer center in Ghana. **Cancer** 2020;126:2365-2378. © 2020 American Cancer Society.

**KEYWORDS:** breast cancer, cancer center of excellence, centralized care, decentralized care, dissemination and implementation science, early diagnosis, health disparities, low- and middle-income countries (LMICs), multidisciplinary evaluation, phased implementation, resource-stratification, supportive and palliative care, treatment, underserved communities.

## INTRODUCTION

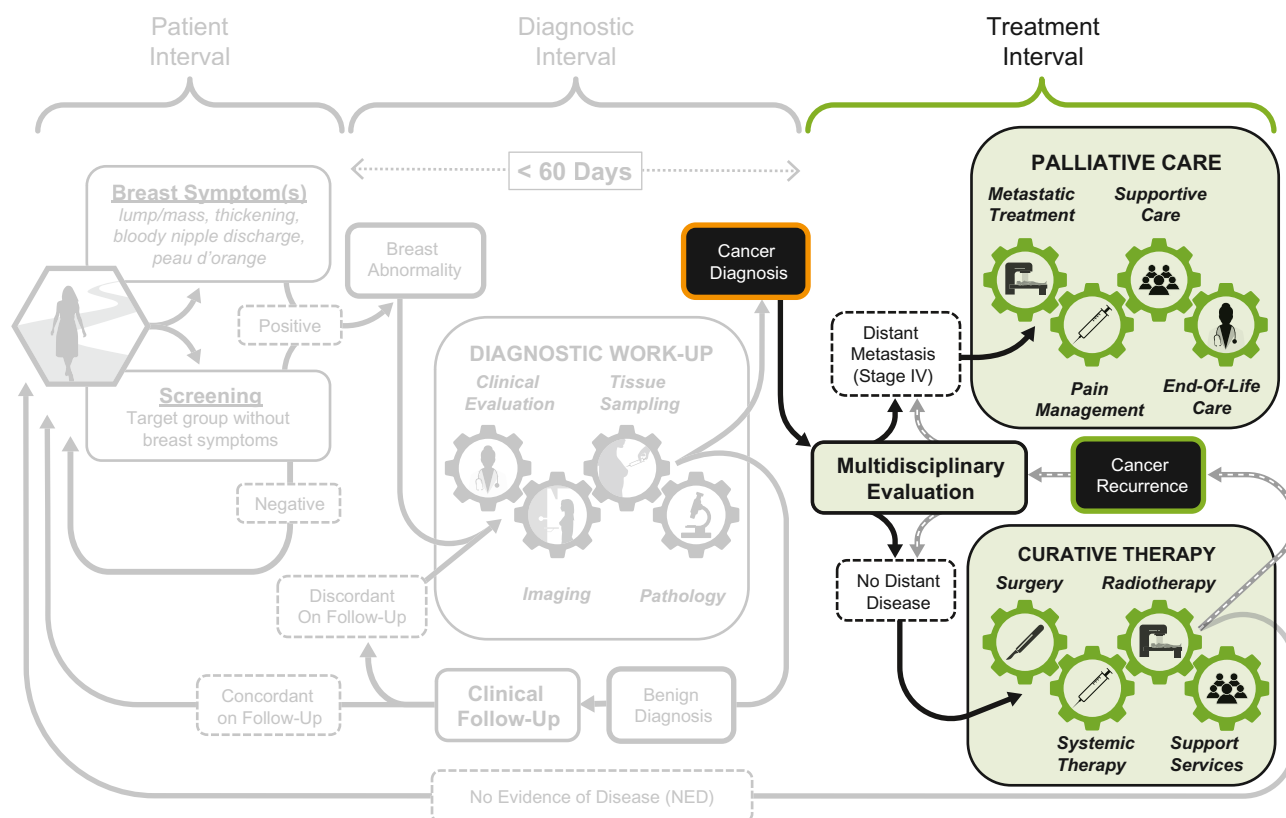
Therapy with curative intent for breast cancer achieves optimal outcomes when it is administered to completion within a defined timeframe; its success depends on appropriate referrals for timely and personalized multimodality treatment after the receipt of a definitive diagnosis.<sup>1</sup> The provision of cancer treatment requires an organized, multidisciplinary approach in which trained providers and skilled personnel working within a functional infrastructure administer the necessary therapies while avoiding excessive financial and logistic burdens on the patient (Fig. 1). For patients presenting with incurable metastatic breast cancer (MBC), supportive therapy and pain management are necessary to palliate patients. Such an infrastructure is especially important in settings where the majority of patients are commonly diagnosed with late-stage disease.

Effective cancer management pathways can be difficult to follow in low- and middle-income countries (LMICs) because of financial constraints, the unavailability of resources, a lack of trained personnel, and poor infrastructure. Optimal

**Corresponding Author:** Alexandru Eniu, MD, PhD, Hôpital Riviera Chablais, Vaud-Valais, Route du Vieux-Sequoia 20, 1847 Rennaz, Switzerland (alexandru.eniu@hopitalrivierachablais.ch).

<sup>1</sup>Breast Surgical Oncology, Aga Khan University Hospital, Nairobi, Kenya; <sup>2</sup>Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington; <sup>3</sup>Section of Surgical Oncology, Department of Surgery, University of Washington, Seattle, Washington; <sup>4</sup>Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland; <sup>5</sup>Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, Maryland; <sup>6</sup>Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland; <sup>7</sup>Center for Bioethics and Research, Ibadan, Nigeria; <sup>8</sup>Endocrine and Breast Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; <sup>9</sup>Kenya Hospices and Palliative Care Association, Nairobi, Kenya; <sup>10</sup>AIC Kijabe Hospital, Kijabe, Kenya; <sup>11</sup>Department of Radiation Oncology, University of Ottawa, Ottawa, Ontario, Canada; <sup>12</sup>Department of Medicine, McGill University, Montreal, Quebec, Canada; <sup>13</sup>Department of Medicine, University of California San Francisco, San Francisco, California; <sup>14</sup>Department of Mastology, Federal University of São Paulo, São Paulo, Brazil; <sup>15</sup>Centro de Referência da Saúde da Mulher, São Paulo, Brazil; <sup>16</sup>Department of Women and Child Health, Catholic University, Rome, Italy; <sup>17</sup>University of Florida Health Jacksonville Breast Center, Jacksonville, Florida; <sup>18</sup>Uganda Women's Cancer Support Organization, Kampala, Uganda; <sup>19</sup>National Cancer Control Program, Ministry of Health, Nairobi, Kenya; <sup>20</sup>Uganda Cancer Institute, Kampala, Uganda; <sup>21</sup>Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; <sup>22</sup>Epidemiology Unit, Instituto Nacional de Cancerología - México, Mexico City, Mexico; <sup>23</sup>Tecnologico de Monterrey, Centro de Cancer de Mama, Hospital Zambrano Hellion, Monterrey, Mexico; <sup>24</sup>American University of Beirut Medical Center, Beirut, Lebanon; <sup>25</sup>Hôpital Riviera Chablais, Vaud-Valais, Rennaz, Switzerland

**DOI:** 10.1002/cncr.32910. **Received:** February 10, 2020; **Revised:** March 31, 2020; **Accepted:** March 31, 2020, **Published online** April 29, 2020 in Wiley Online Library (wileyonlinelibrary.com)



**FIGURE 1.** Universal patient pathway for breast cancer management in 3 sequential intervals of care (patient interval, diagnostic interval, and treatment interval). The treatment interval is highlighted. Patients diagnosed with cancer undergo a clinical evaluation to determine whether they should receive therapy with curative intent, the toxicity of which must be weighed against the likelihood of benefit, or palliative management directed primarily at control symptoms to maintain quality of life. Decision making regarding multidisciplinary treatment choices is based on the extent of disease and/or degree of patient debilitation weighed against the potential for meaningful clinical improvement based on the application of realistically available resources.

treatment outcomes are dependent on a timely diagnosis, but in many LMICs, prolonged diagnostic delays are common because pathology services are few, overwhelmed, and costly.<sup>2</sup> Despite the critical nature of these essential tests for correct multimodality treatment planning, routine and critical ancillary pathology testing may not be performed because of extra costs that must be covered by the patient. These system issues are significant because delays to breast cancer treatment longer than 3 months have been associated with a more advanced disease stage at diagnosis and worsened breast cancer survival.<sup>3,4</sup>

The Breast Health Global Initiative (BHGI) developed an approach to devising resource-adapted recommendations for the comprehensive management of breast cancer throughout the continuum of care.<sup>5</sup> Building on this previous work, BHGI now proposes a phased implementation strategy to create sustainable approaches adapting preexisting frameworks to improve patient care in limited-resource settings.<sup>6,7</sup> Phased implementation

applies evidence-based strategies to address the existing disease burden and define sequentially implementable, scalable models to address the needs of the populations served.

The goal of this article is to provide a roadmap through which different health ecosystems can enhance their level of breast cancer treatment, regardless of their initial baseline status, by describing the core service requirements necessary for implementing, in a stepwise manner, the relevant recommendations into daily practice.

## GOALS OF TREATMENT

### Therapy With Curative Intent

Management with curative intent for invasive breast cancer refers to multimodality treatment prescribed for stage I to III disease, including breast surgery, radiotherapy, and adjuvant/neoadjuvant systemic treatment (cytotoxic chemotherapy, endocrine treatment, and targeted agents), together with appropriate supportive care to manage

cancer-related pain and the toxicities and side effects of cancer-directed therapy.<sup>8-10</sup>

### ***Palliative and Supportive Care***

In contrast to treatment with curative intent, palliative care has traditionally focused on the management of patients with metastatic disease, for whom symptom control is the priority.<sup>11</sup> Today, the definition of palliative care has expanded to include supportive care provisions that should be introduced soon after a breast cancer diagnosis to address symptomatic treatment, including pain management, as well as psychosocial and spiritual support.<sup>12</sup> Because supportive care is fundamental to symptom management, the establishment of palliative and supportive care is a prerequisite for establishing both early-stage and metastatic treatment programs and should not be overlooked in the development of a comprehensive cancer treatment plan.<sup>13</sup>

### **MULTIMODALITY BREAST CANCER TREATMENT IN LMICs**

Patients with nonmetastatic breast cancer require coordinated, multidisciplinary treatment planning. With early-stage disease, surgery is generally the first treatment intervention. In contrast, locally advanced breast cancers (LABCs) are often best managed by initial systemic therapy to downstage disease followed by timely surgery, appropriate adjuvant radiotherapy, and protocol-driven postoperative systemic therapy administered to the completion of the prescribed course.<sup>14</sup> Although the majority of breast cancers are diagnosed at advanced stages in LMICs, there has been a gradual increase in the number of early cancers diagnosed; in the absence of mammographic screening these improvements can be attributed to increasing public awareness campaigns and the rise of patient advocacy.<sup>15-17</sup> Optimal management of both early-stage breast cancers and LABCs requires high-quality histological diagnosis, including immunohistochemical testing, and rigorous staging procedures that will drive multidisciplinary decisions regarding the selection and sequencing of surgery, radiotherapy, and systemic therapy with curative intent.

### ***Surgical Management***

A critical challenge in the management of LABCs in LMICs is that a large fraction or even majority of these cancers are extremely advanced at presentation with large, ulcerated tumors. In these cases, extensive surgical resection is required to achieve complete removal of gross locoregional disease, even after neoadjuvant chemotherapy.<sup>18</sup> Although the traditional radical mastectomy

(removal of the pectoralis muscles as well as the breast and axillary nodes) is rarely performed in high-income countries today, muscle resection frequently continues to be required in sub-Saharan Africa and other LMICs when tumors extensively invade the chest wall. Wide resection of fungating masses with major skin ulceration leaves surgical soft-tissue defects so large that primary closure of the resulting wound cannot be achieved. Myocutaneous flaps or skin grafting is required to cover the large surgical defect and close the wound.

In many LMICs, breast surgery is performed by general surgeons, who may have limited experience in breast cancer management. Although surgical training is intended to be uniform in LMICs, this result is often not achieved in practice. To ensure access to adequate surgical care, general surgeons in LMICs should receive training in the basic tenets of multidisciplinary oncologic care to be certain that they are making correct therapeutic decisions in terms of the patients on whom they operate and when they perform surgery in the sequence of multimodality treatment. Technically, surgeons should receive training in the performance of a standard mastectomy and complete axillary node dissection (the modified radical mastectomy). This may involve in-service training through the local surgical societies or regional colleges. Performance metrics such as postoperative infection rates, positive margin rates, reoperation rates, and number of axillary nodes harvested with a complete node dissection can be followed to help surgeons to track their personal performance and identify opportunities for technical improvement.

Once basic oncologic surgical skills have been disseminated among the general surgical community, specialized surgeons working at referral centers should become equipped to perform oncoplastic breast conservation techniques (which should only be employed when timely access to radiotherapy services is available for breast conservation patients). Less aggressive axillary surgical techniques such as sentinel lymph node biopsy can be offered at specialized centers. Although limited access to radionuclides has previously prevented the initiation of sentinel node biopsy in LMICs, the blue dye technique and the emergence of new mapping technologies are showing promise in low-resource settings.<sup>19,20</sup> New mapping technologies and techniques that do not require nuclear medicine services could improve access to these services to a wider population. In LMICs, some reconstructive skills are necessary to operate on patients presenting with extreme LABCs. In contrast to high-income countries where reconstructive surgeons are generally

available to assist, LMIC surgeons may need to acquire basic reconstructive skills for closing or covering the gaping wound created by complete tumor resection by using simple local tissue flap or skin grafting techniques. As the proportion of early cancers increases, more sophisticated and cosmetically acceptable reconstructive approaches for whole breast reconstruction may be integrated with autologous tissue and implant-based techniques.

### **Radiotherapy Services**

Radiation therapy plays a valuable role in the treatment of breast cancer in both therapeutic and palliative settings.<sup>21</sup> In early-stage disease, radiating the breast after breast-conserving surgery offers oncologic outcomes similar to those from a mastectomy.<sup>22,23</sup> Adjuvant radiation to the breast decreases the local recurrence risk by two-thirds in the ipsilateral breast. With advanced-stage disease, adjuvant locoregional radiation to the chest wall and regional lymph nodes decreases the risk of locoregional recurrence and distant recurrence with a disease-specific overall survival benefit.<sup>24</sup> This benefit is greater with the presence of risk factors such as young age, node positivity, triple-negative molecular markers, lymphovascular invasion, and high-grade carcinoma.<sup>25</sup> However, as radiation volumes are increased to include regional disease, the risk of toxicities, mainly to the lungs and heart, is correspondingly increased.

There often is a benefit in providing radiotherapy to patients presenting with MBC.<sup>26</sup> Palliative radiation can facilitate local control with dermal recurrence or localized disease when surgical resection is not feasible. Radiotherapy often is indicated to treat metastases to the brain or palliate other sites such as bone to maintain or increase quality of life.

Historically, local or local-regional radiation would run over a course of 5 weeks, 5 days a week (amounting to approximately 25 treatments), and it frequently would include an additional boost to the tumor bed after lumpectomy. In recent years, most centers have adopted hypofractionated regimens that reduce the breast fractionation number to approximately 15 sessions; this conserves health care resources and is easier for patients to complete.<sup>27</sup>

### **Systemic Therapy**

Although the treatment principles of systemic therapy for breast cancer (endocrine therapy, cytotoxic chemotherapy, targeted therapy, and immunotherapy) are valid across disease stages and resource levels, the implementation of existing treatment guidelines is hampered by

limited access to essential oncology medications and treatment facilities for feasible and safe cancer drug delivery. Developed to overcome these disparities, resource-sensitive<sup>11</sup> and resource-stratified guidelines<sup>8,28</sup> provide general intervention frameworks for limited-resource settings under the assumption that accurate staging, surgery, and radiotherapy services are available and can be accessed in a timely fashion. However, the practicality of guideline implementation varies markedly in relation to patient volumes, stage distribution, types of available resources, and the completeness of health system support across regions.<sup>29</sup>

Although important advances have been made with the introduction of anti-HER2 therapies and new targeted agents, including antiproliferative medications (CDK4/6 inhibitors), these agents are frequently not accessible in LMICs. With the inclusion of HER2 therapies, the median overall survival of patients with HER2-positive MBC has increased significantly over the past 2 decades.<sup>30</sup> This gain in progression-free and overall survival for HER2-positive patients in both early-stage and metastatic settings is dependent on resource-intensive therapies and accompanying diagnostics that are generally unavailable in LMICs. The same is true of metastatic, hormone receptor-positive breast cancers, for which the addition of CDK4/6 inhibitors has been demonstrated to improve overall survival, but these agents are commonly inaccessible to the general population in LMICs.<sup>31-33</sup>

The lack of reliable hormone receptor status assessment in LMICs hampers the optimal selection of endocrine interventions, and this results in a significant proportion of patients receiving chemotherapy instead of lower toxicity (and potentially more effective) endocrine therapy. Given that more than half of African breast cancers are hormone receptor positive and given the relative ease of administering oral therapies in comparison with other systemic treatments, the role of endocrine therapy and hormone receptor testing warrants careful examination in all resource settings.<sup>34</sup> Thus, one priority in the implementation of systemic therapy is represented by reliable tumor marker assessment to correctly determine the biology of the disease (primarily estrogen receptor and HER2) to allow appropriate selection of patients for endocrine therapy versus chemotherapy treatment as well as HER2 therapies when available.

Once staging studies have proven the patient to have distant metastatic disease and appropriate systemic therapies have been initiated, regular evaluations of response should be implemented using the same method(s) used for the initial identification of metastatic disease.



This practice allows the practitioner to promptly identify disease progression, spare patients from additional treatment toxicity, and avoid the loss of scarce treatment resources that are proving ineffective for controlling demonstrably resistant disease.

Bone-modifying agents (especially bisphosphonates, which have become generic and inexpensive) are an integral part of the treatment for patients with bone disease and should be initiated at diagnosis to reduce skeletal-related effects, which dramatically affect patients' quality of life. Moreover, because of their positive impact on improving quality of life, bone-modifying agents, antiemetics, and corticoids should also be implemented as another high priority.

### **Pain Control**

Pain control is fundamental to managing cancer at all stages; 33% to 64% of breast cancer report pain as a major symptom some time during their course of diagnosis and treatment.<sup>35</sup> Pain management includes regular application of pain assessment tools to closely and accurately monitor patients' pain levels and well-being; nonpharmacologic measures such as physical and occupational therapy; pharmacologic interventions, including the use of opioids; and prompt identification of pain-related emergencies.<sup>12</sup> Essential medicines for pain management include acetylsalicylic acid, ibuprofen, paracetamol, codeine, fentanyl, morphine, and methadone.<sup>36,37</sup> Moreover, because medications used for pain control can themselves cause side effects requiring additional medications to permit adequate palliation and achieve therapeutic targets.

### **Prioritizing Access to Essential Medicines**

Effective management of breast cancer after the receipt of an accurate diagnosis and the development of a treatment plan requires access to essential medicines. Because breast cancer is a priority health condition and important discrepancies exist in access to medicines across the world,<sup>38,39</sup> the World Health Organization (WHO) has labeled the pivotal medicines for its management as essential medicines, which are defined as the "minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions."<sup>40,41</sup> In the case of breast cancer, essential medicines for treatment with curative intent include agents such as doxorubicin, cyclophosphamide, paclitaxel, docetaxel, tamoxifen, aromatase inhibitors, and trastuzumab.<sup>42</sup> For the management of patients with MBC, essential medicines cover first- and second-line treatments for most subtypes; in addition, capecitabine,

vinorelbine, and other agents active in metastatic disease are included in the essential medicine list.<sup>43</sup> Priority should be given to ensure the availability of these essential medicines in LMICs because in many settings they are not, which adversely affects breast cancer survival for these patients.<sup>38,44,45</sup> Advantage can be taken of the lower cost of biosimilars to allow for the availability of trastuzumab in limited-resource settings. The increased use and decreased cost of biosimilars for trastuzumab are another important opportunity for implementing adequate care.

### **Multidisciplinary Coordination of Care**

With few exceptions, cancer management with curative intent requires orchestrated collaboration among cancer specialists in surgery, radiation therapy, and medical oncology. Decision making for these specialists in turn requires the support of imaging and pathology specialists to obtain and interpret critical information regarding the patient and cancer that they are endeavoring to treat. In high-income countries, multidisciplinary teams (MDTs) have become a critical resource for determining patient management strategies. In addition, ancillary services such as nutrition, physical therapy, psychiatry/psychology, and social services are important components of care. Palliative care professionals play an important role on an MDT, especially in the management of patients with complex supportive care needs. Cancer centers typically organize multidisciplinary clinics or tumor boards to review individual cases and develop multimodality treatment programs based on the biology of each patient's cancer in the context of known comorbid health problems.

Despite the encouraging findings of a recent American Society for Clinical Oncology survey,<sup>46</sup> the scarcity of MDT meetings in LMICs impairs optimal treatment planning. MDT meetings not only bring treating clinicians together to decide the best treatment path for a patient but also have a regulatory function because MDTs create a forum for discussing and following institutional, national, or international treatment guidelines. Furthermore, MDT meetings provide specialists with updated information regarding new or evolving cancer treatment strategies being developed by other disciplines.<sup>46</sup>

Patients with MBC at presentation, frequently seen in low-resource settings, are adversely affected by locally advanced tumors in addition to metastatic sites that require special therapeutic consideration. The addition of locoregional treatment (surgery and/or radiation) to the primary tumor in the breast in addition to systemic therapy has not been shown to affect survival in de novo MBC; however, surgical extirpation of a poorly controlled

primary tumor may be required in the metastatic setting to achieve local disease control and improve quality of life. Complex, multidisciplinary management is required for these patients, who are heavily dependent on the availability of resource-intensive, timely interventions, and this cooperation is often lacking in LMICs.

If all cancer cases are reviewed through an MDT meeting, clinicians are more likely to be informed about and follow institutional guidelines, and this means that patients are less likely to have suboptimal care if treatment resources can be made available.<sup>47</sup> MDT meetings increase the likelihood that the correct management pathway, potentially incorporating resource-stratified guidelines such as the BHGI's guidelines or the National Comprehensive Cancer Network's Harmonized Guidelines,<sup>28,48,49</sup> will be followed, regardless of a patient's ability to pay.

## IMPLEMENTATION PHASES

The process of strengthening capacity to deliver high-quality, evidence-based, and resource-appropriate treatment for patients with breast cancer requires stepwise implementation strategies.<sup>50</sup> The implementation phases begin with the bolstering of palliative care capacity, especially in settings where patients commonly present with locally advanced or metastatic disease. When effective therapies are unavailable or inaccessible, a robust palliative care infrastructure is desperately needed to assist patients whose quality of life is compromised. Once a palliative care base is established, the

patient pathway should be examined, and the role of centralized and decentralized care needs to be investigated. The role of decentralized care in LMICs, where access to care in large urban centers may be prohibitive, is particularly important. However, decentralization should be balanced with the establishment of centers of excellence, where training and research can serve to improve care delivery models, keep practitioners abreast of changing demographics and risk factors, test and implement novel care delivery programs locally and nationwide, and monitor the refinement of cancer control plans as increasing cancer treatment resources become available.

### *Phase 1: Supportive Care Framework to Establish Palliative and End-of-Life Care*

In 2014, World Health Assembly resolution WHA67.19 called on WHO and member states "to improve access to palliative care, emphasizing primary health care and community/home-based care." Palliative care is an approach that improves the quality of life of patients stricken by a life-threatening illness. Because it relieves or prevents suffering, palliative care helps to address the needs of families that are often overlooked by correctly assessing and treating pain as well as other common physical, psychosocial, and spiritual problems that typically complicate late-stage cancer management. By reducing unnecessary hospital admissions, palliative care benefits individuals, families, health systems, and society.<sup>51</sup> Text Box 1 describes the development of a national palliative care program in Romania.

#### **Text Box 1.** Romania: From an Isolated Home-Based Service to a National Palliative Care Strategy

Palliative care was introduced into Romania in the early 1990s through the charitable nongovernmental organization Hospice Casa Sperantei. Starting as a home-based, specialized palliative care service, Hospice Casa Sperantei evolved into a complex palliative care service model offering specialist services in home-based settings, inpatient units, day centers, outpatient clinics, and hospital support teams for both adults with cancer and children with life-limiting illnesses. In 2014, Hospice Casa Sperantei was recognized as a model for developing palliative care in resource-restrained settings. The nongovernmental organization has collaborated with governmental agencies in developing palliative care education programs for health care providers as palliative care has been increasingly integrated into the Romanian national health care system.<sup>52</sup> Undergraduate training in palliative care for medical and nursing students is now compulsory. Subspecialty palliative care programs for physicians have been in place since 2000, whereas specialty training for nurses has been available since 2018. New legislation has increased access to pain medications while funding mechanisms for the reimbursement of palliative care services through the health insurance funds. Progress toward national-level palliative care has been funded through the World Bank program targeting health care reforms in Romania. By the end of 2015, Romania had 115 specialized palliative care services in the public, nongovernmental, and for-profit sectors, including 78 palliative care inpatient units, 24 home-based palliative care services, 5 outpatient palliative care clinics, 4 daycare centers, and 4 hospital support teams.<sup>53</sup> Despite this progress, services remain unevenly distributed, with 15 of 41 counties still lacking palliative care services. (Summary provided by Daniela Mosoiu MD, PhD, Transylvania University Brasov Romania).

In LMICs, a significant proportion of patients with breast cancer are diagnosed with either locally advanced or metastatic cancers that have uniformly poor outcomes, especially among women living in poverty who cannot afford treatment. In the absence of optimal treatment options and where high rates of metastatic disease are seen, health systems should ensure that there is a robust strategy in place to provide palliative and supportive care services in addition to improving breast health awareness and management. This requires a paradigm shift in the approach to breast care to address the needs of patients diagnosed with late-stage or metastatic disease, palliative care must be prioritized as a basic-level need.<sup>12</sup> Many LMICs lack any meaningful platform for a palliative care program. A 2011 study of 234 countries found that palliative care services were well integrated in only 20 countries, whereas 32% had no known hospice–palliative care activity.<sup>54</sup>

Even in countries with adequate services, providers may feel reluctance to refer patients for palliative care. Seeing referral as an admission of treatment failure, providers are afraid of upsetting patients and families, while the significant quality-of-life benefits of a palliative care referral may not be fully appreciated.<sup>55</sup> Thus, the first step in implementing palliative and supportive care is to educate providers and stakeholders on the importance of palliative care as a human right, and this should be followed by the development of resource-appropriate guidelines. The fifth BHGI Global Summit was devoted to the development of resource-stratified guidelines for supportive and palliative care in limited-resource settings.<sup>10,12,56,57</sup>

### ***Phase 2: Development of a Centralized Center of Excellence for Cancer Treatment to Achieve Better Quality Care for a Whole Region/Country***

In most LMICs, the fundamental components of cancer diagnosis and treatment, such as biopsy, diagnostic histopathology, surgery, hormonal therapy, systemic therapy, and radiation treatment, require comparatively high levels of resources that are available only in larger cities. As a result, venues with these higher-level resources become institutional hubs for cancer care. Cancer centers of excellence provide the highest level of cancer care in the country, drawing cancer patients from throughout the region. Because cancer centers can become overwhelmed by large numbers of patients seeking care, cancer centers benefit from organizational relationships with 'spoke' institutions to provide lower level supportive services, including prediagnostic evaluations and workup, follow-up for treatment-related side effects and comorbidities, and palliative care. This

model does not require LMICs to make a choice between centralized and decentralized care, but instead recognizes that each level facility has specific roles and responsibilities within the continuum of patient care. In some circumstances, existing community health models (eg, care workers monitoring patients with HIV/AIDS) can be leveraged to provide increased capacity and outreach programs to communities. Text Box 2 describes the establishment of a health care facility in Ghana supported by an international nongovernmental organization that is integrating with existing public facilities to strengthen the existing cancer care network.

In addition to bolstering treatment quality, cancer centers of excellence support training and research that will continue to improve care delivery models, keep practitioners informed about new developments in cancer management, implement and test novel care delivery programs, and provide guidance to policy makers to refine cancer control plans as more resources become available.

In parallel with centralized cancer treatment facilities, centralized palliative care facilities provide supportive management and can be equipped with trained palliative care practitioners to manage or prevent a spectrum of commonly problematic symptoms, such as pain, nausea and vomiting, fatigue, shortness of breath, and depression. Initially, palliative care centers will be limited by the number of patients that they can treat. Like treatment centers of excellence, palliative care centers can act as a hub to establish geographically accessible community-based palliative care, which is especially important in low-resource settings, where traveling to centralized facilities may be too costly for patients. Training mechanisms can support community health workers and community-based nurses in providing palliative care services closer to home.

A disadvantage of the centralized care model is the limited access for patients coming from rural regions and the potential overload of the center due to large numbers of patients seeking care. Thus, effective referral networks are required to develop and coordinate care between centers of excellence in major cities (centralized care, usually at the tertiary level) and less equipped secondary-level centers in smaller cities and primary care in more rural areas, for example (decentralized care).

### ***Phase 3: Diagnosis and Treatment Networking (Decentralization) to Improve Access***

A key to improving access to cancer care services is decentralization to ensure that more services are

**Text Box 2.** Setting Up a Hospital in Ghana: HopeXchange

In Kumasi, Ghana, the nonprofit organization HopeXchange, Inc, has established the HopeXchange Medical Center (<https://hopexchangemedicalcenter.org/>), an academic medical center that provides high-quality patient care, basic- and specialty-level medical training, and biomedical research in fields of special public health significance in Ghana. The center operates with a dedicated staff of 107 full-time Ghanaian physicians, nurses, and technologists and 51 administrative officers (appointed and funded by the Ghana Ministry of Health), who work in collaboration with local consultants and rotating international volunteer medical professionals.

The Women's Cancer Center at the HopeXchange Medical Center leverages the oncology expertise provided by a network of international medical advisors working in collaboration with major Ghanaian health and educational institutions, including the Komfo Anokye Teaching Hospital (KATH), the Kwame Nkrumah University of Science and Technology, and the Ghanaian Ministry of Health. Patients with symptomatic breast lesions undergo diagnostic imaging (breast ultrasound and mammography), biopsy, histologic analysis, and, when indicated, cancer treatment. Confirmed breast cancer cases are discussed at the KATH tumor board. Surgical treatment is performed at the HopeXchange Medical Center, whereas chemotherapy and radiotherapy are scheduled at KATH. This synergy ensures that services provided at the HopeXchange Center effectively increase the access of the Ghanaian public to quality cancer services.

available and accessible to a larger sector of the population. Decentralization ensures that patients are managed more effectively and efficiently because it decongests referral centers, which typically are overwhelmed by massive numbers of patients, which translate into significant treatment delays. As long as quality can be maintained, decentralization of services helps to ensure that care-for-all happens in a timelier fashion. Typically, the focus of decentralization is to maintain oversight of quality and provide guidance on patient management from the tertiary centers and to decentralize aspects of surgical treatment to regional, second-level facilities, with the understanding that functional referral networks with good communication protocols are key to success. However, even decentralized facilities may be difficult to access for patients who lack transport options. Partnerships with local transport companies, both public and private, can increase access to care, as seen in some regions of South Africa where cancer centers partner with public transportation services.

Treatment planning can be performed by MDTs at the tertiary care centers in collaboration with physicians from more peripherally located facilities, using cellphone, electronic teleconferencing, and videoconferencing connections to facilitate dialogue and analysis. With proper training and coordination, mastectomy and axillary lymph node dissection can be performed at secondary-level, regional facilities. Such organized multiorganizational planning requires political will, national and regional cancer control planning, and cooperation between academic public and private sectors in addition to trustworthy, transparent planning, adequate resource

allocation, and cooperation with international institutions, societies, and health organizations.

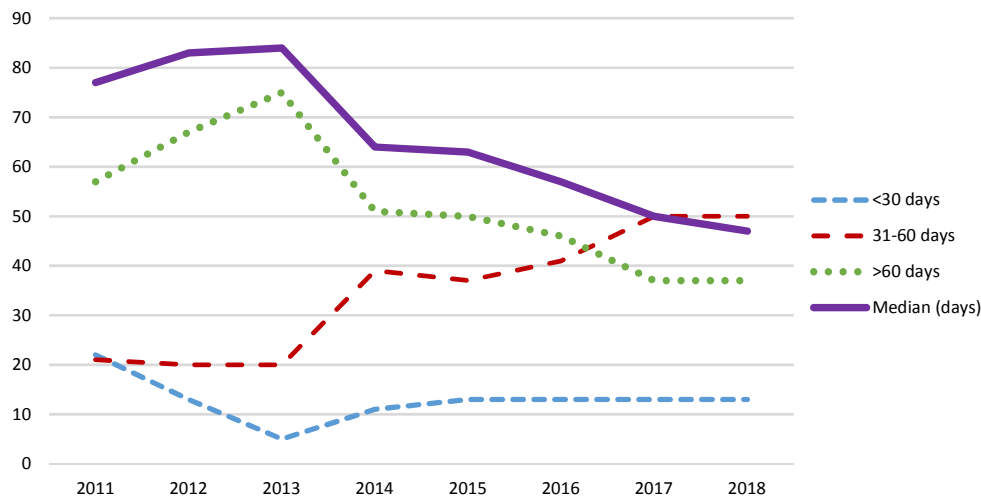
Equally relevant to system improvement in cancer treatment are the innovation and adaptation of pathology and diagnostic imaging services. A major bottleneck to the management of breast cancers lies in the diagnosis of these cancers, and treatment decentralization should also be linked to the distribution of diagnostic services to both improve patient access and improve timely decision making for patient management based on diagnostic findings. Diagnostic ultrasound, mammography, and percutaneous tissue sampling can be made available at secondary care facilities. Images can be transferred electronically, and specimens can be shipped to tertiary centers for proper pathology reading, as can immunohistochemical stains for hormone receptor and HER2 onco-gene determination. Having basic imaging tools such as ultrasound machines and trained clinicians (eg, radiologists and radiographers) at regional or district hospitals could further aid with making diagnoses, performing biopsies, and shortening delays. Text Box 3 describes an example of a program that successfully reduced the time from presentation through breast diagnosis to the initiation of treatment in São Paulo, Brazil. Decentralized facilities can offer comprehensive services by performing core biopsies and ensuring correct pre-analytic handling of specimens, and their eventual processing and reading of these specimens will assist with timely diagnoses. These services should be viewed as a core-level requirement for these units. Because of cost and quality control, developing a centralized network of laboratories, where more



**Text Box 3.** One-Stop Clinic for Diagnosis in Brazil

In Brazil, 60,000 patients were diagnosed with breast cancer annually, the majority of whom (80%) presented with symptoms. Approximately 70% of the patients received treatment through the public health system (Sistema Único de Saúde). The mean time from presentation to diagnosis (via diagnostic mammography and ultrasound) was more than 60 days, whereas the mean time from tissue biopsy to results was more than 90 days. These delays were most severe in the northern and northeastern regions of Brazil, where there was a higher proportion of advanced cases (55%). Reducing late-stage diagnoses by reducing the time from presentation to diagnosis was, therefore, identified as a national priority.

In May 2013, Brazil passed the 60-Day Law (12.732/12), which mandates that patients with cancer begin treatment in the Sistema Único de Saúde within 60 days of a confirmed breast cancer diagnosis. In response, the One-Stop Clinic at the Women's Reference Center (Pérola Byington Hospital) was established in São Paulo, a city of 12 million people. After screening in primary care units, patients with suspicious findings were referred for diagnostic imaging and ultrasound-guided core-needle biopsy performed by trained breast surgeons or gynecologists during the same visit. After 15 days, patients returned to receive the biopsy results and schedule treatment (surgery or neoadjuvant chemotherapy) as needed. Although this reduced the time between biopsy and receipt of results, the time to the initiation of treatment still exceeded 60 days, especially among patients with comorbidities. The clinic has subsequently established a preoperative consultation with a surgeon (stages I and II) or an oncology consultation to schedule the initiation of neoadjuvant chemotherapy (stages III and IV) at the first One-Stop Clinic visit. This intervention has successfully reduced diagnostic and treatment delays to less than 60 days (Fig. 2).



**FIGURE 2.** Percentages of patients and average days to the start of treatment for 10,532 patients with breast cancer treated from January 2011 to December 2018 at Pérola Byington Hospital in São Paulo, Brazil.

complex tests such as immunohistochemistry can be run in batches and the information can be readily conveyed back to the satellite laboratories, could also help to ensure quicker turnarounds and fewer spurious false-negative results. Other iterations, such as 1-stop centers where on-site cytology and histology are performed concurrently to rapidly diagnose cancers, could ensure that patients are referred through the system in a timely manner. Workshops

for core biopsy training and specimen processing improve proper diagnoses and thus help to avoid surgical biopsies and prevent 'diagnostic' mastectomies, which continue to occur in LMICs. Text Box 4 provides an example of treatment decentralization in Kenya, which is sponsored through Kenya's national cancer control plan and is improving patient access. However, this approach does have cost implications that will need to be addressed.

**Text Box 4.** National Cancer Control Plan Implementation in Kenya

The Kenyan government adopted a national cancer control plan calling for decentralization of services through the establishment of 4 comprehensive cancer centers to increase access to cancer care to reduce congestion at the national referral hospital. In the first implementation phase, 12 regional chemotherapy centers were established across 8 provinces to improve geographic access to treatment. In the second phase, 3 government-funded radiotherapy centers are under construction; a fourth treatment center is planned through a public-private partnership.

Insurance coverage for treatment remains problematic.<sup>58</sup> Comprehensive treatment of a locally advanced breast cancer in Kenya commonly exceeds US \$5000, which exceeds the Kenyan annual gross national income per capita (US \$3440 in 2018).<sup>59</sup> Universal health coverage through the National Health Insurance Fund has started, but less than 50% of the population is currently covered.<sup>60</sup> Uninsured patients with breast cancer have the option to join the national plan, but benefits become accessible only after 3 months. As a result, some patients opt for the lower cost option of surgery without neoadjuvant therapy. Once their insurance benefits are active, they then go on to receive adjuvant chemotherapy.

Finally, quality control is essential for effective scale-up of decentralized services. National certification processes can help to ensure that the integrity and quality of provided services are maintained in decentralized units. Services provided in decentralized units should not be inferior or suboptimal in comparison with similar services provided in the referral centers. Referrals from smaller units to larger centers in LMICs can be due to frequent stockouts of medication and a lack of consistent personnel working at these units. Strengthening the service provision at these units requires investment in both human resources and infrastructure.

## TOOLS FOR PHASED IMPLEMENTATION PLANNING

### **Resource-Stratified Guidelines**

When resources are limited, prioritization based on rational principles pioneered by the BHGI are valuable for addressing health care equity, which is a prerequisite for optimizing population-level outcomes.<sup>61</sup> BHGI proposed a 4-tiered system, depending on the availability of resources (basic, limited, enhanced, and maximal), for stratifying health care resources on the basis of treatment efficacy and cost-effectiveness to account for discrepancies that exist among various regions of the world.<sup>62</sup> Although treatment recommendations have evolved in the last 10 years since the publication of the original BHGI resource allocation tables (RATs)<sup>8</sup>, they maintain their validity today. The expanded roles for adjuvant aromatase inhibitors in premenopausal women, trastuzumab in the adjuvant setting, pertuzumab with trastuzumab in the neoadjuvant setting, and the approval of new agents in the metastatic setting do not alter the fundamental prioritization principles established in those early guideline publications. Other national

and international organizations have now embraced and are developing resource-stratified guidelines by using approaches that are adapted from the BHGI model.<sup>63</sup> Text Box 5 describes a current treatment paradigm in India, where governmental commitment to basic-level cancer care is leading to stepwise improvement in surgical care services for locally advanced disease.

### **Situation Analysis Tools**

Implementation planning requires that initial situation analyses be performed with the goal of identifying current levels of performance whereby improvement priorities can be identified and implementation targets can be set.<sup>71</sup> Survey tools provide a situational snapshot to identify existing treatment resources and system organization. Site visits are helpful in determining whether the system is functioning as expected or there are functional barriers that hinder effective resource utilization.

### **Implementation Checklists**

Resource checklists define required inventories for therapeutic interventions to help to identify missing elements and highlight system gaps. Specialty-specific checklists can be applied to examine the strengths and weaknesses for each of the core cancer treatment modalities—surgery, radiotherapy, and systemic therapies—by weighing their benefits and risks while describing the minimum resources required to appropriately deliver the interventions. BHGI created and updates checklists of the resources required to deliver treatment safely and effectively. WHO published the *WHO List of Priority Medical Devices for Cancer Management*, which has a special chapter on cancer management that provides a comprehensively detailed list of required equipment for cancer management.<sup>72</sup> Checklists

**Text Box 5.** Evolving Breast Cancer Management Strategies in India

In the absence of a population-based breast cancer screening program in India, governmental and nongovernmental organizations have promoted breast cancer awareness and emphasized the importance of early breast cancer diagnosis. Cancer centers have benefitted from an increased government commitment to implementing a minimum standard of care for all patients with increased financial assistance for the poor. Although these efforts have contributed to downstaging of disease, locally advanced breast cancers remain a major problem, especially in rural and remote hospitals,<sup>64</sup> because patients often visit multiple physicians or seek alternative therapy before presenting to a cancer hospital.<sup>65</sup> Although the proportion of patients presenting with locally advanced breast cancer continues to be high, the number of neglected, fungating late stage breast cancers is decreasing.<sup>64</sup> More patients are receiving neoadjuvant chemotherapy followed by mastectomy and axillary clearance; a small select subgroup successfully undergoes breast conservation treatment after successful neoadjuvant chemotherapy.<sup>64</sup> The provision of free or low-cost generic cytotoxic medications through government-financed, low-cost pharmacies or nongovernmental organizations has increased access to drug therapy<sup>66</sup> and improved the standard of care.<sup>67,68</sup> The majority of breast conservation patients are offered adjuvant radiotherapy, but many are unable to undergo treatment because of poor infrastructure or geographic inaccessibility.<sup>69</sup> Radiotherapy infrastructure, though improving, remains inadequate for the volume of patients needing treatment, and this has led to long waiting lists and treatment delays. The adoption of hypofractionation regimens has contributed to more efficient radiotherapy utilization, which has increased radiotherapy compliance.<sup>70</sup>

such as those developed by BHGI, WHO, and others can be used during situation analyses to identify the portfolio of procedures and therapies that are adequately resourced versus those for which additional or modified resources are going to be required.

In a phased implementation model, checklists of available services are equally valuable for facilitating the identification of immediate targets for treatment system improvement. For example, a facility may be able to deliver cytotoxic chemotherapy but lacks pharmacy services to safely compound the medications; once identified, this becomes a high-priority service for implementation. In examining services, attention to functionality and quality is essential.

**Gap Analysis and Phased Implementation Planning**

In a practical approach for implementing comprehensive breast cancer treatment strategies in settings where patchy resource availability exists, we propose 2 analytic phases. The first phase makes use of checklists to inventory the therapeutic interventions that have all the required elements and identify the missing elements that provide the targets for implementation. In the second phase, the RATs are used to complete the gap analysis between the current situation and the logical next step to be targeted for implementation.

**Process Metrics**

Meaningful phased implementation requires the measurement of process performance quality to determine

whether implementation strategies are working. When BHGI proposed resource stratification for treatment resources, key metrics were simultaneously defined to assess the care delivery effectiveness stratified by treatment modality and stage of disease at each resource level as defined in the RATs.<sup>8</sup> By assigning practical process metrics (eg, the percentage of patients who received the RAT-specified intervention to completion within a defined time period) and setting a target threshold for that metric to be achieved (eg, 75%-90%), one can assess health system performance at specified resource levels, and when that performance threshold has been achieved or surpassed, the next phased implementation step can reasonably be initiated. For example, BHGI defined basic-level process metrics to include the proportion of patients with estrogen receptor-positive MBC who receive endocrine therapy within 120 days of diagnosis. This metric is a performance measure for basic-level palliative care and at the same time creates an implementation benchmark for systemic treatment to guide programmatic decisions.

Similar approaches had been used to develop quality measures in the United States by the National Comprehensive Cancer Network (NCCN) and the American Society for Clinical Oncology (ASCO), although BHGI was the first to adapt breast cancer care quality measures to limited-resource settings. A systematic review of the English-language literature up to August 2017 identified 521 published quality measures for the diagnosis and treatment of breast cancer, including 419 measures from 27 peer-reviewed journal articles: 25 of

these articles (93%) originated from high-income countries, 1 originated from an upper-middle-income country (China), and 1 (BHGI) focused on LMICs.<sup>73</sup>

Most recently, efforts are underway to adapt and validate quality measures for the assessment of breast cancer care in local settings in Rwanda, South Africa, and Tanzania.<sup>74,75</sup> The teams in Rwanda and South Africa have used quality measures to identify performance gaps and opportunities for improvement, whereas the Tanzania team has used quality measures in a pre-post assessment regarding the impact of a specific implementation strategy for national guidelines in cancer management.

BHGI has also developed process metrics focusing on the overall performance of health care systems, such as the amount of time elapsing from the diagnosis date to the beginning of treatment and the proportion of patients who receive treatment in comparison with the number diagnosed.<sup>76</sup> The selected key metrics are assumed to serve as indicators of the quality of care provided to patients with breast cancer by the health care system as a whole. These process metrics are intended to provide benchmarks for monitoring and evaluating the performance of breast health care programs, to identify areas for implementation research and continued improvement opportunities, and to inform policy decisions regarding future resource expansion.

In conclusion, phased implementation strategies are improving access to and delivery of breast cancer multimodality treatment. Beginning with the establishment of palliative care services, cancer services are increasingly being provided in LMICs through centers of excellence. Collaboration among public and private entities are successful in improving cancer treatment services. Public and professional education regarding the importance of an early diagnosis for breast cancer is a necessary prerequisite for successful breast cancer treatment. Financial and logical obstacles continue to limit or delay improvement, but stepwise programmatic implementation yields some success. There is a constant need to balance centralized specialty services with distributed decentralized diagnostic and support services. Political will to make systematic improvements is required.

## FUNDING SUPPORT

The Breast Health Global Initiative Global Summit was funded by grants from the Fred Hutchinson Cancer Research Center, Susan G. Komen (grant GSP18BHGI001), the National Comprehensive Cancer Network, the US National Institutes of Health (grant 1R13CA224776-01A1), the National Cancer Institute Center for Global Health, the American

Society of Clinical Oncology, the American Society for Clinical Pathology, the *Journal of Global Oncology*, the National Breast Cancer Foundation, Inc, pH Trust, the Seattle Cancer Care Alliance, the Union for International Cancer Control, and the University of Washington Department of Global Health. Support from unrestricted educational grants came from Cepheid, Inc, GE Healthcare, Novartis, Pfizer, Inc, and UE LifeSciences. Additional funding to cover publication costs was provided by GE Healthcare and Novartis. The Susan G. Komen Leadership Grant (SAC170082) supported Benjamin O. Anderson, Catherine Duggan, and Allison Dvaladze.

## CONFLICT OF INTEREST DISCLOSURES

Nagi S. El Saghir reports honoraria from Roche, Novartis, Eli Lilly, Pfizer, and AstraZeneca outside the submitted work. Julie R. Gralow reports other from Roche/Genentech, Novartis, Puma, AstraZeneca, Pfizer, Sandoz/Hexal, Genomic Health, and Radius outside the submitted work. Alexandru Eniu reports grants from Celltrion, Roche, and Pfizer outside the submitted work. The other authors made no disclosures.

## AUTHOR CONTRIBUTIONS

**Miriam Mutebi:** Study design, text writing, and manuscript editing. **Benjamin O. Anderson:** Study design, text writing, and manuscript editing. **Catherine Duggan:** Study design, text writing, and manuscript editing. **Clement Adebamowo:** Text writing and manuscript editing. **Gaurav Agarwal:** Text writing and manuscript editing. **Zipporah Ali:** Text writing. **Peter Bird:** Text writing. **Jean-Marc Bourque:** Text writing. **Rebecca DeBoer:** Text writing. **Luiz Henrique Gebrim:** Text writing. **Riccardo Masetti:** Text writing. **Shahla Masood:** Text writing. **Manoj Menon:** Text writing. **Gertrude Nakigudde:** Manuscript editing. **Anne Ng'ang'a:** Manuscript editing. **Nixon Niyonzima:** Text writing. **Anne F. Rositch:** Study design, text writing, and manuscript editing. **Karla Unger-Saldana:** Text writing and manuscript editing. **Cynthia Villarreal-Garza:** Text writing. **Allison Dvaladze:** Study design, text writing, and manuscript editing. **Nagi S. El Saghir:** Study design and manuscript editing. **Julie R. Gralow:** Study design and manuscript editing. **Alexandru Eniu:** Study design, text writing, and manuscript editing.

## REFERENCES

- Ginsburg O, Yip CH, Brooks A, et al. Breast cancer early detection: a phased approach to implementation. *Cancer*. 2020;126(suppl): 2365-2378.
- Anglade F, Milner DA, Brock JE. Can pathology diagnostics for cancer be stratified and serve global health? *Cancer*. 2020;126(suppl): 2431-2438.
- Unger-Saldana K, Miranda A, Zarco-Espinosa G, Mainero-Ratchelous F, Bargallo-Rocha E, Miguel Lazaro-Leon J. Health system delay and its effect on clinical stage of breast cancer: multicenter study. *Cancer*. 2015;121:2198-2206.
- Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet*. 1999;353:1119-1126.
- Anderson BO, Cazap E, El Saghir NS, et al. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. *Lancet Oncol*. 2011;12:387-398.
- Rositch AF, Unger-Saldana K, DeBoer RJ, Ng'ang'a A, Weiner BJ. The role of dissemination and implementation science in global breast cancer control programs: frameworks, methods, and examples. *Cancer*. 2020;126(suppl):2394-2404.
- Duggan C, Dvaladze AL, Tsu V, et al. Resource-stratified implementation of a community-based breast cancer management programme in Peru. *Lancet Oncol*. 2017;18:e607-e617.
- Eniu A, Carlson RW, El Saghir NS, et al. Guideline implementation for breast healthcare in low- and middle-income countries: treatment resource allocation. *Cancer*. 2008;113(8 suppl):2269-2281.
- El Saghir NS, Eniu A, Carlson RW, Aziz Z, Vorobiof D, Hortobagyi GN. Locally advanced breast cancer: treatment guideline implementation



- with particular attention to low- and middle-income countries. *Cancer*. 2008;113(8 suppl):2315-2354.
10. Cardoso F, Bese N, Distelhorst SR, et al. Supportive care during treatment for breast cancer: resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. *Breast*. 2013;22:593-605.
  11. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol*. 2018;29:1634-1657.
  12. Distelhorst SR, Cleary JF, Ganz PA, et al. Optimisation of the continuum of supportive and palliative care for patients with breast cancer in low-income and middle-income countries: executive summary of the Breast Health Global Initiative, 2014. *Lancet Oncol*. 2015;16:e137-e147.
  13. Stoltenberg M, Spence D, Daubman BR, et al. The central role of provider training in implementing resource-stratified guidelines for palliative care in LMICs: lessons from the Jamaica Cancer Care and Research Institute (JACCRI) in the Caribbean and Universidad Catolica in Latin America. *Cancer*. 2020;126(suppl):2448-2457.
  14. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2). *Ann Oncol*. 2014;25:1871-1888.
  15. Knox S. The European patient advocacy perspective on specialist breast units and accreditation. *Breast*. 2015;24:287-289.
  16. Lamyian M, Hydarnia A, Ahmadi F, Faghizadeh S, Aguilar-Vafae ME. Barriers to and factors facilitating breast cancer screening among Iranian women: a qualitative study. *East Mediterr Health J*. 2007;13:1160-1169.
  17. Azenha G, Bass LP, Caleffi M, et al. The role of breast cancer civil society in different resource settings. *Breast*. 2011;20(suppl 2):S81-S87.
  18. Sayed S, Moloo Z, Bird P, et al. Breast cancer diagnosis in a resource poor environment through a collaborative multidisciplinary approach: the Kenyan experience. *J Clin Pathol*. 2013;66:307-311.
  19. Teshome M, Wei C, Hunt KK, Thompson A, Rodriguez K, Mittendorf EA. Use of a magnetic tracer for sentinel lymph node detection in early-stage breast cancer patients: a meta-analysis. *Ann Surg Oncol*. 2016;23:1508-1514.
  20. Coufal O, Fait V, Lzicarova E, Chrenko V, Zaloudik J. SentiMag—the magnetic detection system of sentinel lymph nodes in breast cancer [in Czech]. *Rozhl Chir*. 2015;94:283-288.
  21. Bese NS, Munshi A, Budrukkar A, Elzawawy A, Perez CA. Breast radiation therapy guideline implementation in low- and middle-income countries. *Cancer*. 2008;113(8 suppl):2305-2314.
  22. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233-1241.
  23. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227-1232.
  24. Braunstein LZ, Taghian AG, Niemiako A, et al. Breast-cancer subtype, age, and lymph node status as predictors of local recurrence following breast-conserving therapy. *Breast Cancer Res Treat*. 2017;161:173-179.
  25. Vrieling C, van Werkhoven E, Maingon P, et al. Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC Boost vs No Boost Trial: a randomized clinical trial. *JAMA Oncol*. 2017;3:42-48.
  26. McGale P, Taylor C, Correa C, et al; EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014;383:2127-2135.
  27. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010;362:513-520.
  28. Carlson RW, Scavone JL, Koh WJ, et al. NCCN Framework for Resource Stratification: a framework for providing and improving global quality oncology care. *J Natl Compr Canc Netw*. 2016;14:961-969.
  29. Jazieh AR, Al-Saggabi AH, McClung M, et al. Facing the global challenges of access to cancer medication. *J Glob Oncol*. 2018;4:1-7.
  30. National Cancer Institute. SEER Cancer Statistics Review, 1975-2016. Accessed April 14, 2020. [https://seer.cancer.gov/csr/1975\\_2016/](https://seer.cancer.gov/csr/1975_2016/)
  31. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. 2019;381:307-316.
  32. Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor–positive, ERBB2-negative breast cancer that progressed on endocrine therapy—MONARCH 2: a randomized clinical trial. *JAMA Oncol*. 2020;6:116-124.
  33. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382:514-524.
  34. Vanderpuye V, Grover S, Hammad N, et al. An update on the management of breast cancer in Africa. *Infect Agent Cancer*. 2017;12:13.
  35. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol*. 2007;18:1437-1449.
  36. Krakauer EL, Kwete X, Verguet S, et al. Palliative care and pain control. In: Jamison DT, Gelband H, Horton S, et al, eds. *Disease Control Priorities: Improving Health and Reducing Poverty*. 3rd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017, Chapter 12.
  37. World Health Organization. WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. Geneva: World Health Organization; 2018.
  38. Cherny NI, Sullivan R, Torode J, Saar M, Eniu A. ESMO International Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in countries outside of Europe. *Ann Oncol*. 2017;28:2633-2647.
  39. Tabernero J, Vyas M, Giuliani R, et al. Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open*. 2016;1:e000142.
  40. World Health Organization. World Health Organization Model List of Essential Medicines, 21st List, 2019. Geneva: World Health Organization; 2019.
  41. Robertson J, Barr R, Shulman LN, Forte GB, Magrini N. Essential medicines for cancer: WHO recommendations and national priorities. *Bull World Health Organ*. 2016;94:735-742.
  42. Shulman LN, Wagner CM, Barr R, et al. Proposing essential medicines to treat cancer: methodologies, processes, and outcomes. *J Clin Oncol*. 2016;34:69-75.
  43. Eniu A, Torode J, Magrini N, Bracalli G. Back to the 'essence' of medical treatment in oncology: the 2015 WHO Model List of Essential Medicines. *ESMO Open*. 2016;1:e000030.
  44. Cherny N, Sullivan R, Torode J, Saar M, Eniu A. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. *Ann Oncol*. 2016;27:1423-1443.
  45. Cortes J, Perez-Garcia JM, Llombart-Cussac A, Saghir N. Enhancing global access to cancer medicines. *CA Cancer J Clin*. Published online February 18, 2020. doi:10.3322/caac.21597
  46. El Saghir NS, Charara RN, Kreidieh FY, et al. Global practice and efficiency of multidisciplinary tumor boards: results of an American Society of Clinical Oncology international survey. *J Glob Oncol*. 2015;1:57-64.
  47. Independent Cancer Taskforce. Achieving World-Class Cancer Outcomes: A Strategy for England 2015-2020. Accessed April 14, 2020. <http://bit.ly/1ldwf5W>
  48. Swarm RA, Dans M. NCCN frameworks for resource stratification of NCCN guidelines: adult cancer pain and palliative care. *J Natl Compr Canc Netw*. 2018;16:628-631.
  49. Koh WJ, Anderson BO, Carlson RW. NCCN resource-stratified and harmonized guidelines—a paradigm for optimizing global cancer care. *Cancer*. 2020;126(suppl):2416-2423.
  50. Horton S, Camacho Rodriguez R, Anderson BO, et al. Health system strengthening: integration of breast cancer care for improved outcomes. *Cancer*. 2020;126(suppl):2353-2364.
  51. World Health Organization. Palliative care. Accessed April 14, 2020. <https://www.who.int/news-room/fact-sheets/detail/palliative-care>
  52. Centeno C, Sitte T, de Lima L, et al. White paper for global palliative care advocacy: recommendations from a PAL-LIFE expert advisory group of the Pontifical Academy for Life, Vatican City. *J Palliat Med*. 2018;21:1389-1397.
  53. Mosoiu D, Mitrea N, Dumitrescu M. Palliative care in Romania. *J Pain Symptom Manage*. 2018;55:S67-S76.

54. Lynch T, Connor S, Clark D. Mapping levels of palliative care development: a global update. *J Pain Symptom Manage*. 2013;45:1094-1106.
55. Hawley P. Barriers to access to palliative care. *Palliat Care*. 2017;10:1178224216688887.
56. Ganz PA, Yip CH, Gralow JR, et al. Supportive care after curative treatment for breast cancer (survivorship care): resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. *Breast*. 2013;22:606-615.
57. Cleary J, Ddungu H, Distelhorst SR, et al. Supportive and palliative care for metastatic breast cancer: resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. *Breast*. 2013;22:616-627.
58. Atieno OM, Oponga S, Martin A, Kurdi A, Godman B. Pilot study assessing the direct medical cost of treating patients with cancer in Kenya: findings and implications for the future. *J Med Econ*. 2018;21:878-887.
59. World Bank. GNI, Atlas method (current US\$). Accessed April 14, 2020. <https://data.worldbank.org/indicator/NY.GNPATLS.CD>
60. Jamison DT, Alwan A, Mock CN, et al. Universal health coverage and intersectoral action for health: key messages from *Disease Control Priorities*, 3rd edition. *Lancet*. 2018;391:1108-1120.
61. Carlson RW, Anderson BO, Chopra R, et al. Treatment of breast cancer in countries with limited resources. *Breast J*. 2003;9(suppl 2):S67-S74.
62. Eniu A, Carlson RW, Aziz Z, et al. Breast cancer in limited-resource countries: treatment and allocation of resources. *Breast J*. 2006;12(suppl 1):S38-S53.
63. Duggan C, Cruz TA, Porto MRT, et al. Improving breast health care in the State of Sergipe, Brazil: a commentary. *J Glob Oncol*. 2018;4:1-3.
64. Agarwal G, Rajan S, Gambhir S, Lal P, Krishnani N, Kheruka S. A comparative validation of primary surgical versus post-neo-adjuvant chemotherapy sentinel lymph node biopsy for stage III breast cancers. *World J Surg*. 2016;40:1583-1589.
65. Kumar A, Bhagabaty SM, Tripathy JP, Selvaraj K, Purkayastha J, Singh R. Delays in diagnosis and treatment of breast cancer and the pathways of care: a mixed methods study from a tertiary cancer centre in North East India. *Asian Pac J Cancer Prev*. 2019;20:3711-3721.
66. Pramesh CS, Badwe RA, Borthakur BB, et al. Delivery of affordable and equitable cancer care in India. *Lancet Oncol*. 2014;15:e223-e233.
67. Ghosh J, Gupta S, Desai S, et al. Estrogen, progesterone and HER2 receptor expression in breast tumors of patients, and their usage of HER2-targeted therapy, in a tertiary care centre in India. *Indian J Cancer*. 2011;48:391-396.
68. Singh KR, Agarwal G, Nanda G, et al. Morbidity of chemotherapy administration and satisfaction in breast cancer patients: a comparative study of totally implantable venous access device (TIVAD) versus peripheral venous access usage. *World J Surg*. 2014;38:1084-1092.
69. Gupta S, Rastogi K, Bhatnagar AR, Singh D, Gupta K, Choudhary AS. Compliance to radiotherapy: a tertiary care center experience. *Indian J Cancer*. 2018;55:166-169.
70. Chatterjee S, Arun Singh M, Agrawal S, et al. Outcomes following a moderately hypofractionated adjuvant radiation (START B type) schedule for breast cancer in an unscreened non-Caucasian population. *Clin Oncol (R Coll Radiol)*. 2016;28:e165-e172.
71. Duggan C, Dvaladze A, Scheel JR, Stevens LM, Anderson BO. Situational analysis of breast healthcare systems: context matters. *Cancer*. 2020;126(suppl):2405-2415.
72. World Health Organization. WHO List of Priority Medical Devices for Cancer Management. Geneva: World Health Organization; 2017.
73. Schleimer LE, Keating NL, Shulman LN, et al. Review of quality measures for breast cancer care by country income level. *J Glob Oncol*. 2018;4(suppl 3):41s.
74. DeBoer RJ, Ndumbalo J, Buckle G, et al. Implementation of guideline-based clinical practice at Ocean Road Cancer Institute in Tanzania. *J Glob Oncol*. 2018;4(suppl 3):12s.
75. O'Neil DS, Keating NL, Dusengimana JMV, et al. Quality of breast cancer treatment at a rural cancer center in Rwanda. *J Glob Oncol*. 2017;4:1-11.
76. Harford J, Azavedo E, Fischietto M; Breast Health Global Initiative Healthcare Systems Panel. Guideline implementation for breast healthcare in low- and middle-income countries: breast healthcare program resource allocation. *Cancer*. 2008;113(8 suppl):2282-2296.