Original Article

Breast Cancer Early Detection: A Phased Approach to Implementation

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When breast cancer is detected and treated early, the chances of survival are very high. However, women in many settings face complex barriers to early detection, including social, economic, geographic, and other interrelated factors, which can limit their access to timely, affordable, and effective breast health care services. Previously, the Breast Health Global Initiative (BHGI) developed resource-stratified guidelines for the early detection and diagnosis of breast cancer. In this consensus article from the sixth BHGI Global Summit held in October 2018, the authors describe *phases* of early detection program development, beginning with management strategies required for the diagnosis of clinically detectable disease based on awareness education and technical training, history and physical examination, and accurate tissue diagnosis. The core issues address include finance and governance, which pertain to successful planning, implementation, and the iterative process of program improvement and are needed for a breast cancer early detection program to succeed in any resource setting. Examples are presented of implementation, process, and clinical outcome metrics that assist in program implementation monitoring. Country case examples are presented to highlight the challenges and opportunities of implementing successful breast cancer early detection programs, and the complex interplay of barriers and facilitators to achieving early detection for breast cancer in real-world settings are considered. ***Cancer* 2020;126:2379-2393**. © *2020 American Cancer Society*.

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INTRODUCTION

The World Health Organization (WHO) has defined 2 distinct but related strategies to promote the early detection of cancer: *early diagnosis*, which is the recognition of symptomatic cancer at an early stage, and *screening*, which is the identification of asymptomatic disease in a target population of apparently healthy individuals[1] (Fig. 1). In low-income and middle-income countries (LMICs), a large proportion of women with breast cancer present or ultimately are diagnosed with later stage (locally advanced or metastatic) disease.[2] In such settings, efforts to promote early diagnosis are a necessary prerequisite to population-based screening because early diagnosis will improve outcomes for all

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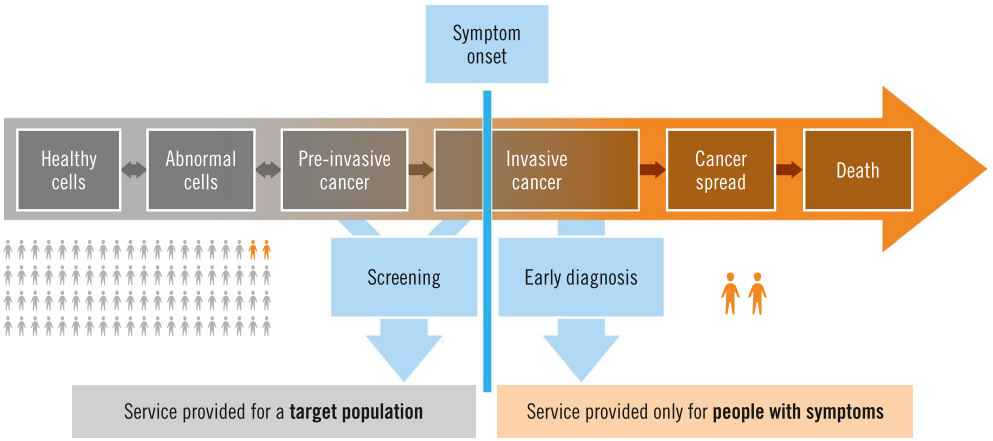

FIGURE 1. Distinguishing screening from early diagnosis is illustrated according to symptom onset (WHO Guide to Early Diagnosis, 2017).

patients with breast cancer, whereas less than one-half of breast cancers are screen-diagnosed even in the most effective screening programs. As such, early diagnosis efforts initially should be prioritized over opportunistic or organized, population-based screening until both infrastructure and organizational requirements for screening are in place to consider this additional activity. Health planners, policymakers, and other stakeholders, including clinicians, educators, community members, and advocates, should be aware of the health system requirements, as well as overall costs of these approaches to breast cancer early detection, to make effective investments, plans, and policies.

Resource-stratified guidelines for the early detection of breast cancer were developed as a framework by the Breast Health Global Initiative (BHGI).[3,4] Here, we expand on this work to develop a more nuanced framework for health planners and policymakers. We describe *phases* of early detection program development, beginning with management strategies required for the diagnosis of clinically detectable disease based on history and physical examination. In general, each phase requires continuous evaluation and improvement to establish and maintain quality; however, phased implementation is based on the premise that there are both prerequisites and a specific order to the implementation and scale-up of certain interventions to advance high-quality breast health care. The phases can be implemented sequentially (in series) or in an overlapping fashion (in parallel), depending on the specific environment in which implementation is taking place. Figure 2 presents an overview of this approach, which is described in more detail in the sections below.

We address some of the core feasibility issues, including those regarding finance and governance, that are key to effective planning and implementation of effective breast cancer early detection programs, as well as an iterative process of program improvement necessary for success in any resource setting. We also present examples of implementation, process, and clinical outcome metrics that allow measurement of program feasibility, implementation adoption, and success, among others. Country case examples are presented to highlight the challenges and opportunities, and we consider the complex interplay of barriers and facilitators to achieving early detection for breast cancer in real-world settings.

IMPLEMENTATION PHASES

Early Diagnosis: Management of Clinically Detectable Disease

A primary challenge to the successful implementation of any breast cancer program is the ability to manage clinically detectable disease and to do so in an equitable manner for the target population, that is, for all adult women with signs and/or symptoms suggestive of breast cancer. A significant proportion of breast cancer in LMICs is diagnosed at an advanced stage (American Joint Committee on Cancer stage III or IV), ranging from 30% to 50% in Latin America to 75% in Sub-Saharan Africa.[5,6] The great majority of these advanced cancers are initially detected by the patient herself based on changes that she appreciates as a lump, thickening, or other progressive change.[7,8] Once she presents to the health care system with signs and/or symptoms in the breast, diagnostic services need to be available such that a prompt and accurate diagnosis (benign vs malignant) can be provided.

The capacity to effectively diagnose and treat clinically detectable breast cancer begins with clinical breast

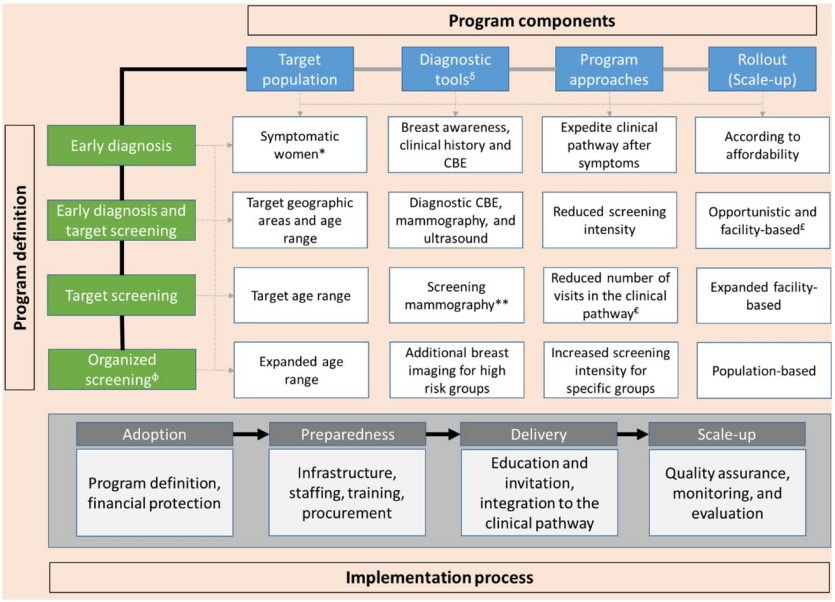

FIGURE 2. This is an overview of implementation phases for early diagnosis and detection pathways. Pathology services are the basis for breast cancer diagnosis regardless of age or domicile. Some middle-income countries introduce clinical breast examination (CBE) combined with mammography to reduce mammography intensity or as a stand-alone test for expanded age groups. Systematic screening is offered to women who attend health services for any reason, including in response to media campaigns that promote breast cancer early detection. Definition of the number of visits in the clinical pathway (range, 1-3 visits) include screening, complementary studies, and diagnosis. In organized screening (as opposed to opportunistic screening), as early detection programs are successfully implemented, early diagnosis services need to be continually supported for all women. BSE indicates breast self-examination.

assessment by taking a medical history and performing a focused physical examination, including clinical breast examination (CBE). CBE is followed by diagnostic imaging and tissue sampling with pathologic evaluation, the so-called *triple-test* of breast diagnosis.[9] As detailed in previous BHGI publications[4,10] and explored further in this series (treatment consensus articles), prompt diagnosis followed by surgery (at least a quality-modified radical mastectomy) and systemic therapy (chemotherapy and endocrine therapy, as appropriate) must be affordable for patients and accessible in a timely manner. The availability of medication for pain and symptom management is also imperative.[11] Only after these essential diagnostic and treatment modalities are available should more advanced imaging and management options, such as breast-conserving surgery, radiotherapy, or additional targeted systemic therapy, be considered.[12]

Delays in breast cancer treatment >3 months have been associated with more advanced disease stage at diagnosis and poorer survival.[7,13] At the same time, the education of primary care providers to recognize the early signs and symptoms of breast cancer is necessary for prompt referral through the health care system. Barriers to care should be identified and addressed. These are complex and multifactorial, including structural, sociocultural, personal, and financial factors that can influence a woman's opportunities to seek and receive care.[14] Even when a patient seeks care soon after the onset of symptoms (ie, *early presentation*), this does not always translate into an early diagnosis. For example, if the provider she first sees (or even subsequently sees) does not have the appropriate training or knowledge to recognize an early breast cancer, does not know where or how to refer for necessary diagnostic intervention(s), and/or the health system is fragmented in a way that prevents the patient from making her way through the entire care pathway, then diagnostic delay will result. Figure 3 provides an overview of interventions or strategies to overcome common barriers to early diagnosis.

Once high-quality, accessible services are in place to diagnose and treat clinically apparent disease, early detection in the form of screening programs can then be considered in addition to continuing to ensure effective early diagnosis for all women. If a screening program, however well intentioned, is introduced into a health care system that is not equipped to refer, diagnose, and treat the abnormalities it detects, then the program will not succeed and may be counterproductive if it reinforces preexisting

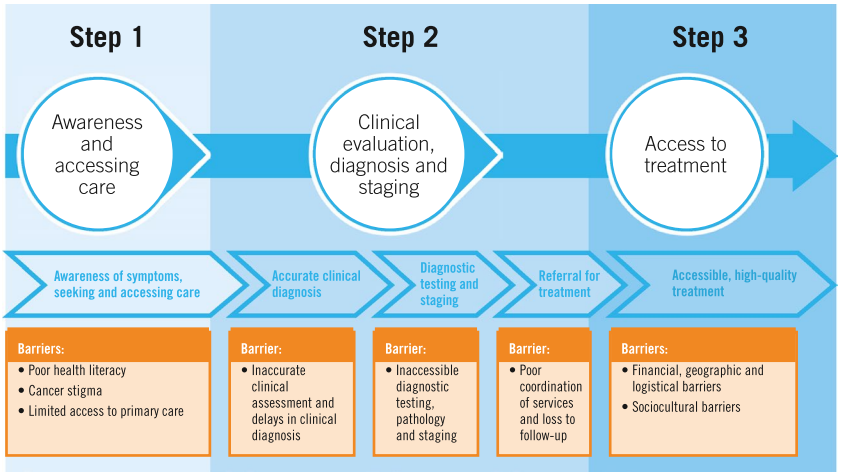

FIGURE 3. Common barriers to early diagnosis and potential interventions to strengthen early diagnosis are illustrated. From: World Health Organization (WHO) Guide to Cancer Early Diagnosis (2017).

beliefs that cancer cannot be cured, thereby perpetuating a cycle of late presentation.

Early Diagnosis: Management of Image-Detected Disease

Breast imaging, if available, is used to evaluate women who have breast symptoms or suspicious clinical findings. Ultrasound is portable, valuable in the assessment of breast masses, and has uses beyond breast imaging, making it more widely available than mammography in LMICs.[15,16] However, ultrasound is highly operator-dependent. If used for screening rather than for the assessment of palpable disease, it has the potential for a high false-negative rate.[17]

In contrast, mammography has a high specificity.[18] However, mammography has reduced sensitivity in women with high breast density. Mammogram machines are expensive, and their only application is in breast imaging, limiting their accessibility in LMICs. For mammography to be effective, whether for screening or diagnostic purposes, the health system must support training for radiologists and radiographers with ongoing quality control, patient tracking, effective communication for patient follow-up, and provider feedback, all of which are associated with significant and ongoing operating costs.

Diagnostic (or *targeted*) ultrasound is indicated as the sole imaging test to evaluate women aged <30 years who have focal breast signs and symptoms and is seen as equivalent to mammography in women aged 30 to 39 years at an average risk for breast cancer based on family history.[19] Ultrasound can distinguish between cysts, probable benign masses, and suspicious masses. This imaging modality is affected less by breast density than mammography, which makes it the preferred imaging tool in younger women who more commonly have dense breast tissue. Although mammography shows diagnostic accuracy similar to that of ultrasound in women aged 30 to 39 years, ultrasound is preferred because it has potential to identify treatable causes of symptoms (eg, a cyst) and does not use radiation. Ultrasound is also useful in women aged ≥40 years, either as the only available imaging modality where mammography is not available or as an adjunct to mammography for diagnostic workup, including evaluation of the axilla.

Diagnostic mammography is indicated for women aged ≥40 years with breast signs and symptoms and has the added benefit of simultaneously screening for breast cancer unrelated to the presenting symptoms.[19] Mammography and ultrasound are used in combination to characterize masses as likely benign or suspicious. Ultrasound is indicated for findings seen on the mammogram with *probably benign* features to determine whether a benign-appearing cyst versus a mass is present. Probably benign masses can be followed by repeated imaging studies at intervals (typically 6 months). Ultrasound is also indicated to further evaluate mammographic findings that are suspicious and to determine whether an ultrasound-guided biopsy can be performed. If mammography is not available, then ultrasound should be performed. Medical imaging, although reassuring, is not perfect. Women with a negative imaging workup (ie, no findings or benign findings only) should be followed clinically. In some cases, when a clinician has concerns regarding apparent discordance between the

physical examination and imaging findings, a surgical biopsy should be performed.

There are 3 basic methods for tissue sampling of a mass or other abnormality detected by physical examination or imaging: namely, fine-needle aspiration (FNA), core biopsy, and excisional biopsy,[4] each of which has differing characteristics in terms of sensitivity, specificity, positive predictive value, and negative predictive value, along with different training and health system requirements. It should be noted that excisional biopsy should not be done routinely as a (first) diagnostic procedure.

Population-Based Screening

There is limited evidence for the efficacy of CBE as a population-based screening modality[20] for settings in which mammography is not routinely performed. Although several studies have demonstrated clinical downstaging,[21] none have yet demonstrated improved breast cancer-specific survival (in any time frame) or a reduction in mortality. However, important caveats remain. If clinical downstaging can be achieved with screening by CBE, mortality might be reduced, assuming that timely and high-quality diagnostic services coupled with effective treatment and follow-up care are readily available, accessible, and affordable. Although the WHO does not recommend population-based, organized screening with CBE in any resource setting, in the absence of well organized, mammogram-based screening programs, CBE is considered a reasonable approach in a lower resource setting, provided it is evaluated in a research context.[22] A recent cross-sectional study of women with newly diagnosed breast cancer in Peru[8] demonstrated that women who had undergone a previous CBE (unrelated to their current diagnosis) had shorter delays from symptom development to presentation and were more likely to be diagnosed with earlier stage disease (American Joint Committee on Cancer stages 0, I, and II) compared with women who had never had a CBE. This also suggests that CBE as part of comprehensive breast health awareness may have value in improving the opportunities for early diagnosis of a (potential) future breast cancer.

A recent study from Brazil demonstrated that early detection policies introduced in 2004, which included raising public awareness and implementing screening with CBE and mammography, was not associated with a shift from late-stage to early stage disease. It was estimated that, in 2012, 2500 breast cancer deaths could have been averted by effective mammographic screening. However, it was estimated that, if from 50% to 80% of patients diagnosed at stage III or IV in the previous 5 years had been downstaged to stage II, then 8000 deaths could have been prevented.[23] Those authors concluded that clinical downstaging would have a greater effect than mammographic screening on breast cancer deaths for settings in which women present with late-stage disease. This highlights the need for further research to understand and overcome barriers to the early diagnosis of breast cancer.[24]

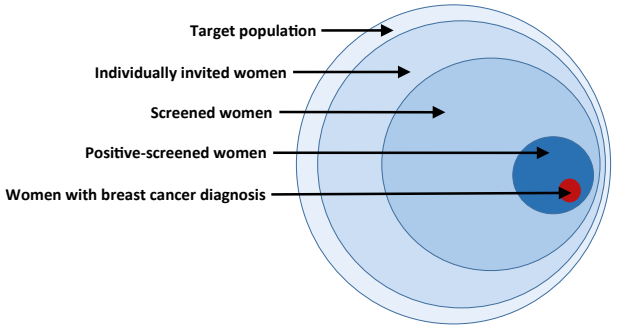

FIGURE 4. The paradigm of early detection through population-based screening is illustrated.

In contrast to screening with CBE, population-based screening with mammography has been associated with significant reductions of approximately 20% in breast cancer mortality from studies based on high-income countries where such data are available.[20,22,25] However, for population-based screening with mammography to succeed in reducing mortality, many criteria must be met, including the identification of every individual in the target population, individual invitation, and individual follow-up throughout the whole clinical pathway to ensure access to the screening, diagnostic, and treatment procedures (Fig. 4). In addition, a strong health system, sustainable financing, and the number of systems requirements that include quality control, feedback, monitoring, and evaluation criteria must be in place.

Irrespective of screening modality, the development of a population-based screening program should be considered within the framework of a national cancer control plan and within the national health financing strategy. The financial costs, at both national and societal levels, are considerable, beginning with the costs of mammography and including supportive and programmatic costs, as outlined above, and should be balanced against competing health priorities.[26]

Offering appropriate diagnostic and treatment services involves ensuring geographic access, which is determined by the available infrastructure and workforce. Some programs have used mobile units to improve access to screening and diagnosis[27]; however, evidence

of the effectiveness of these interventions is currently limited.[28]

SITUATIONAL ANALYSIS

Breast cancer survival varies widely across the globe and is strongly associated with a country's gross domestic product as well as its public spending on health.[29] Complex mechanisms underlie the contribution of human development—national income, life expectancy, education, and/or fertility rates—in conjunction with the strength of the health system, to a woman's likelihood of experiencing long-term survival from breast cancer.[30] However, disease stage at diagnosis can be considered as a starting point because it is the first measurable factor that most directly influences survival.

A recent review of cancer control plans in 158 countries reported that that there were fewer breast cancer early detection programs in LMICs compared with high-income countries.[31] Even in high-income countries, there are large cancer health disparities, including access to early detection, diagnosis, and treatment, for women with breast cancer.[32-35] Ineffective and redundant referral pathways cause system delays and are a major contributor to cancer disparities worldwide.[36] Delays from symptom onset to diagnosis range from weeks to many months in Sub-Saharan Africa.[37] Less than one-half of cancer plans recently surveyed elaborate the role of primary care physicians and referral pathways in early breast cancer diagnosis.[31] Untrained health workers are more likely to misdiagnose cancer.[38] Therefore, the importance of both system and patient-related delays cannot be underestimated.

Expanding cancer awareness or early diagnosis programs without planning the concurrent expansion of diagnostic and treatment facilities results in dismal outcomes by increasing the number of women who present with disease at a health system that lacks the capacity to diagnose and treat them effectively. This negates the benefits of early detection, builds mistrust of the public health system, increases reliance on unorthodox treatment methods, and forces patients to seek high-cost care in the private sector. An earlier review from Thailand found that, despite an increase in the number of mammograms available, the majority were in private facilities that demanded high out-of-pocket payment, thereby overstretching the few in public facilities.[39]

In addition to geographic, financial, and other structural factors, access to breast cancer early detection is also determined by the quantity and quality of human resources for health. However, human resource needs for breast cancer screening or early diagnosis depend on national policies and guidelines. The availability of human resources for health depends on the capacity of the education system to produce various cadres of providers and the ability of the health system to attract, motivate, and retain them.[40] Policymakers must consider the future demand created by a growing and ageing population, combined with a rising incidence of breast and other cancers, as part of developing a long-term plan for the workforce. The prime focus for workforce staffing should be to strengthen diagnostic skills in primary care[41] and introduce essential diagnostic tools comprising CBE, breast imaging (mammography and ultrasound), and histopathologic capacity.[42] Task-sharing and task-shifting approaches have been used successfully in different settings to surmount the workforce shortage for breast cancer early detection, including training and centralized services. Additional support can be supplied through digital or *e-health* and telemedicine.[40,43-47]

In general terms, all diagnostic tools are performer-dependent, thus prompting a trade-off between access and accuracy: the greater the level of performer training, the greater the accuracy and the lower the access.[48,49] No data on the early diagnosis of symptomatic disease are available, but the need to strengthen diagnostic skills (not screening) throughout the health system is suggested,[41] with a lower burden for diagnostic services (breast imaging and pathology), making this approach more suitable for low-income settings (WHO). Indeed, data from high-income countries show an increasing demand and the shortage of a trained workforce for breast imaging in both organized and opportunistic screening.[50,51]

The Breast Cancer Initiative 2.5 Toolkit for Breast Cancer Situational Analyses

The Breast Cancer Initiative 2.5 (BCI2.5)[52] is a global campaign to reduce disparities in breast cancer outcomes and improve access to breast health care worldwide. It is not an institution itself but, rather, a mechanism for collaboration, advocacy, and information dissemination to increase the effectiveness of independent and collective efforts while catalyzing greater global investment and commitment to breast health care. Since 2014, collaborations under BCI2.5 have produced educational resources and reports to assist policymakers and health planners to identify bottlenecks in the delivery of breast health care and determine appropriate interventions for specific settings. The BCI2.5 self-assessment toolkit developed by BHGI can help countries conduct a comprehensive breast health care situational analysis.[53]

Text Box 1. Improving Access to Breast Cancer Screening in Appalachian Ohio

Appalachia is a 13-state region defined by the Appalachian mountain range and was designated by the Appalachian Regional Commission in 1969 in response to deficits in income, education, and poverty. In Ohio, 32 counties are part of Appalachia. In addition to lower income, education, and employment rates, compared with national statistics, this area suffers from disparities in access to care, including mammography services. Six of these counties do not have dedicated mammography services, and public transportation options to travel to nearby counties are limited. In response to this deficit, the Ohio State University Comprehensive Cancer Center's (OSUCCC) Center for Cancer Health Equity obtained grants from the Susan G. Komen Foundation in Columbus, Ohio, to initiate a continuum-of-care breast screening program. There are 3 integral pieces to this program: a mobile mammogram van (owned and operated by the Speilman Breast Center at the OSUCCC, community health workers (CHWs), and a patient navigator (PN). This program employs CHWs, who are native Appalachians, to go into the community (in both community and one-on-one settings) and educate women on the need for regular breast screening. Once a woman is found who needs and wants screening, the CHW links the woman with a PN at the OSUCCC Center for Cancer Health Equity. The PN establishes how the mammogram will be paid for (ie, by insurance [including qualifying for Medicaid], the Ohio Breast and Cervical Early Detection Program, Susan G. Komen Foundation grant funds, or charity care), where the woman will get screened (mobile mammography scheduled in the respective county or a local facility), when the woman can obtain her mammogram (ie, an appointment is made), and what barriers need to be resolved for the woman to keep her appointment. The PN and CHW work as a team to assure that the woman completes her scheduled appointment and receives follow-up for any abnormality found and through treatment, if necessary. To date, 952 women in Appalachia have received a mammogram from this program, 73 women have had an abnormality detected, 70 women have been followed through diagnostic resolution, and 6 women have been diagnosed with breast cancer (4 at an early stage).

We present examples of 5 different scenarios to highlight the challenges faced and opportunities to achieve early detection for breast cancer in a target population. In an underserved community in Appalachian Ohio, a breast cancer early detection program allows a woman to undergo screening mammography and uses patient navigation to ensure that any abnormalities are followed until resolution (see Text Box 1). In China (Text Box 2), The Eastern Michigan University Center for Health Disparities received a grant to increase breast cancer awareness and early detection in 6 provinces. The program trained 2000 breast cancer survivors to be breast health ambassadors as well as 800 health care providers, with support from multiple stakeholders to ensure the treatment of positively screened patients. However, the impact of the program has not yet been evaluated. The Mexico case (Text Box 3) shows that, despite specific efforts of the government, civil society, and academia, there continue to be challenges to achieving early detection for women with breast cancer. It is also a salient example of how, regardless of how well intentioned, efforts to improve breast cancer early detection can be ineffective and even wasteful. In Panama, low participation in a screening program prompted the Ministry of Health to conduct a situational analysis, which found that diagnostic delays occurred in almost every step from referral to biopsy, and an implementation strategy to reduce delay is urgently required (Text Box 4). Finally, a case from Tanzania (Text Box 5) provides a description of the BCI2.5-facilitated situational analysis and subsequent recommendations. Although this approach can provide a model for countries that are similarly challenged with competing health priorities, the effect and feasibility of the conclusions remain to be determined.

In all case studies, the essential issue is the same: late stage at diagnosis is the main driver of poor survival, even in some higher income and ostensibly better resourced settings. Efforts to overcome these challenges need to be multipronged and to consider a variety of factors that ultimately can influence a woman's opportunities for breast cancer early detection.

Metrics for Early Detection of Breast Cancer

Identifying a set of measures to monitor and evaluate a breast cancer early detection program is essential for program improvement and progress along a defined resource-stratified pathway. High-quality metrics should be appropriate for available resources and programs, feasible to measure, and focus on program elements that can be acted upon, improved, and regularly reported to all relevant stakeholders. Ideally, the metrics used will have been

Text Box 2. China

Breast cancer is the most common cancer among Chinese women. The 5-year breast cancer-specific survival rate has been increasing but remains lower in China than in many high-income countries. Currently, there is no population-based screening for breast cancer in China. The Chinese National Breast Cancer Screening Program, which began in 2005, was terminated because of lack of funding and concerns about the false-positive rate. The national guidelines released in 2018 recommend that women aged 40 to 69 years should undergo mammographic screening every 1 or 2 years, annual clinical breast examination (CBE), and monthly breast self-examination (BSE) and that women aged 70 years and older should continue with monthly BSE and annual CBE. Nevertheless, opportunistic screening rates for mammograms, CBE, and BSE in China were only 21.7% to 33.8%. Therefore, effective strategies for improving breast awareness are needed, along with capacity-building to improve early detection.

The Eastern Michigan University Center for Health Disparities Innovation and Studies received a grant from the Susan G. Komen Foundation to increase breast cancer awareness and early detection in China. Several components were instituted based on Breast Health Global Initiative recommendations: 1) training breast cancer survivors as *breast health ambassadors* to deliver breast health messages that improve health literacy and debunk myths regarding breast cancer; 2) the education of community-level health care providers to ensure that early cancer signs and symptoms are correctly identified and referred to appropriate diagnostic services (consequently, the program produced approximately 2000 breast health ambassadors in 6 provinces and >800 health care providers in Chengdu, Guang Zhou, Inner Mongolia, and Xi'An); and 3) Multilevel collaboration involving the Political Union, the All China Women Federation, hospitals and health systems, business partners, and municipal center for disease control office to increase the infrastructure capacity for follow-up and treatment of positively screened patients. Although the national population-based screening program is still developing, the ultimate success of cancer control for breast cancer will rely on measures to improve early diagnosis and treatment in the health system as well as the general public's participation to increase awareness and promotion of early detection.

previously associated with reduced breast cancer mortality; however, the evidence to identify such measures in LMICs is scarce.

Although the ultimate goal of an early detection program is to reduce breast cancer mortality, several metrics can evaluate the program's progress toward that long-term goal. At the *enhanced* and *maximal* resource levels, at which screening mammography is provided to a target population, performance indicators can be adapted from high-income settings and, at a minimum, include the proportion of the target population screened within the past 24 months.[54]

Here, we expand on the metrics relevant to all resource levels. An essential metric is the proportion of cancers diagnosed at different stages, to allow monitoring of temporal trends in this stage distribution, given the clear link between stage at diagnosis and breast cancer survival. In a basic-resource setting in which a new program is being implemented, the provision of early detection services across health facilities is important to monitor short-term and ongoing progress on service availability and allow early challenges to be explored and addressed. Table 1 provides some additional examples of metrics that can be used to assess local, regional, or national early detection programs, grouped by the lowest resource levels to which they are pertinent.

Financing Early Detection of Breast Cancer

Financing of interventions for the early detection of breast cancer is justified from a public health, economic, and equity perspective. Numerous studies have documented the catastrophic health expenditures and economic hardships associated with a late-stage diagnosis in patients with breast cancer in different world regions, regardless of resource level.[55-57] There also are considerable nonmedical costs (transport, lodging, child care), which can account for up to 50% of total costs and must be taken into consideration to reduce the risk of impoverishment.[55]

Effective prevention and early detection strategies can help reduce costs and achieve significant savings both to health systems and individuals because cancers at earlier stages are less expensive to treat. An analysis of the total economic savings of a prevention/early detection/treatment strategy, compared with a *treatment-only* approach, was estimated at roughly 60% across all world regions.[58]

Cost-effectiveness analysis can help inform how resources should be allocated for *best-buy* interventions.

Text Box 3. Mexico

The first Mexican Official Normative (NOM-041) for the control of breast cancer was published in 2003 and updated in 2011. The NOM-041 recommends: 1) monthly breast self-examination for women starting at age 20 years, 2) annual clinical breast examination starting at age 25 years, and 3) screening mammogram every 2 years for women aged 40 to 69 years. Since 2007, treatment is covered by the government for all uninsured Mexican patients with breast cancer. Despite these policies for early detection, the majority of women with breast cancer are diagnosed with locally advanced or metastatic disease. The median time from symptom discovery to treatment initiation is 7 months, and the longest delays occur between the patient's first contact with health services and diagnostic confirmation.

Since 2007, the main focus has been the promotion of screening mammography, despite the ongoing controversy in high-income countries regarding cost-effectiveness and overdiagnosis. Public investment in breast cancer preventive services (mainly mammography screening promotion) accounted for approximately $43.6 million (US dollars) in 2015. However, national screening coverage remains low, at approximately 23%, and only 15% of patients with breast cancer have disease detected through mammography screening, which is attributed to the lack of available human resources for mammography interpretation. The required financial and human resources to increase breast cancer screening above the minimal 70% level recommended by the World Health Organization are insurmountable for a middle-income country like Mexico, with many competing priorities.

The efforts to increase mammography screening coverage have resulted in an increased but disorganized offer of mammograms in private facilities and services, subcontracted by the government, without guarantee of study quality, patient follow-up, or access to diagnosis and treatment of patients with abnormal results. Meanwhile, patients with breast cancer who present symptomatically face long delays in diagnosis and treatment because of a weak health care and referral system. The more important issues, such as strengthening the first level of care to manage women with suspected breast cancer, ensuring the quality of diagnostic imaging tests, access to high-quality pathology services, and expedited referral routes to cancer care facilities, are neglected. With the change of government administration at the end of 2018, there are plans to revise current breast cancer early detection practices and shift priorities toward the strengthening of early breast cancer diagnosis programs.

In volume 3 of the publication *Disease Control Priorities* (DCP3), a set of cost-effective and affordable interventions are identified for most LMICs, including public education for target populations to raise awareness of the value of early detection, risk factors, and breast health awareness.[59] The additional cost of the DCP3 *essential package* of cost-effective cancer interventions would cost annually roughly $1.7, $1.8, and $5.7 (US dollars) extra per capita in low-income countries, lower middle-income countries, and upper middle-income countries, respectively. The 2017 WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases did not include population-based screening with mammography (every 2 years for women aged 50-69 years) or diagnosis and treatment of stage I and II breast cancer among the best-buy interventions.[60] The Report of the WHO Commission on Macro-Economics and Health suggests that interventions that are not cost-effective (ie, costing <3 times the gross domestic product per capita for each disability-adjusted life-year averted) should be supported by the international community if a country cannot afford to undertake them on its own.[61]

The essential package funded in each country will depend on what is affordable. Governments may decide to offer subsidized care to a targeted population, or they may initially cover fewer interventions and increase them over time, as resource envelopes rise, as has been done in several LMICs, including Mexico[62] and Thailand.[63,64]

A combination of different sources of financing needs to be considered with an emphasis on domestic financing. Public financing remains key, particularly for *public goods* that cannot be withheld from those who do not pay for them, such as public education. A case study in Malaysia found that the incidence of patients presenting with late-stage breast cancer declined from 77% to 37% after a country-wide drive to increase awareness.[65] With competing demands on health budgets, and even under the scenario of growing per capita incomes, prioritization of health interventions and mobilization of additional public funding will be essential.[66]

Text Box 4. Panama

Health care delivery in Panama is governed by the Ministry of Health (MINSA), which also provides health care services to those lacking health coverage under the Social Security System. MINSA approved an opportunistic screening program for breast cancer, but participation rates were low, and most women presented at primary care facilities with symptomatic disease. Women with breast symptoms are subsequently referred to secondary level facilities for diagnostic workup, including diagnostic imaging, tissue biopsy, and diagnostic pathology. Confirmed breast cancer cases are referred to the National Oncology Institute in Panama City for molecular pathology and treatment, which are free for all patients.

Three years ago, MINSA identified low levels of breast cancer knowledge at the primary level and weak referral pathways as 2 key areas for improving the early diagnosis of breast cancer. The country has since developed and implemented standardized trainings in each province to increase the capacity of primary level health care providers to identify early signs of breast cancer and to refer patients to the appropriate level of care using the Pan American Health Organization's virtual platform and blended learning. In 2018, the ministry invited the Breast Health Global Initiative and the Susan G. Komen Foundation to visit the National Oncology Institute of Panama, along with primary and secondary facilities in 2 regions of Panama, to assess barriers to effective early diagnosis.

The Breast Health Global Initiative team identified the following opportunities to work with MINSA to further improve breast cancer early diagnosis: 1) continue developing a standardized and more efficient referral system, with emphasis in the diagnostic phase; 2) shift to greater use of needle biopsies for breast cancer diagnosis because most biopsies performed at second level facilities are excisional and are performed by surgeons, causing significant delays; and 3) plan for the inevitable increased influx of patients to the National Oncology Institute as screening rates grow.

MINSA has recently completed the new National Cancer Plan 2019 to 2029, as it continues strengthening early diagnosis. MINSA is currently working with the Breast Health Global Initiative in developing an implementation strategy based on the Exploration, Preparation, Implementation, Sustainment framework to support transition to increased rates of core-needle biopsies, with the aim of reducing diagnostic delays.

Social health insurance represents the most equitable way to fund interventions that have a large *private good* content, such as early detection, diagnosis, and early treatment of breast cancer, incorporating progressively key interventions in benefit packages. There may also be some element of cost-sharing and cross-subsidization of out-of-pocket spending through supplementary private health insurance. It may be important to consider a tiered approach to increasing coverage as social health insurance schemes mature, and adequate resources can be generated to make them financially sustainable.

Countries may also consider innovative financing options (eg, tobacco, alcohol, and sugar taxes; airline and mobile phone levies). External financing will play a critical role to: 1) lower costs of inputs in the spirit of *bending the curve* on the high costs of treatment, and 2) support technical assistance and research.[59] It is worth mentioning here that public-private partnerships have been proposed as a solution to overcome some of the bottlenecks in the public health system. However, strong oversight, including accreditation, regulatory capacity, and good governance mechanisms, should be in place to ensure that such arrangements reach intended beneficiaries who present for care without escalating costs for patients or governments.

IMPLEMENTATION FRAMEWORK

Policies and Governance

The BHGI stratified guidelines and phased implementation strategy provide a framework to define early detection policies according to the level of resources,[3] upgrading from breast cancer early diagnosis alone to the addition of highly organized screening; however, implementing the same policy may differ across settings, depending on health system capacity and characteristics.

Therefore, the development and implementation of breast cancer early detection policies must rely on accurate situational analyses, including assessment of the sociopolitical and economic context, workforce capacity, infrastructure, distribution of equipment and facilities (as determinants of geographic access), social structures, and funding.[67] Consideration should also be given to the

Text Box 5. Tanzania

In Tanzania, inefficient clinical pathways for women with breast health concerns result in significant delays in detection, diagnosis (80% diagnosed at advanced stages) and treatment. In 2016, at the invitation of the Government of Tanzania, the Susan G. Komen Foundation partnered with the Breast Health Global Initiative (BHGI), the Women's Health Equity Through Mobile Approaches (a non-profit organization to support women's health in Tanzania), and the Ocean Road Cancer Institute to conduct a situational analysis of breast health care in Tanzania. Breast health care services were assessed using tools developed by the BHGI/Breast Cancer Initiative (2.5) at the primary, district, regional, zonal, and national levels using via questionnaires, in-person interviews, and site visits in Dar es Salaam, Mbeya, Moshi, and Mwanza.

Findings from this initiative include: 1) protocols and guidelines for breast cancer early detection, diagnosis, and treatment are not standardized; 2) inefficient/hierarchical referral systems add delays and costs and increase rates of attrition; 3) financial conditions—both institutional and individual—present significant barriers to care (eg, treatment is free with a confirmed diagnosis, but diagnostic fees are paid for out-of-pocket); 4) lack of a trained, specialized health care workforce, including pathologists, radiologists skilled in breast ultrasound, specialized breast surgeons, and medical oncologists; 5) frontline, primary, and district-level health care workers lack training in breast health education, clinical breast examination, and the referral pathway; and 6) communication between facilities is poor, and there is no feedback loop to relay diagnostic results.

On the basis of these findings, the BHGI developed a resource-stratified phased implementation framework to integrate early detection programs with accurate diagnosis and timely, accessible, and effective treatments, beginning with the management of palpable disease. The prerequisites for this framework include situational analysis, referral/patient pathways, standardized guidelines, protocols, and a trained workforce. Phase 1 consists of the systematic triage and diagnosis of palpable breast disease. Phase 2 consists of strengthening resource-appropriate, patient-centric care pathways (treatment planning and patient navigation) and reducing access barriers. Phase 3 consists of scaling up targeted education interventions for the public and for health care staff and clinical breast examination to promote the downstaging of clinically detectable disease. Phase 4 consists of the systematic upgrading of image-based diagnostic systems (ultrasound and mammography imaging used first for diagnostic workup as a prerequisite to image-based screening). This partnership has resulted in new collaborations and continued engagement in the improvement of breast health care in Tanzania, including harmonization of the National Guidelines for Early Diagnosis and Referral for Treatment with the assessment findings, training of primary care providers and health systems, and implementation research.

inclusion of social scientists (including gender scholars) and representatives from the target population in policy development to ensure that policies and interventions are acceptable, equitable, and inclusive.

Basic components of breast cancer early detection policies comprise identifying the target population, defining the diagnostic tools, delineating the programmatic approaches, and elaborating the rollout and scale-up process (Fig. 4). For each component, different alternatives might be adopted, thus resulting in diverse strategies. In addition, mechanisms for financial protection should be established to minimize the risks of incomplete diagnosis or treatment and impoverishment, and the inclusion of early detection interventions in essential health packages is critical because treatment of early disease is less expensive and will generate savings on medical costs.[68]

Policy implementation should ensure sustainability. In limited-resource settings, the expansion of health services by governmental agencies is less likely to occur because of financial constraints and the presence of competing needs.[69] Medical societies, breast cancer survivors, and nongovernmental organizations frequently step in to fill gaps in the delivery of breast cancer awareness and related health services for early detection in low-resource settings and underserved populations[67] by the provision of infrastructure, equipment, and staffing. However, if these services are not integrated into the existing health system and coordinated with the relevant ministries and institutions, then these efforts may have limited effects. Furthermore, there must be a strategy at the outset for transitioning nongovernmental organization-supported initiatives to government ownership. Hence, nongovernmental organizations should play an active role in transitioning from the delivery of early detection services to mainstreaming these interventions in the health system with full governmental commitment to ensure sustainability.

TABLE 1. Examples of Metrics to Identify and Track Outcomes

Metric	Resource Level: Basic, Core, Enhanced	Metric Type: Process, Implementation, Health Outcome	User of the Metric
Community breast cancer awareness: Percentage of population aware of breast cancer symptoms, percentage of population knowing where to go for a breast health concern	Basic	Implementation, health outcome	System wide: Community level/ regional ministry
Provider breast cancer awareness: Percentage of providers trained to provide high-quality CBE; percentage of providers who know proper care referrals for positive CBE	Basic	Implementation, health outcome	System wide: Medical education oversight? Health facility
Among women with suspected breast cancer, median no. of days from symptom onset to first presentation at a health facility	Basic	Process	System wide: Community awareness and access to care
Among women with suspected breast cancer, median no. of days from first presentation at a health facility to diagnosis	Basic	Process	Health facility
Among patients diagnosed with breast cancer, median days from diagnosis to first treatment	Basic	Process	Health facility/network
Percentage of patients with breast cancer diagnosed as early stage (stage I or II) disease	Basic	Health outcome	System wide: Health facility/ network
Percentage of patients lost to follow-up after initial presentation with a breast mass	Basic	Health outcome	Health facility/network
Percentage of relevant health facilities offering early detection services (penetration)	Basic, CBE; core, ultrasound; enhanced, mammography	Implementation	Health system/ministry
Uptake (population coverage) of routine screening services	Basic and core, CBE; enhanced, mammography	Implementation	System wide
Cost	All levels	Implementation	System wide

Abbreviation: CBE, clinical breast examination.

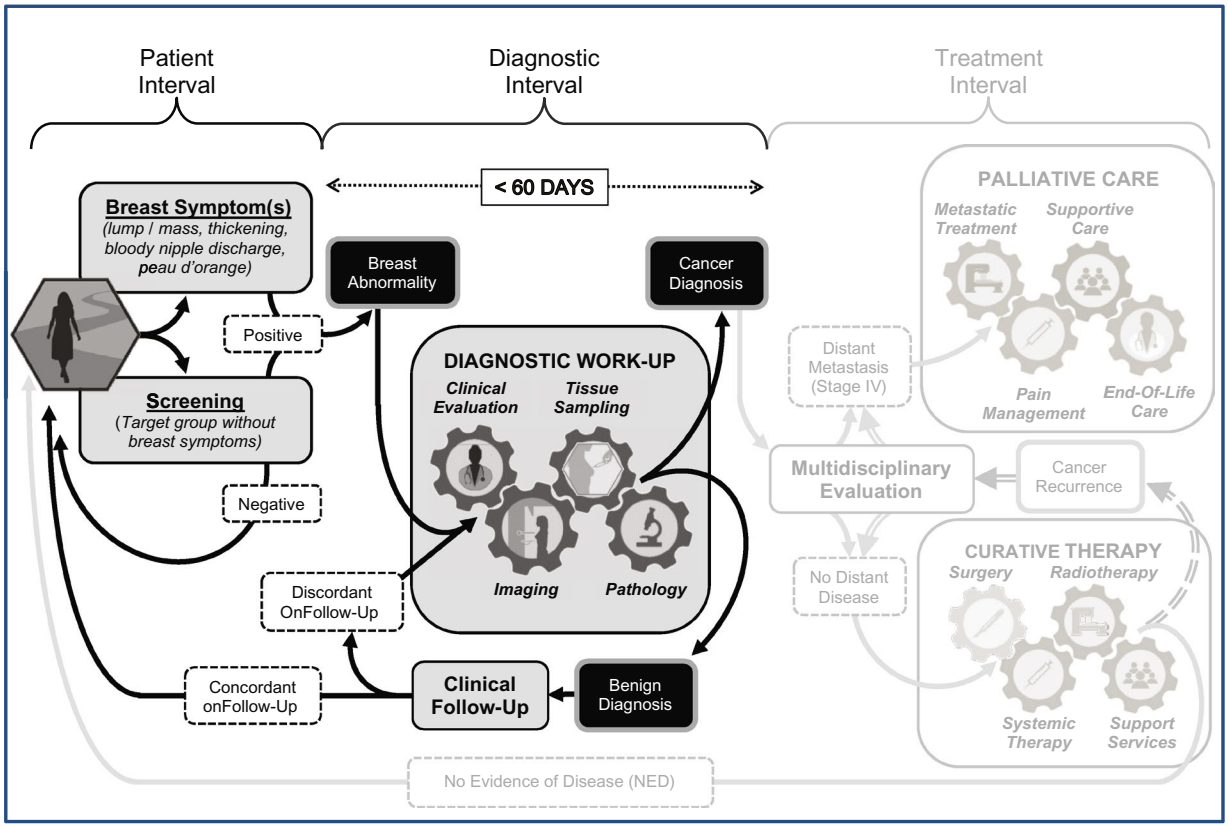

FIGURE 5. The universal patient pathway for breast cancer management is illustrated in 3 sequential intervals of care (patient interval, diagnostic interval, and treatment interval), highlighting the patient and diagnostic intervals of care. The *patient interval* begins with the onset of clinical symptoms or an abnormal screening examination and extends to the time the patient presents for diagnostic workup of a recognized or suspected breast abnormality. During the *diagnostic interval*, the identified breast abnormality undergoes a *triple-test* workup based on clinical evaluation, imaging, and tissue sampling to achieve a definitive benign or malignant diagnosis. The health system should endeavor to complete the diagnostic workup within a 60-day (2-month) period because worsened survival outcomes can result from diagnostic delays extending significantly beyond 3 months.

Conclusion

All countries are challenged to meet the ambitious targets of the WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases (NCDs) and to achieve the related Sustainable Development Goals target: a one-third reduction in mortality from NCDs by the year 2030.[70] Breast cancer is the most common cancer in women globally in all but 42 countries, where cervical cancer still predominates. Breast cancer survival depends largely on a woman's access to timely, effective, and affordable care. Early detection is critical to breast cancer survival. When coupled with timely access to treatment, appropriate follow-up, and survivorship care, there can be significant reductions in breast cancer mortality.

The complex interplay between barriers in access to early detection and examples of interventions to overcome these barriers are presented here, along with sample metrics and governance considerations that can be used as a practical framework to the phased approach to breast cancer early detection for a population in any setting. A robust health system is a prerequisite to providing the facilities for treatment of breast cancers that are diagnosed through the early detection programs, whether with symptomatic breast cancer or through screening. Although patient and health provider education may shorten the patient interval, to achieve a diagnostic interval target of less than 60 days requires coordination of the diagnostic pathway elements of clinical evaluation, imaging, tissue sampling, and pathologic assessment (Fig. 5).

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