World Health Organization

Global Breast Cancer Initiative Implementation Framework

Assessing, strengthening and scaling up services for the early detection and management of breast cancer

Abstract

Breast cancer is the most common cancer worldwide and the leading cause of cancer deaths among women, disproportionately affecting individuals in low- and middle-income countries. Breast-cancer five-year survival rates in high-income countries exceed 90%, compared with 66% in India and 40% in South Africa. The WHO Global Breast Cancer Initiative (GBCI), established in 2021, has set the goal to reduce breast cancer mortality by 2.5% per year, which over a 20-year period would save 2.5 million lives.

This GBCI Implementation Framework provides national programme managers, policy makers and multisectoral actors the guidance needed to assess, strengthen and scale-up services for the early detection and management of breast cancer. The Framework presents key strategies using three pillars:

- Pillar 1. Health promotion for early detection (prevention and pre-diagnostic interval)
- Pillar 2. Timely breast diagnostics (diagnostic interval)
- Pillar 3. Comprehensive breast-cancer management (treatment interval).

Implementation strategies are specified, which include how governments can operationalize this Framework to improve access to breast-cancer services in their settings. Using this Framework, all stakeholders can achieve the Initiative's goal to assure feasibility and quality by providing evidence-based recommendations for a phased approach to implementing interventions and strengthen health systems towards the attainment of universal health coverage.

World Health Organization

Global Breast Cancer Initiative Implementation Framework

Assessing, strengthening and scaling up services for the early detection and management of breast cancer

Global breast cancer initiative implementation framework: assessing, strengthening and scaling-up of services for the early detection and management of breast cancer

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Foreword

There are more than 2.3 million cases of breast cancer each year, making it the most common form of cancer among men and women combined. In 95% of countries, breast cancer is the first- or second-leading cause of female cancer deaths.

The incidence and number of lives lost to breast cancer are increasing. By the year 2040, more than 3 million cases of breast cancer and 1 million deaths are predicted to occur each year worldwide. Breast cancer must be a priority for ministries of health and governments everywhere.

Countries with weaker health systems are least able to manage the increasing burden. Low- and middle-income countries have the highest avoidable rates of breast-cancer deaths, with over 70% occurring among women under 70 years of age. This places a tremendous strain on individuals, families, communities, health systems, and economies. In sub-Saharan Africa, half of breast-cancer deaths occur in women under the age of 50. In many countries around the world, a breast cancer diagnosis can trigger generational impoverishment and cycles of poverty.

We have the tools and the know-how to prevent breast cancer and save lives. Countries with strong health systems have reduced breast cancer mortality by 40% since 1990. This shows the need for strategic investments in health systems founded on established principles of health promotion for early detection, timely diagnosis, and access to comprehensive management as part of universal health coverage. The Framework of the Global Breast Cancer Initiative lays out a roadmap for immediately implementable strategies for countries with diverse health systems.

Implementing the strategies laid out in the Framework could save 2.5 million lives by 2040. By applying a stepwise, resource-appropriate approach founded on strengthening health systems and framed by women's health and gender equity, we can improve the health and well-being of women, families, and communities for generations to come.

We are gathering momentum. The 2022 World Health Assembly passed a resolution committing to prioritizing cancer. Governments must now prioritize investments and implement policies to optimize health services; ministries must optimize health worker roles and provide access to health products; civil society must mobilize communities; development partners and donors must reflect the urgency and scale of the breast cancer burden in their strategic priorities; individuals must make healthy choices; and industry must promote access and innovation. For its part, WHO has developed integrated initiatives related to women's and children's cancers, having also called for the elimination of cervical cancer and a doubling of childhood cancer survival.

Together we can and we must succeed. Our children and future generations rely on us.

Dr Tedros Adhanom Ghebreyesus

Director-General

World Health Organization

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Document preparation

To create this technical package, WHO organized the global experts into five working groups (on health education, rapid diagnosis, comprehensive cancer management, partnership, and implementation research) the members of which served as writers and content reviewers. The working groups were balanced for gender, geographic representation, and area of expertise. All contributors were volunteers who underwent formal WHO-conflict-of-interest reviews. Based on a comprehensive outline, the original text was prepared by the working-group contributors in assigned sections, as guided by the

GBCI working-group leadership teams. The final document was collated and edited by the GBCI writing team, in consultation with the GBCI working-group leadership. The final text was reviewed for content and relevance by WHO experts from outside the WHO cancer group at WHO headquarters and the WHO regional offices. WHO is indebted to the members of this global expert group who generously volunteered their time and expertise to make the creation of this document possible.

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Abbreviations

ABC	advanced breast cancer (stages III or IV disease)
ABC-DO	African breast cancer - disparities in outcomes cohort study
ASR	age-standardized rate
BCR	benefit-to-cost ratio
BMI	body mass index
BSE	breast self-examination
CBA	clinical breast assessment
CBE	clinical breast examination
CHWs	community-health workers
CSOs	civil-society organizations
EBC	early breast cancer
EoLC	end-of-life care
ER	estrogen receptor
GBCI	Global Breast Cancer Initiative
HER2 oncogene	human-epidermal-growth-factor receptor 2

HER2-	HER2 receptor negative (does not overexpress HER2 oncogene)
HER2+	HER2 receptor positive (overexpresses HER2 oncogene)
HER2/neu	Same as HER2
HICs	high-income countries
IHC	Immunohistochemistry
KPI(s)	key performance indicator(s)
LABC	locally advanced breast cancer (stage III)
LMICs	low- and middle-income countries
MBC	metastatic breast cancer (stage IV if metastasis present at initial diagnosis)
MG	mammography
m/RNA	messenger RNA
NCDs	noncommunicable diseases
NGOs	nongovernmental organizations
PABC	Pregnancy associated breast cancer
PR	progesterone receptor
RCA	root-cause analysis
TNM staging	A globally recognized cancer-staging system, describing the amount and spread of cancer in a patient's body based on tumour size, invasion of cancer into nearby tissue (T), spread of cancer to nearby lymph nodes (N) and presence/absence of distant metastatic disease (M).
UHC	universal health coverage

Glossary of terms

Age-standardized mortality rates

An age-standardized mortality rate is the weighted average of the age-specific mortality rates per 100 000 population , where the weights represent the proportions of people in the corresponding age-groups of the WHO standard population.

Benefit-to-cost ratio[1]

This is the ratio of project benefits to project costs. It involves adding up the total discounted benefits gained by a project over its entire duration/life span and dividing it over the total discounted costs of the project [1].

$$BCR = \frac{[\Sigma B_i / (1+d)^i]}{[\Sigma C_i / (1+d)^i]} \quad \text{added up over 1 = 0 to n years}$$

Where: Bi = the project's benefit in year i, where i = 0 to n years Ci = the project's costs in year i, where i = 0 to n years, n = the total number of years of project duration/life span, d = the discount rate.

Breast-cancer-control programmes

A breast-cancer prevention-and-control programme comprises an organized set of activities aimed at preventing and reducing morbidity and mortality from breast cancer. A comprehensive programme includes a plan of action specifying the work to be done, those responsible, timelines, and resources for implementation. In addition, it describes the evidence-based interventions needed to reduce the high and unequal burden that breast cancer imposes on women and health systems in low- and middle-income countries (LMICs).

Breast self-examination (BSE)

BSE is a visual and tactile examination of the breast performed by the individual to assess the presence of persistent changes or abnormalities, thereby helping the individual learn over time what looks and feels normal for her. During a BSE, the individual inspects her breasts in the mirror, looking for asymmetries, puckering, dimpling, or localized skin changes, then feels the entire breast and armpits with the arm and shoulder extended to flatten the breast on the chest wall.

Clinical breast assessment (CBA)

CBA refers to the set of clinical tools essential for the early diagnosis of breast cancer at the primary-care level. To conduct a CBA, a provider takes a medical history to learn what changes (if any) the patient has noted in the breast, such as lumps, thickenings, asymmetries, or skin changes, as well as the time course over which these changes have occurred. The provider then performs a general medical examination, including a clinical breast examination (CBE) (see below) to correlate the historical findings with those present on physical examination. The findings of the CBA are used by the clinician to formulate a differential diagnosis, request diagnostic imaging, and determine if tissue sampling (biopsy) is warranted.

1 Pan American Health Organization, WHO Regional Office for the Americas. Smart hospitals toolkit. Washington, DC: Pan American Health Organization; (https://www.paho.org/disasters/dmdocuments/SmartHospitalsToolkit.pdf, accessed 15 February 2023).

Clinical breast examination (CBE)

CBE is a systematic and specific clinical examination of the breast, the nipples, and the areola, axillary, infraclavicular and supraclavicular lymph nodes, performed by a health-care provider. Abnormal findings on CBE generally warrant diagnostic imaging and may require tissue sampling to make a definitive diagnosis. CBE, which is required for CBA, is performed in conjunction with breast-cancer early-diagnosis programmes and can be deployed as part of a breast-cancer screening programme.

Clinical (care) process

Clinical processes or clinical-care processes encompass all health-care provider activities and other prescribed health-care activities that are implemented to address identified or specified health issues. These involve the GBCI Breast Cancer Care Pathway, which is a series of clinical-care processes grouped into three sequential intervals (pre-diagnostic, diagnostic and treatment) in alignment with the three GBCI Pillars to facilitate early detection, diagnosis and management of breast abnormalities and cancers.

Early detection

Early detection is the overall process whereby breast cancer is detected at earlier stages (0, I or II) when treatment is on average more effective. Early detection requires “early-diagnosis” approaches among the general population and may include “screening” a prespecified subgroup of individuals without breast symptoms. Both early diagnosis and screening programmes achieve “stage shifting” in which a greater fraction of breast cancers in the population is diagnosed at earlier stages of disease progression. The goal of an early detection breast-cancer programme is to promote stage shifting so that >60% of women diagnosed with invasive breast cancer have stages I or II disease.

Early diagnosis programme

Breast cancer early-diagnosis programmes are the initial step in establishing a breast-cancer early-detection programme. To facilitate breast cancer early diagnosis, individuals with early, subtle symptoms of breast cancer are encouraged to seek care and undergo evaluation and definitive diagnostic work-ups (imaging +/- tissue sampling) to determine which individuals have cancer and which do not. Distinct from screening programmes of women without symptoms, where testing is limited to a prespecified age group at heightened risk of breast cancer, all individuals with breast-cancer symptoms warrant evaluation, regardless of age. The goal of early-diagnosis programmes is to implement clinical approaches so that >60% of women found to have invasive breast cancer have stages I or II disease.

Mammogram

A mammogram is an X-ray examination (radiogram) of the breast, including multiple views of one or both breasts. It is used to detect and diagnose breast disease in women who have breast problems, such as a lump, pain, or nipple discharge (diagnostic mammogram), and in women with no breast complaints (screening mammogram).

Mammography

Mammography comprises the radiology and diagnostic-imaging services that are devoted to the practice of mammography. It involves a combination of equipment and human resources aimed at applying low-energy X-rays to the examination of breasts. Regardless of whether mammography is used for screening or diagnostic purposes, a quality-assurance programme is required to maximize the benefits and minimize the harms associated with this procedure.

Metastatic breast cancer (MBC)

MBC refers to the spread of the primary breast tumour from the breast through the circulation and lymphatics to distant sites and organs, most often bone, lung, liver and brain. Advanced breast cancers (ABCs) may initially present with distant metastases (MBC stage IV) or may recur with distant metastases following initial treatment (metastatic recurrence of stages I – III disease).

Monitoring

This involves the systematic collection of data for measuring the achievements of breast-cancer-control programmes, which are assessed periodically, using a set of measurable indicators.

Multimodality treatment

Multimodality treatment is prescribed for patients on an individualized basis, utilizing multiple modes of therapy (surgery, radiation therapy, anti-cancer medication) to minimize the risk of cancer recurrence. Specific treatment programmes are determined in alignment with evidence-based cancer guidelines, based on the cancer's biological features and the extent and stage of the disease.

Screening programme

A breast-cancer-screening programme is a public health, early-detection approach whereby women without known signs or symptoms of breast cancer are invited, on a repetitive basis, to undergo testing for cancer before it causes recognizable signs or symptoms. To consistently find cancer at early stages of the disease, the screening test must be repeated in the same individuals at regular intervals (every 1–2 years). To avoid excessively high numbers of false-positive test results, the subgroup of individuals invited for screening should be limited to those whose degree of breast-cancer risk exceeds a prespecified risk threshold. Screening-selection criteria are based primarily on age and gender and secondarily on other recognized risk factors, including genetic or familial risk, reproductive history and breast density.

Stage shifting

This is the shifting at diagnosis from one stage to the stage below, or the diagnosis of cancer earlier in the stage. This is often a result of early-detection programmes.

Systemic (anti-cancer medicine) therapy/treatment

Systemic anti-cancer therapies are a group of medicines prescribed to kill cancer cells that have spread beyond the primary tumour. Standardized multi-medication treatment regimens are individually prescribed based on breast-cancer subtyping as determined by tumour-marker testing (ER, PR and HER2 expression) and may include cytotoxics/chemotherapy, endocrine (hormonal) treatments, and/or targeted (or biological) therapies. Systemic therapy is given in conjunction with other therapeutic interventions to control disease in the breast and lymph-node beds (surgery and radiotherapy). Systemic anti-cancer therapies can be administered following (adjuvant) or prior to (neoadjuvant) surgical resection of the primary breast tumour.

Supportive services

Supportive services are an essential component of cancer management for patients at all stages of the disease, including the management of physical symptoms resulting from cancer and its treatment (pain, nausea, hair loss, fatigue, lymphedema), some of which can be long-lasting. Supportive services also address the psychosocial and spiritual challenges that cancer and its treatments can trigger (anxiety, depression, feelings of social isolation).

Treatment completion

Treatment completion means the fulfilment of all components or steps of the therapeutic sequence, unless interruption is indicated for medical reasons.

Treatment abandonment

Treatment abandonment refers to the failure to complete the treatment regimen for reasons other than medical indications for treatment disruption.

Executive summary

Breast cancer from the global health perspective

Breast cancer has become the most diagnosed form of cancer globally, accounting for nearly 12% of all cancer cases worldwide, and is the leading cause of cancer deaths among women.[1] During 2020, 2.3 million women were diagnosed with breast cancer, with 685 000 deaths globally. At the end of 2020, 7.8 million women who had been diagnosed with breast cancer in the previous five years were still alive, making breast cancer the most prevalent malignancy. Breast cancer is the most common cancer among women in 158 of 183 countries (86%) and the leading cause of female cancer deaths in 107 of 183 countries (58%). It is the leading or second leading cause of female cancer-related deaths in 173 of 183 countries (95%), suggesting that **no ministry of health can overlook breast cancer if they intend to address cancer as a significant public health issue in their country.**

Global breast-cancer control is a gender-equity and human rights issue. Women play central roles in society; protecting women from breast cancer also protects their families, communities, and the economy as a whole. **The burden of avoidable breast-cancer deaths disproportionately affects low- and middle-income countries (LMICs)** where over 70% of breast-cancer deaths are premature, occurring in individuals under 70 years of age.

The 5-year breast-cancer survival rates exceed 90% in high-income countries (HICs), compared to 66% in India and 40% in South Africa. In sub-Saharan Africa, where half of all breast-cancer deaths occur in individuals under 50 years of age, 100 deaths from breast cancer at this young age causes 210 children to become maternal orphans.[2] Thus, **the chronic social disruption and financial harm that come with breast cancer will continue to have an impact on LMICs for generations to come.**

If current trends remain unchecked, the breast-cancer burden is projected to increase to 2.74 million new cases and 857 000 deaths annually by 2030, and to 3.19 million cases and 1.04 million deaths by 2040.[3] **The projected increases in breast cancer incidence and mortality will impact all WHO regions (Table ES.1) with a greater relative impact on countries with the most limited resources** as measured by the United Nations Human Development Index (HDI) (Table ES.2).

Major improvements in breast-cancer outcomes have been achieved over the past four decades. Between 1990 and 2020, 20 countries successfully achieved reductions in breast-cancer mortality of at least 2% per year for three consecutive years.[4] This led to an overall 40% reduction in breast-cancer mortality in several HICs during the same period. By contrast, limited progress has been made in LMICs, a striking inequality that also marks an opportunity for improving the lives of women globally. **Higher breast-cancer fatality rates in LMICs and among disadvantaged populations result from late-stage diagnosis and limited access to quality treatment, which in several LMICs is compounded by a lack of awareness regarding the benefits of early detection and effective therapies.**[5]

There is a clear need to strengthen health systems so they are to be able to respond to the growing burden of breast cancer, using sustainable, cost-effective, and equitable breast-cancer early detection and treatment services, particularly in LMICs. To be successful and sustainable, **these efforts must be integrated within a community-health framework that engages primary-care facilities, secondary (district) level hospitals, and tertiary-care centres**. These efforts would not only support health promotion, but also empower women to seek and receive health care throughout the life cycle.

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1 Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M et al. Cancer today. Lyon: International Agency for Research on Cancer; 2020 (https://gco.iarc.fr/today, accessed 3 January 2023).

2 Galukande M, Schüz J, Anderson BO, Zietsman A, Adisa C, Anele A et al. Maternally orphaned children and intergenerational concerns associated with breast cancer deaths among women in sub-Saharan Africa. JAMA Oncol. 2021;7(2):285-89.

3 Ferlay J, Laversanne M, Ervik M, Lam F, Colombet M, Mery L et al.. Cancer tomorrow. Lyon: International Agency for Research on Cancer; 2020 (https://gco.iarc.fr/tomorrow, accessed 3 January 2023).

4 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7-33. doi:0.3322/caac.21708 (https://pubmed.ncbi.nlm.nih.gov/35020204/, accessed 6 February 2023).

5 Sharp JW, Hippe DS, Nakigudde G, Anderson BO, Muyinda Z, Molina Y et al. Modifiable patient-related barriers and their association with breast cancer detection practices among Ugandan women without a diagnosis of breast cancer. PLoS One. 2019;14:e0217938. doi: 0.1371/journal.pone.0217938.

Table ES.1. Estimated increases (%) in new cases of and deaths from breast cancer, WHO regions, 2020–2040[3]

Projected increases in 2020–2040 (both sexes, all ages)	WHO Regions					
	African Region	Region of the Americas	South-East Asia Region	European Region	Eastern Mediter-ranean Region	Western Pacific Region
	%					
New breast-cancer cases	91.2	39.1	50.7	12.8	80.5	21.0
Breast-cancer deaths (both sexes, all ages)	93.0	52.3	62.3	25.5	94.2	45.2

Table ES.2. Estimated increases (%) in new cases of and deaths from breast cancer based on country classification, using the United Nations Human Development Index (HDI), 2020–2040[3]

Projected increases in 2020–2040 (both sexes, all ages)	Low HDI	Medium HDI	High HDI	Very High HDI
	%			
New breast-cancer cases	97.2	59.6	30.8	15.8
Breast-cancer deaths (both sexes, all ages)	98.9	69.2	53.6	30.0

3 Ferlay J, Laversanne M, Ervik M, Lam F, Colombet M, Mery L et al.. Cancer tomorrow. Lyon: International Agency for Research on Cancer; 2020 (**https://gco.iarc.fr/tomorrow**, accessed 1 February 2023).

GBCI: evidence-based framework to reduce breast-cancer mortality

To provide strategic guidance and coordination aimed at reducing global breast-cancer mortality in LMICs, WHO established the Global Breast Cancer Initiative (GBCI) in 2021. The goal of the Initiative is to provide evidence-based recommendations for a phased approach to implementing interventions focused on improving early detection, diagnosis, treatment, and supportive services. To improve existing health-care delivery systems, it is necessary to monitor programmatic inputs, outputs, and outcomes to determine possible gaps in care delivery. Three evidence-based key performance indicators (KPIs) have been proposed to identify system gaps that may exist.

GBCI has established the following **three pillars** towards achieving its primary objective.

Pillar 1

Health promotion for early detection (pre-diagnostic interval)

KPI: >60% of invasive cancers are stage I or II at diagnosis

Pillar 2

Timely breast diagnostics (diagnostic interval)

KPI: diagnostic evaluation, imaging, tissue sampling and pathology within 60 days

Pillar 3

Comprehensive breast-cancer management (treatment interval)

KPI: >80% undergo multimodality treatment without abandonment

Pillar 1

Health promotion for early detection

Breast-cancer risk factors include inherited high-risk gene mutations, such as BRCA1 and BRCA2, but these inherited mutations only explain 10–20% of breast cancers at the population level. Hormone-related risk factors associated with reproduction, such as ages at puberty and menopause, pregnancy history and breast-feeding history, have a low impact on breast-cancer risk. However, these factors, like inherited gene mutations, largely cannot be manipulated or controlled to reduce breast-cancer risk. **One of the strongest modifiable breast-cancer risk factors is alcohol consumption**, which in 2016 contributed to 3 million deaths globally and was responsible for 5.1% of the global burden of disease and injury.[3,4] Unfortunately, the significant majority of breast cancers cannot be prevented or avoided through risk-factor modification ("primary prevention"). Therefore, countries need to focus on breast-cancer early-detection programmes so that at least 60% of breast cancers are diagnosed and treated early in their progression (stages I or II), when treatment is most effective, best tolerated and least costly.

The KPI benchmark of Pillar 1 (at least 60% of invasive breast cancers are stage I or II at diagnosis) is based on data showing that every country that has undergone a sustained decline in breast-cancer mortality rates of 2% per year or more for at least three consecutive years has achieved this level of early detection. Conversely, no country where late-stage breast cancer detection is below this level has shown a sustained decline in breast cancer mortality. These findings urge governments to focus on the development of functional, resource-appropriate early-detection programmes.

Early-detection programmatic strategies will vary based on health-system readiness at the national and/or subnational levels. In settings where late-stage breast-cancer presentation is common, and women present with cancers that are easily felt or seen, **stage shifting** is required to increase the fraction of patients initially diagnosed with early-stage disease. Early detection begins with breast-health awareness through the establishment of **early-diagnosis** programmes. These programmes focus on identifying people with signs and symptoms suggesting malignancy and linking them with cancer diagnostic services. **Breast-cancer screening** (an alternate early-detection programmatic strategy in which women in a target age group without recognized signs or symptoms of breast cancer are invited to undergo testing yearly or every other year) may be an aspirational goal once health-system prerequisites have been established. However, organized, population-based screening is not an appropriate or practical initial step in any setting until the required infrastructure and quality-control measures are in place and fully functional. Thus, **all health-care systems require the capacity to diagnose symptomatic breast complaints, such as lumps, thickenings or other clinical detectable abnormalities,** regardless of whether they can afford and effectively organize mammographic-screening programmes.

6 Global status report on alcohol and health 2018. Geneva: World Health Organization. 2019 (**https://apps.who.int/iris/handle/10665/274603**, accessed 10 January 2023).

7 Anderson BO, Berdzuli N, Ilbawi A, Kestel D, Kluge HP, Krech R et al. Health and cancer risks associated with low levels of alcohol consumption. Lancet Public Health. 2023;8(1):e6–e7. doi:10.1016/S2468-2667(22)00317-6.

Pillar 2

Timely breast diagnostics

The KPI benchmark of Pillar 2 (breast cancers diagnosed within 60 days (two months) of initial presentation) is based on the concept that the clinical detection of breast cancers early in their course will improve breast-cancer outcomes only if the pathologic diagnosis and initiation of high-quality treatment are timely. Cancers vary in terms of time to progression, depending on their underlying biology. Thus, health systems must be able to distinguish promptly between malignant and benign breast findings. **Treatment should start within three months of initial presentation** as studies have identified that delay beyond this period leads to lower rates of breast-cancer survival. By securing a definitive diagnosis within two months, the stage is set for initiating treatment within three months.

A **balance between the centralization and decentralization of diagnostic services** is required to achieve prompt breast diagnosis. The achievement of prompt diagnosis within two months of referral requires the coordinated effort of radiologists, pathologists and surgeons and depends on having an **organized patient navigation system** from the primary-care level facility where the patient first presents to the higher-level facility where diagnostic evaluation takes place. **A diagnostic centre needs to be available and accessible to conduct a work-up of breast abnormalities.** By centralizing diagnostic services, quality is better maintained; however, centralized services are less convenient for patients who need to travel to access them, and this can be a source of diagnostic delay. It is undesirable to locate all diagnostic services at a tertiary-care facility, since the number of patients requiring services would be many times larger than the number of those who are ultimately found to have cancer. **Secondary-level hospitals may be the best location for breast diagnostic services** as they are more likely to be geographically accessible, if they can secure the specialized expertise required to maintain quality.

Pillar 3

Comprehensive breast-cancer management

Access to and the affordability of standard breast-cancer treatment is a major obstacle to improving breast-cancer outcomes. **The KPI benchmark of Pillar 3 (>80% of breast-cancer patients complete their recommended treatment)** is based on the notion that access to, including the affordability of, standard breast-cancer treatment is a major barrier in most LMICs. **A large problem in LMICs is the failure to complete treatment, or to its being delayed to such a degree that its therapeutic benefits are limited.** Patients might not be able to complete the full course of treatment for a variety of reasons, including inadequate access to services and unaffordable out-of-pocket expenses. Incomplete treatment leads to poorer patient outcomes, including recurrence and death. Lack of treatment completion also negatively affects quality of life; patients suffer the side-effects of treatment while it is ongoing but do not have the possibility of receiving the full clinical benefits that it has to offer.

Treatment begins with **multidisciplinary planning** whereby a patient-specific management plan based on **evidence-based, resource-adapted guideline-compliant treatment** is formulated. The term "abandonment" refers to failure to complete the planned treatment in its designated time course for reasons other than medical indications for treatment disruption. Abandonment is often the result of health-system failures that are beyond the patient's control. **The rates of, and reasons for, abandonment should be tracked** with the aim of addressing system failures that may have contributed to it. The health system is responsible for assessing itself to determine whether the delivery of cancer treatment for individual patients is in fact realistic and feasible. The **standardization of patient-centred metrics** regarding access to treatments – including patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) – is necessary. In addition to the cancer-directed treatments (surgery, radiotherapy, systemic anti-cancer medications), **supportive services** are essential to patient compliance and effective care delivery during treatment, as well as to recovery following therapy.

Implementation strategies for success

The GBCI Implementation Framework document aims to provide guidance on resource-appropriate strategies for improving the prompt diagnosis of breast cancer at an early-stage and the timely completion of multimodality treatment to improve breast-cancer mortality rates in LMICs. It is anticipated that these measures will stimulate the following.

1

The establishment of national priorities and countrywide engagement to:

- Raise political will for improving outcomes in cancer and other noncommunicable diseases (NCDs)
- Integrate national strategies in a common stepwise approach to health-system strengthening
- Align multiple United Nations and international partners through stakeholder mapping and engagement
- Assess current country capacity and workforce utilization and identify opportunities for improvement
- Establish coherency within national cancer-control planning (including the development of national action plans)
- Generating investments cases for mobilizing domestic and external resources for breast-cancer programmes
- Help in prioritizing technology and infrastructure investments for cancer management not limited to breast cancer

2

The implementation of shared work plans on:

- Developing national standards for the diagnosis and treatment of cancer and the supportive care of people with the disease
- Providing education and training opportunities to balance workforce delegation and ensure task-specific competency
- Improving access to essential medicines and health products
- Promoting community participation

3

Measurement of the impact and quality of steps taken to:

- Strengthen registries and information systems
- Develop quality improvement processes and procedures
- Develop a monitoring and evaluation framework for breast health as an essential component of women's health care, aimed at supporting stakeholders in monitoring and evaluating implemented strategies for addressing deficits in breast-health care

Breast cancer from the global health perspective

Key messages from this chapter

Implementing action according to the three-pillar framework of the breast-cancer patient-care pathway successfully reduces breast-cancer mortality at the population level.

Pillar 1	Pillar 2	Pillar 3
Heath promotion for early detection (pre-diagnostic interval)	Timely breast diagnostics (diagnostic interval)	Comprehensive breast-cancer management (treatment interval)

In line with these three pillars, the three evidence-based key performance indicators (KPIs) make it possible to identify the extent of any system gaps.

Pillar 1	Pillar 2	Pillar 3
KPI benchmark for Pillar 1: >60% of invasive cancers are stage I or II at diagnosis	KPI benchmark for Pillar 2: diagnostic evaluation, imaging, tissue sampling and pathology completed within 60 days	KPI benchmark for Pillar 3: >80% undergo multimodality treatment to completion without abandonment

These strategies are not alternatives. It is necessary to implement action to achieve the KPIs of all three pillars and thus meaningful mortality reductions in line with the GBCI target of 2.5% per year.

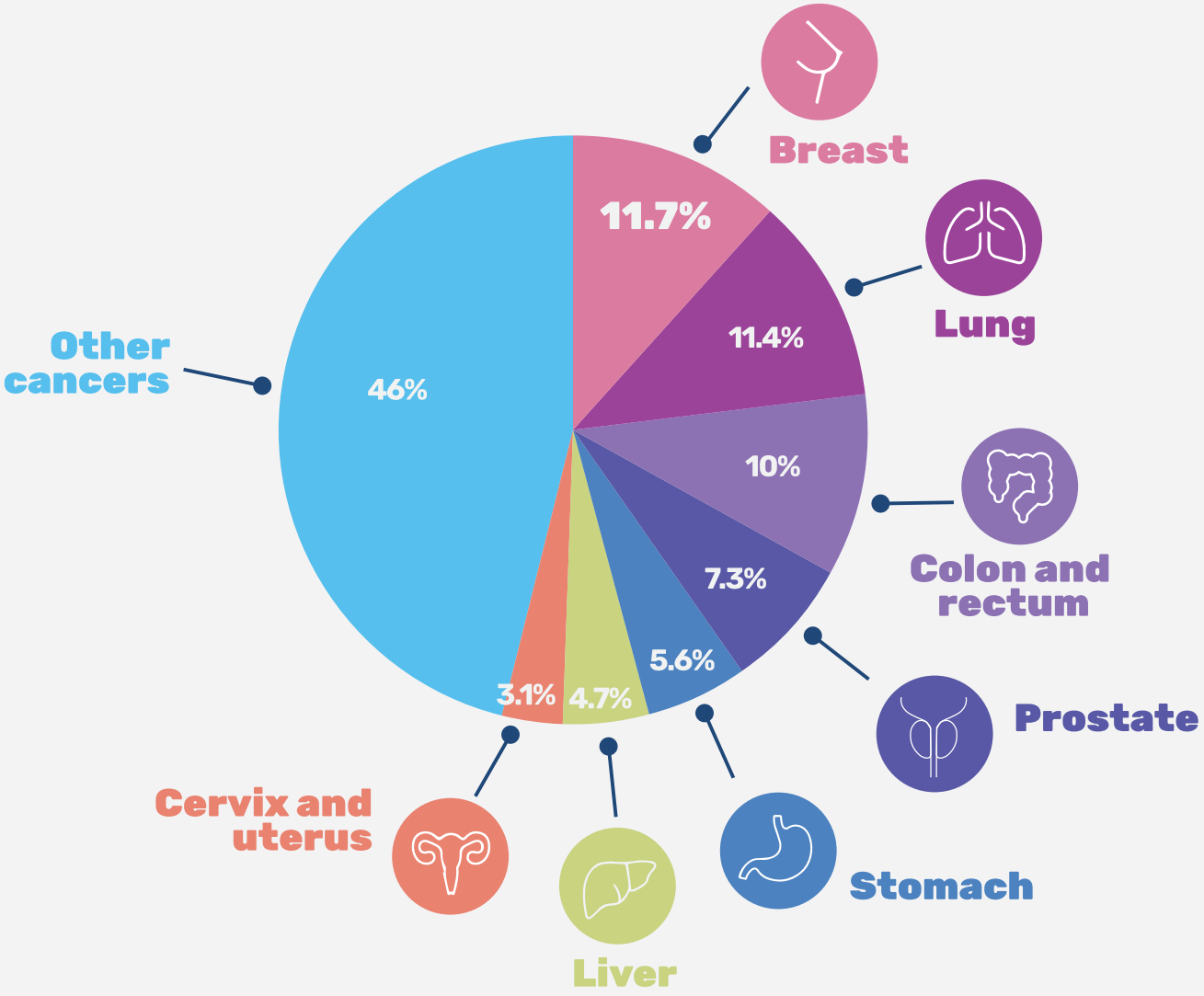
What is breast cancer?

Breast cancer is a malignant growth that arises in the ducts (85%) or lobules (15%) of the breast gland. Initially, the cancerous growth is confined to the duct (in situ) where, generally, it causes no symptoms and has minimal potential for distant spread (metastasis) through the lymphatics to the lymph nodes, or through the blood to distant organs (most commonly the lung, liver, bones, or brain). Over time, these in situ (stage 0) cancers can progress and invade the surrounding breast tissue (invasive breast cancer). Invasive cancers have the potential to spread to the nearby lymph nodes (regional metastasis) or to other organs in the body (distant metastasis). Reducing the fraction of patients presenting with distant metastasis is essential to improving breast-cancer survival rates at the population level.

Epidemiology

Breast cancer has become the form of cancer most commonly diagnosed globally, accounting for nearly 12% of all cancer cases worldwide in 2020 (Fig. 1). The disease can also arise in males although these cases represent fewer than 1% of all cancer cases worldwide *(1)*. In 2020, 2.3 million women were diagnosed with breast cancer, with 685 000 deaths globally. At the end of 2020, 7.8 million women who had been diagnosed with breast cancer in the previous five years were still alive, making this form of cancer the most prevalent in the world *(2)*.

Fig. 1. Percentage of cancer cases in 2020 worldwide, including both sexes and all ages



Source: reproduced with permission of the publisher, International Agency for Research on Cancer, from Ferlay et al (*2*).

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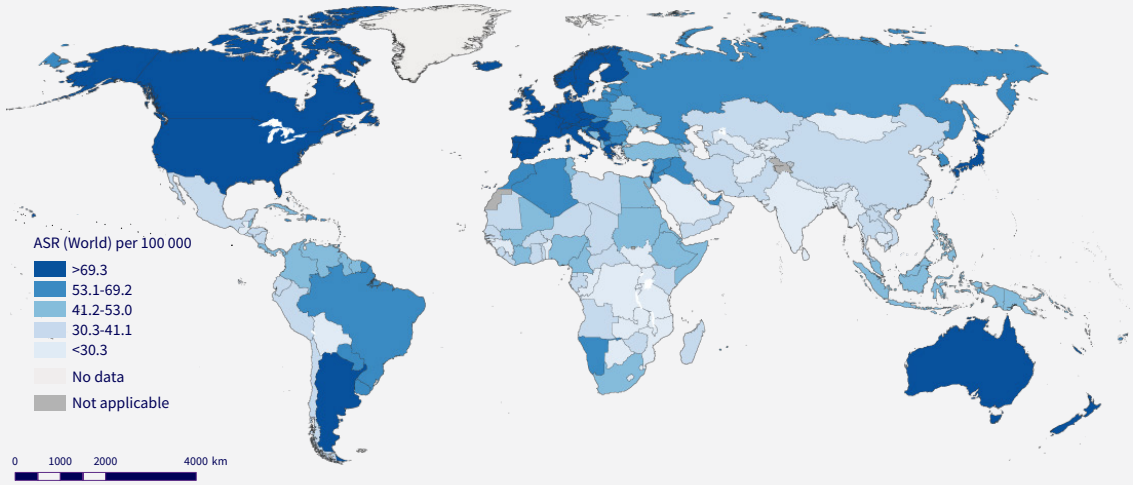
HICs have the highest incidence of breast cancer, in part because of successful breast-cancer screening programmes that initially lead to increased rates of breast-cancer diagnosis (Map 1a). Even in the absence of screening, breast cancer is the most common cancer among women in 158 of 185 countries around the globe (Map 1b). Breast-cancer mortality disproportionately affects LMICs) where over 70% of breast-cancer deaths are premature, occurring in individuals under 70 years of age (Box 1).

Box 1. Breast-cancer mortality rates

Mortality rates from breast cancer have been declining in many HICs. This change is attributable to the combination of greater population awareness, an increase in early detection, timely diagnosis, and effective treatment strategies.

Map 1a. Estimated age-standardized incidence rates for female breast cancer, by country, all ages, 2020



Data Source: GLOBOCAN 2020, International Agency for Research on Cancer (IARC), http://gco.iarc.fr/today
Map Creation Date: 02 December 2022
Map Production: WHO GIS Centre for Health, DNA/DDI

Notes. HICs in North America, Western Europe and Australasia have the highest rates of breast-cancer incidence globally, attributable in part to their having active early-detection programmes, including but not limited to mammographic screening.
ASR = age-standardized rate.
Source: reproduced with permission of the publisher International Agency for Research on Cancer from Ferlay et al *(2)*.

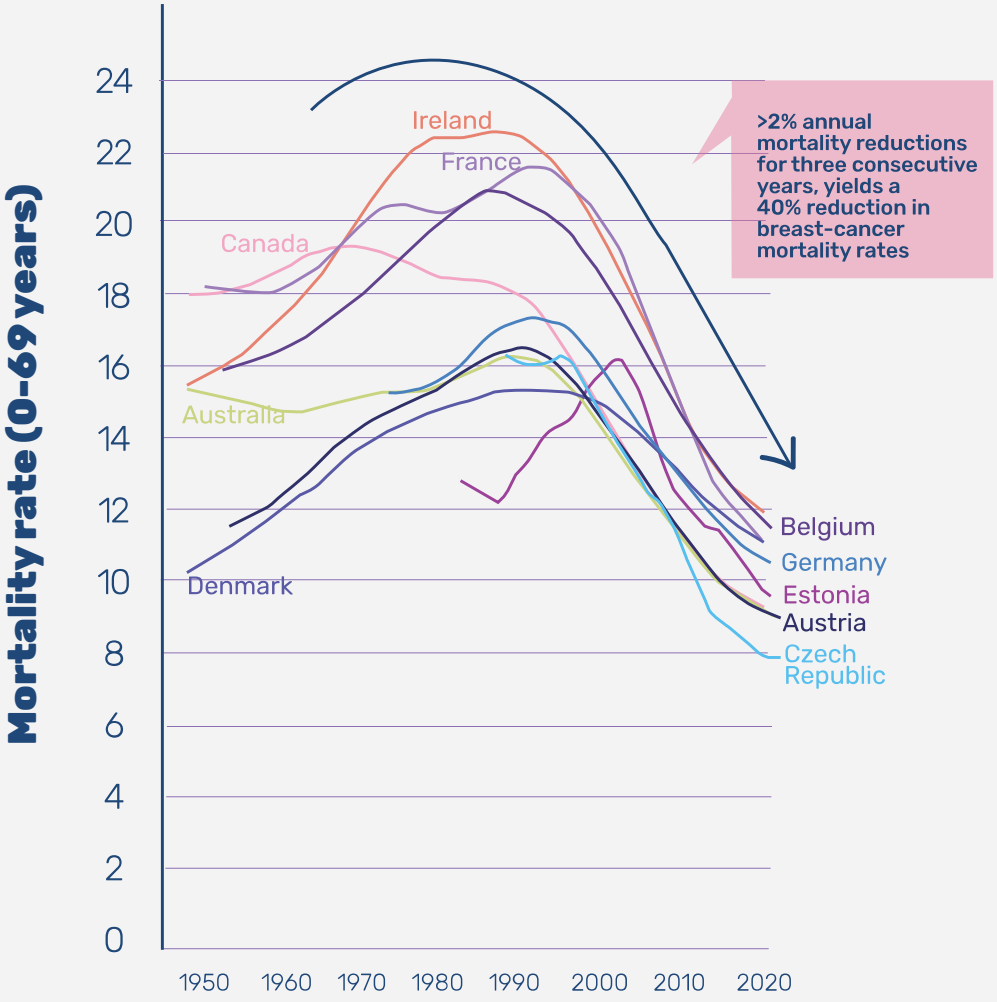
Map 1b. Ranking of female breast cancer based on estimated age-standardized incidence rates, by country, all ages (excluding non-melanoma skin cancers), 2020

Data Source: GLOBOCAN 2020, International Agency for Research on Cancer (IARC), http://gco.iarc.fr/today
Map Creation Date: 02 December 2022
Map Production: WHO GIS Centre for Health, DNA/DDI

Note. In 160 out of 185 countries in the world, breast cancer is the most common cancer among women and the second most common cancer in 23 countries. Only two countries in the world do not list breast cancer as the first or second most common cancer among women.
ASR = age-standardized rate.
Source: reproduced with permission of the publisher, International Agency for Research on Cancer, from Ferlay et al *(2)*.

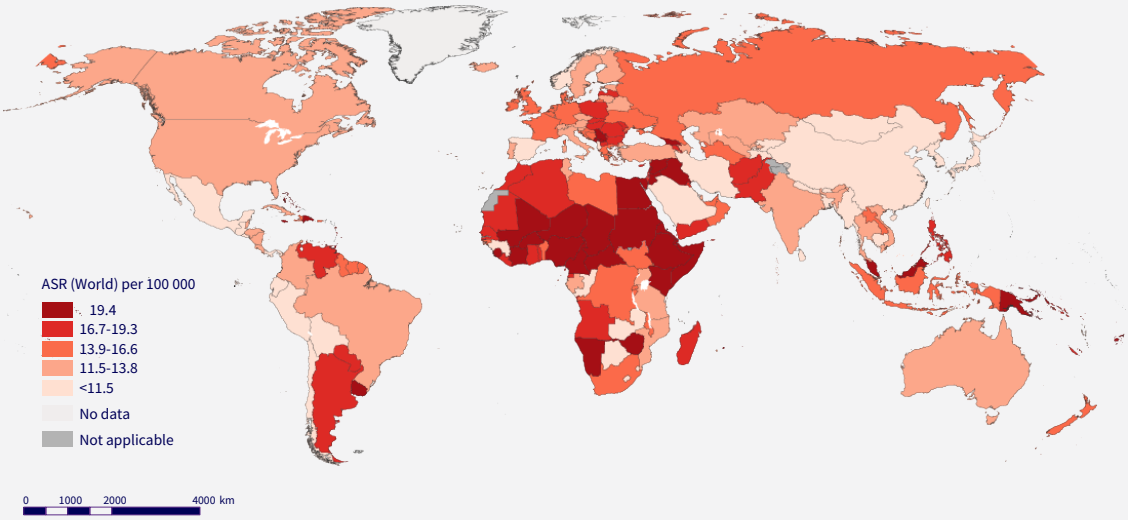
Breast cancer was the leading cause of cancer-related deaths among women in HICs, including the United States of America, for at least two decades from 1950 through the mid-1980s at which point lung cancer surpassed breast cancer as the leading cause of female cancer-related deaths *(3)*. In 1990, multiple HICs began to show a uniform decline in breast-cancer mortality rates of 2% per year or more (Fig. 2) *(4)*. While breast cancer mortality has decreased by 40% in HICs over the past three decades, it remains stubbornly high in the significant majority of LMICs (Map 2a). In 2020, breast cancer was the leading cause of cancer deaths in 107 of 184 countries (Map 2b), a number that is anticipated to rise in the coming years.

Fig. 2. Age-standardized breast-cancer mortality rates in 10 countries with established cancer-care systems, 1950–2020



Note. Between 1990 and 2020, each of these selected countries demonstrated >2% annual mortality reductions for at least three consecutive years, yielding a 40% overall breast-cancer-mortality reduction. For a complete analysis of 148 countries, their national health-system characteristics, breast-cancer stages at diagnosis and breast-cancer mortality, see Duggan et al 2021 *(4)*.
Source: reproduced with permission from the publisher, Elsevier Ltd., from Duggan et al *(4)*.

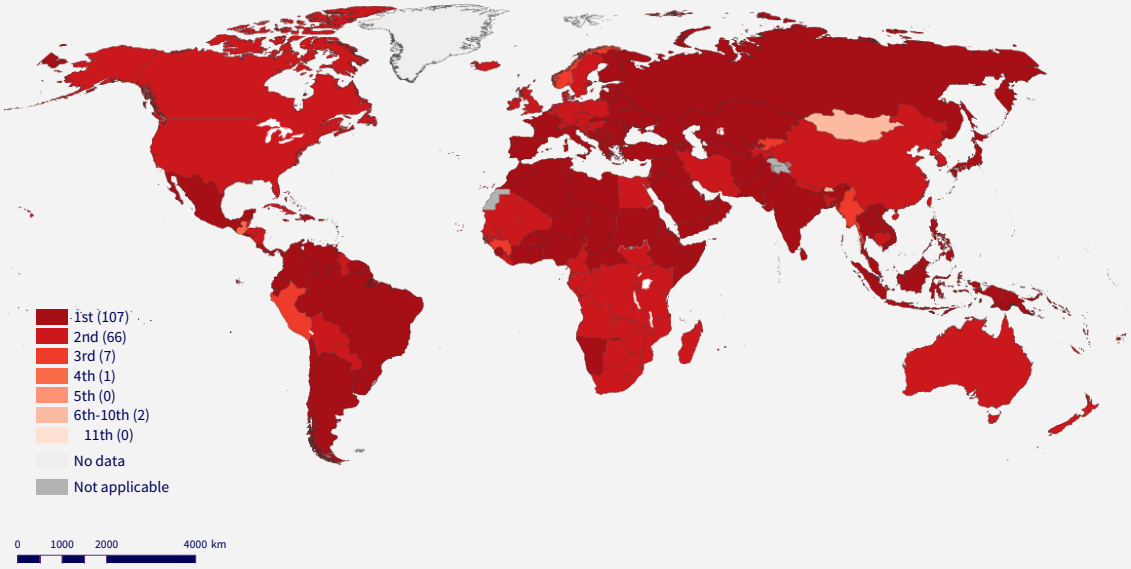
Map 2a. Estimated age-standardized mortality rates for female breast cancer, by country, all ages, 2020.



Data Source: GLOBOCAN 2020, International Agency for Research on Cancer (IARC), http://gco.iarc.fr/today
Map Creation Date: 02 December 2022
Map Production: WHO GIS Centre for Health, DNA/DDI

Note. The highest age-standardized breast-cancer mortality rates (>19.4/100 000 women) are found in LMICs on all continents, with the greatest breast-cancer mortality rates in Africa, Latin-America, eastern Europe, the Middle East and the Western Pacific.
ASR = age-standardized rate.
Source: reproduced with permission of the publisher International Agency for Research on Cancer, from Farlay et al *(2)*.

Map 2b. Ranking of female breast cancer based on estimated age-standardized mortality rates, by country, all ages (excluding non-melanoma skin cancers), 2020.



Data Source: GLOBOCAN 2020, International Agency for Research on Cancer (IARC), http://gco.iarc.fr/today
Map Creation Date: 02 December 2022
Map Production: WHO GIS Centre for Health, DNA/DDI

Note. Breast cancer is the first or second most likely cause of female cancer deaths among 175 of 185 countries around the world.
Source: reproduced with permission of the publisher, International Agency for Research on Cancer, from Farlay et al *(2)*.

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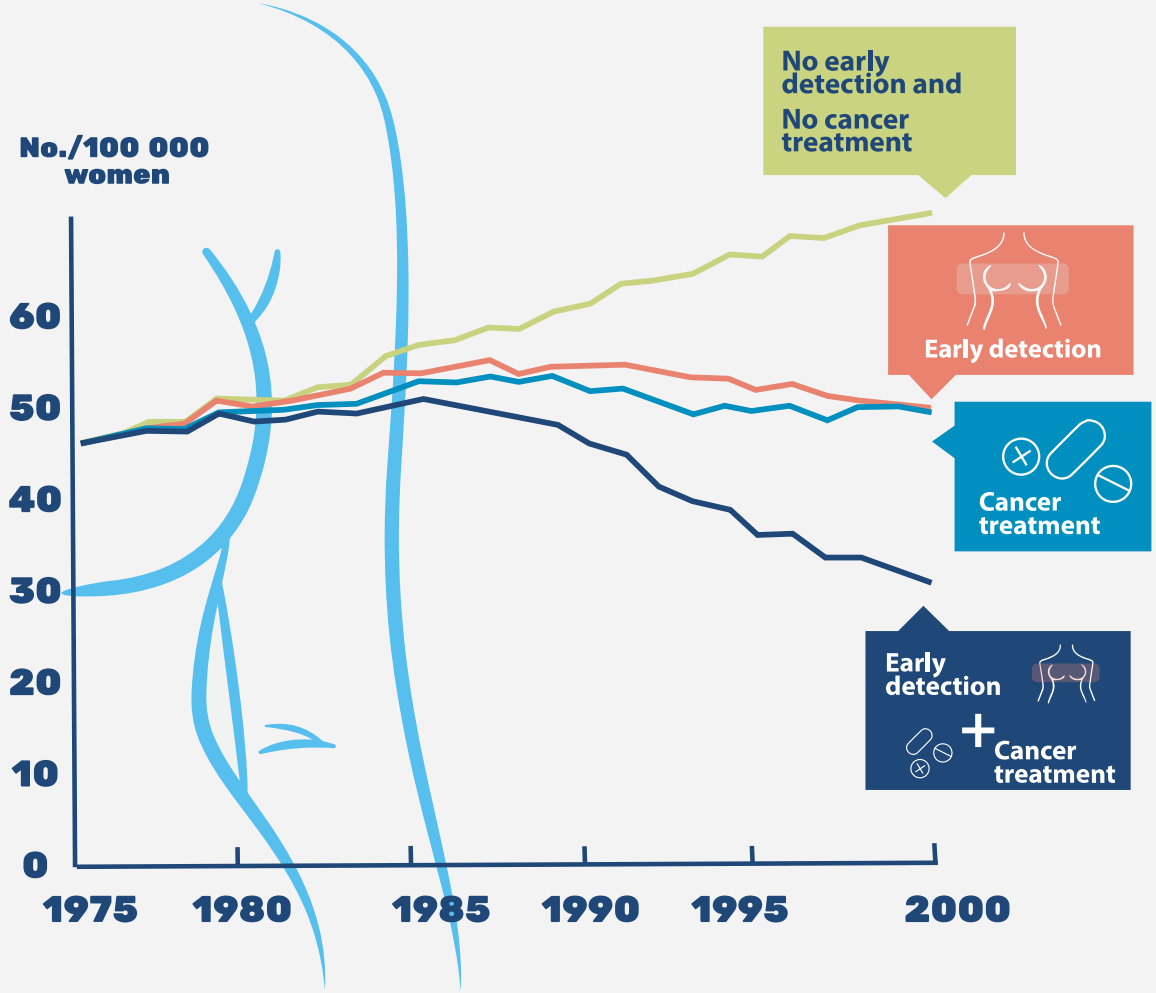
Linked strategies for improving breast-cancer outcomes

A combination of three strategies have successfully reduced breast-cancer mortality at the population level: **(1) early detection (including both early-diagnosis and screening programmes)**; **(2) prompt and accessible diagnostic services (to distinguish malignant from benign breast abnormalities);** and **(3) effective multimodality therapy (including surgery, radiotherapy and systemic anti-cancer treatment regimens)**. These strategies are not alternatives as it is necessary to administer all three in sequence to achieve meaningful mortality reductions (Fig. 3). **Countries where the majority of cases present at a late stage are unlikely to improve their national breast-cancer mortality rates.** In those where a sustained reduction in breast-cancer mortality has been achieved, at least 60% of the invasive cancers diagnosed were stages I or II *(4)*. However, early detection alone cannot reduce breast-cancer mortality rates even when cancers are promptly diagnosed. **Once diagnosed, breast cancer must be treated according to evidence-based, stage-appropriate guidelines if survival outcomes are to be improved.** While policy-makers may feel compelled to focus on the procurement of expensive biological medications, such as trastuzumab, a more important priority is the establishment of timely access to standard treatment regimens, using cytotoxics/chemotherapy and endocrine (hormonal) medications, without which targeted biological therapies will be predictably ineffective. Of historic note, the improved breast-cancer survival rates observed in HICs during the 1990s were achieved several years before targeted biological therapies were employed for the management of non-metastatic breast cancer. It is equally important to recognize that **systemic treatment regimens can only be successful when the full treatment courses are administered to completion.** Treatment abandonment, in which patients prematurely discontinue treatment for non-medical reasons, may be the worst outcome for a cancer programme, because it exposes patients to the toxicity and side effects of costly treatment while failing to achieve the evidence-based clinical benefit that is predicted with treatment completion.

In 2021, WHO launched the **Global Breast Cancer Initiative (GBCI)**, the primary objective of which is to reduce global breast-cancer mortality by increasing access to early measures of breast-cancer detection, ensuring prompt comprehensive cancer management, and adapting practical and sustainable approaches to the local contexts and available resources in LMICs *(5)*. **The Initiative's goal is to assure feasibility and quality in these countries by providing evidence-based recommendations for a phased approach to implementing interventions focused on improving early detection, diagnosis, and treatment.** In addition, monitoring and evaluation related to these interventions are also recommended before scaling up programmes. The participation of advocacy groups, stakeholders and policy-makers is strongly encouraged to increase involvement and investment in programme sustainability (Box 2) *(5)*.

Fig. 3. Modelled breast-cancer death rates with early detection and/or multimodality treatment



Source: reproduced with permission of the publisher, Massachusetts Medical Society, from Berry et al. *(6)*.

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Box 2. GBCI recommendations

The GBCI recommendations are intended for dissemination to a broad target audience, including ministries of health, other governmental and allied policy-makers, nongovernmental organizations (NGOs) (including professional organizations, researchers and the academic community), and programme managers. They represent a call for action to each of the allies regarding the development of implementation projects in a variety of settings globally (with an emphasis on LMICs), and in underrepresented and under-resourced communities in HICs *(5)*.

The GBCI approach for improving global breast-cancer outcomes is to leverage what has been learned in HICs about effective breast-cancer prevention, detection, and management strategies for designing country-specific, resource-appropriate health systems for the delivery of breast-cancer care *(5)*. These systems are the same as those required to manage other solid cancers (e.g., cervical, gastrointestinal, prostate, and lung cancers) since they utilize similar combinations of surgery, radiotherapy, and systemic treatment (cancer-directed medicines) that, together with supportive-care medicines and services, make the completion of treatment regimens possible. Thus, it can be anticipated that **the establishment of this general approach to strengthening health systems would have synergistic benefits for other malignant and non-malignant noncommunicable diseases (NCDs) as well.**

Features of effective breast-cancer control programmes

A WHO analysis performed in 2021, involving 148 countries *(4)*, identified two characteristics of national health systems that are associated with lower breast-cancer age-standardized mortality rates, namely: a higher number of public cancer centres per 10 000 cancer patients (availability and quality of care) and higher degrees of universal health coverage (UHC) (financial protection). Neither the creation of public cancer centres nor the establishment of UHC is a simple intervention at the health-system level, especially when meaningful steps in health-system strengthening must be sustainable over time to be effective. Nonetheless, these findings illustrate that when patients lack access to diagnostic and treatment services for cancer, or **when the receipt of cancer treatment depends on patient out-of-pocket payment – that predictably leads to treatment interruptions or failure to complete the full course of therapy** (treatment abandonment) – a decrease in breast-cancer mortality rates over time cannot be anticipated (Box 3).

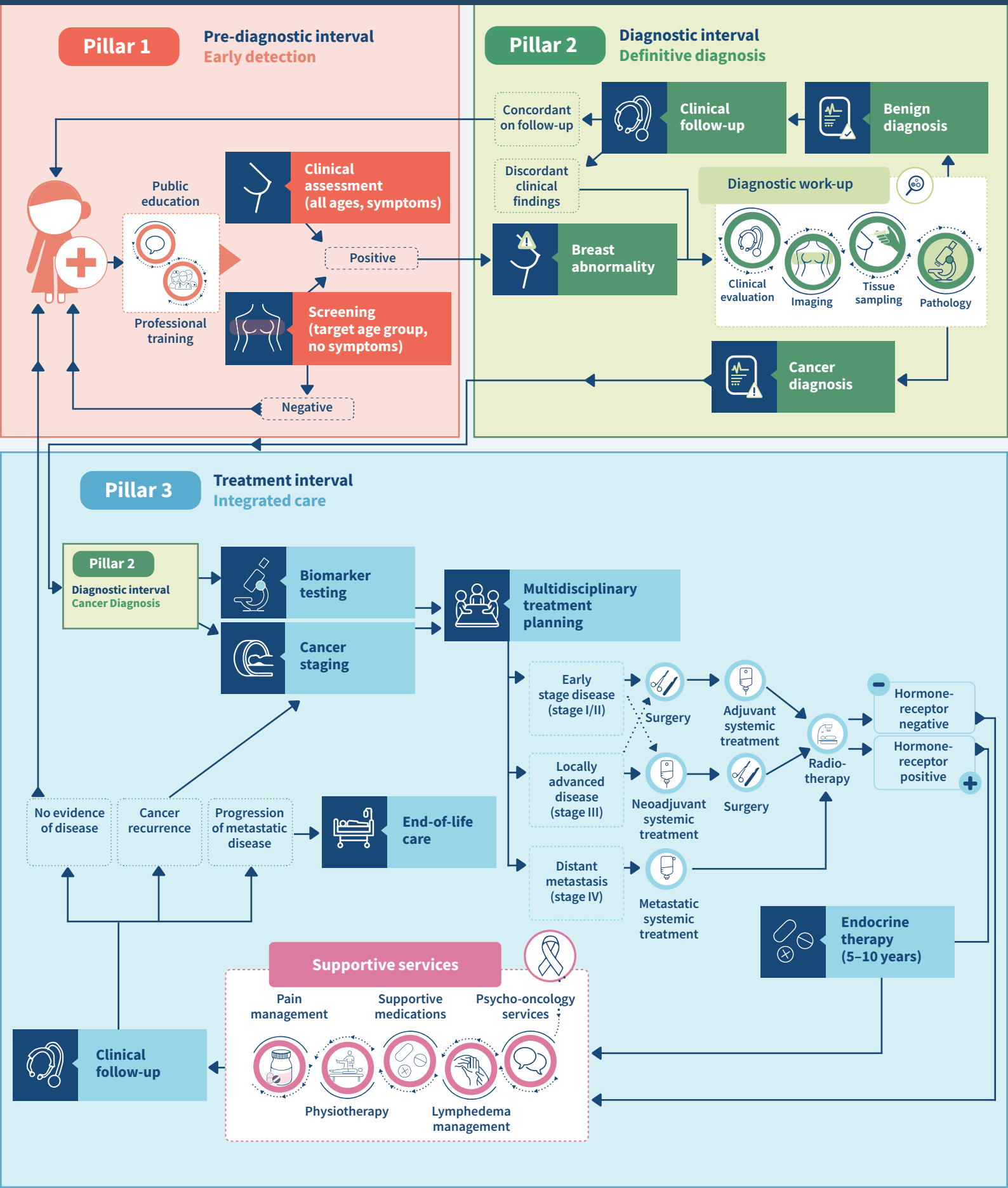
To create a framework for organizing the functioning of these resources, **the GBCI defines three pillars based on the breast-cancer patient-care pathway** (Fig. 4) *(5)*. These pillars illustrate how patients in health systems that have successfully reduced breast-cancer mortality are able to access the required services. In addition to defining specific clinical processes and outcomes to be achieved, **the proposed framework identifies health-system requirements for implementation of the recommended interventions in the case of each GBCI pillar.**

Box 3. Elements of successful breast-cancer-control programmes

Beyond geographic access and funding for diagnosis and treatment, successful breast-cancer-control programmes provide:

1. accurate and actionable information (for the public) about strategies for the reduction and prevention of cancer risk, and early detection of the disease;
2. access to prompt diagnostic services for work-ups with a view to possible breast malignancies;
3. multidisciplinary treatment planning linked to the delivery of quality treatment and supportive care (through the course of disease management).

Fig. 4. The three pillars of the GBCI breast-cancer patient-care pathway



Overview of the three GBCI pillars

Within a health-system framework, the breast-cancer patient-care pathway is defined by three sequential intervals (Fig. 4) (Box 4). This pathway, through which all patients must navigate to address their breast-health needs, is based on the biological features of the disease, and has the same patient-management structure, regardless of the economic level or resource status of the country in question. Each GBCI pillar defines specific clinical processes to be followed and outcomes to be achieved during a patient-care interval *(5)*.

In addition to these fundamental components that facilitate the early detection, diagnosis and treatment of the disease, supportive services (including palliative care) are available to patients throughout the course of disease management. These minimize the adverse impact of both the disease and the treatment. These services encompass the physical, psychological, social, and spiritual support of patients through the continuum of the disease.

The three pillars of the breast-cancer patient-care pathway summarize complex information, establishing a common needs-based understanding and integrated approach for all stakeholders working to improve breast-cancer outcomes (Box 4) *(5)*.

Box 4. The three-pillar framework of the breast-cancer patient-care pathway

This framework requires:

- policy-makers to assess policies related to health-system strengthening and determine any gaps, based on clinical targets and goals;
- health-care administrators to recognize system gaps for which they need resources and personnel to perform required tasks within appropriate timeframes;
- clinicians to define and explain the services they need to diagnose and manage breast cancer in their settings;
- community-based organizations and patient and advocacy groups to define the services they require to improve outcomes at the patient, family and community levels, and to frame advocacy messages *(5)*.

Pillar 1

The pre-diagnostic interval

GBCI defines the pre-diagnostic interval as the period that begins when the patient first presents to the health-care system for an evaluation of a breast complaint and/or seeks to participate in breast-cancer early-detection programmes and ends with referral for diagnostic evaluation of possible breast abnormalities. Individuals enter the detection phase of the pre-diagnostic interval either by: (i) presenting to the clinic or other centre with a breast symptom, such as a lump, mass, or breast change, that may require diagnostic evaluation; or (ii) presenting without symptoms, but wishing to undergo early-detection measures because they are appropriate candidates for breast-cancer screening and have access to a system with the resources and quality controls necessary to support and maintain a screening programme. The timing of a patient's entry into the health system will be impacted by activities, such as awareness education. This makes public education and professional training programmes integral components of Pillar 1 before the start of the pre-diagnostic interval *(5)*.

An individual with symptomatic breast cancer can navigate through the local health-care system in a variety of ways before receiving a clinical evaluation and diagnostic testing. For example, health care is organized in many countries in a three-tier system whereby health posts or health clinics provide primary-care services for a variety of medical issues, thus serving as the first entry point. Primary- or secondary-level hospitals may be equipped with the appropriate health-care providers, supplies and tools to provide diagnostic or surgical interventions, or a more complex level of medical care. Tertiary or referral hospitals may serve as comprehensive, specialized facilities that provide complex medical treatment, such as multidisciplinary care for breast-cancer patients.

Pillar 2

The diagnostic interval

Patients with clinical or image-based findings transition to the diagnostic interval when they are referred for diagnostic work-up. Breast-cancer diagnosis involves obtaining tissue from clinically or radiologically suspicious lesions. The options for biopsy procedures include core-needle biopsy (gold standard), fine-needle aspiration, or incisional biopsy. The optimal sampling methodology will vary, depending on the availability of equipment and trained staff, which includes radiologists and clinicians to perform needle-biopsy procedures and pathologists to interpret the results of the needle samples *(5,7)*.

Pillar 3

The treatment interval

Personalized multidisciplinary treatment consists generally of surgery +/- radiation therapy to control the disease in the breast, lymph nodes and surrounding areas (locoregional control), and systemic therapy (anti-cancer medicines given orally or intravenously) to treat and/or reduce the risk of the cancer spreading (metastasis). The prescribed treatment regimen is planned by a team of multidisciplinary health-care providers in surgery, radiation oncology, medical oncology, pathology and radiology, with the support and advice of nurses and social workers to determine what treatment plans can be realistically carried to completion. The goal of the treatment is to cure the patient, that is to completely eradicate the disease. This can be achieved with effective treatment in over 90% of women diagnosed with early-stage disease (stages I or II). The optimal effectiveness of breast-cancer therapies depends on initiating treatment within three months of the detection of symptoms, and on completion of at least 80% of the full course of treatment *(5)*.

Key performance indicators for the three GBCI pillars

To improve existing health-care delivery systems, it is necessary to monitor programme input, output, and outcomes to determine possible gaps in care delivery. Three evidence-based key performance indicators (KPIs) have been proposed to identify where these may exist (Table 1).

Table 1. KPIs and targets to evaluate the breast-health-care system

Title	Indicator	Concept	Benchmark
Pre-diagnostic interval			
TNM stage distribution	Proportion of TNM breast-cancer cases diagnosed at stages 0–IV	Achievement of reductions in mortality rates and a sustained (>2 years) national TNM stage of >60% stage I or II	>60% stage I or II invasive cancers, excluding unstaged and stage 0 *(4)*
Diagnostic interval			
Time to diagnosis	Timeliness of confirmatory diagnosis of invasive breast cancer in patients with suspicious breast complaints	Scope of the health-system to diagnose patients with signs and/or symptoms of breast cancer within two months of presentation at a facility with the capacity for diagnosing breast cancer	> 80% of patients to receive a diagnosis within two months of initiation of diagnostic evaluation at a facility with capacity for diagnosing breast cancer *(8)*
Treatment interval			
Treatment completion	Proportion of breast-cancer patients who complete the recommended therapy without abandonment	The association of completion of recommended treatment with improvements in outcomes	>80% of patients with a diagnosis of invasive breast cancer initiate and complete their recommended course of treatment without abandonment *(9)*

Pillar 1

The pre-diagnostic interval

KPI benchmark for Pillar 1: 60% or more of invasive breast cancers are stage I or II at diagnosis

Every country that has shown a sustained decline in breast-cancer mortality rates of 2% per year or more for at least three consecutive years has achieved the above benchmark *(4)*.

No country with late-stage breast-cancer detection has shown a sustained decline in breast-cancer mortality. These findings urge countries to focus on early detection strategies *(5)*.

Importantly, a cancer is staged when it is first diagnosed, after a complete diagnostic work-up and prior to the initiation of treatment. Therefore, assessment of stage distribution in a population and adherence to this KPI is also part of the pre-diagnostic interval (Pillar 1) *(5)*.

Pillar 2

Diagnostic interval

KPI benchmark for Pillar 2: breast cancers diagnosed within 60 days (two months) of initial presentation

The clinical detection of breast cancers early in their course will improve breast-cancer outcomes only if the pathologic diagnosis and initiation of high-quality treatment is timely. Cancers vary in terms of time to progression, depending on their underlying biology. Thus, health systems must be able to distinguish promptly between malignant and benign breast findings. Treatment should start within three months of diagnosis as studies have identified that delay beyond this period leads to lower rates of breast-cancer survival *(8)*. By securing a definitive diagnosis within two months, the stage is set for initiating treatment within three months.

Pillar 3

Treatment interval

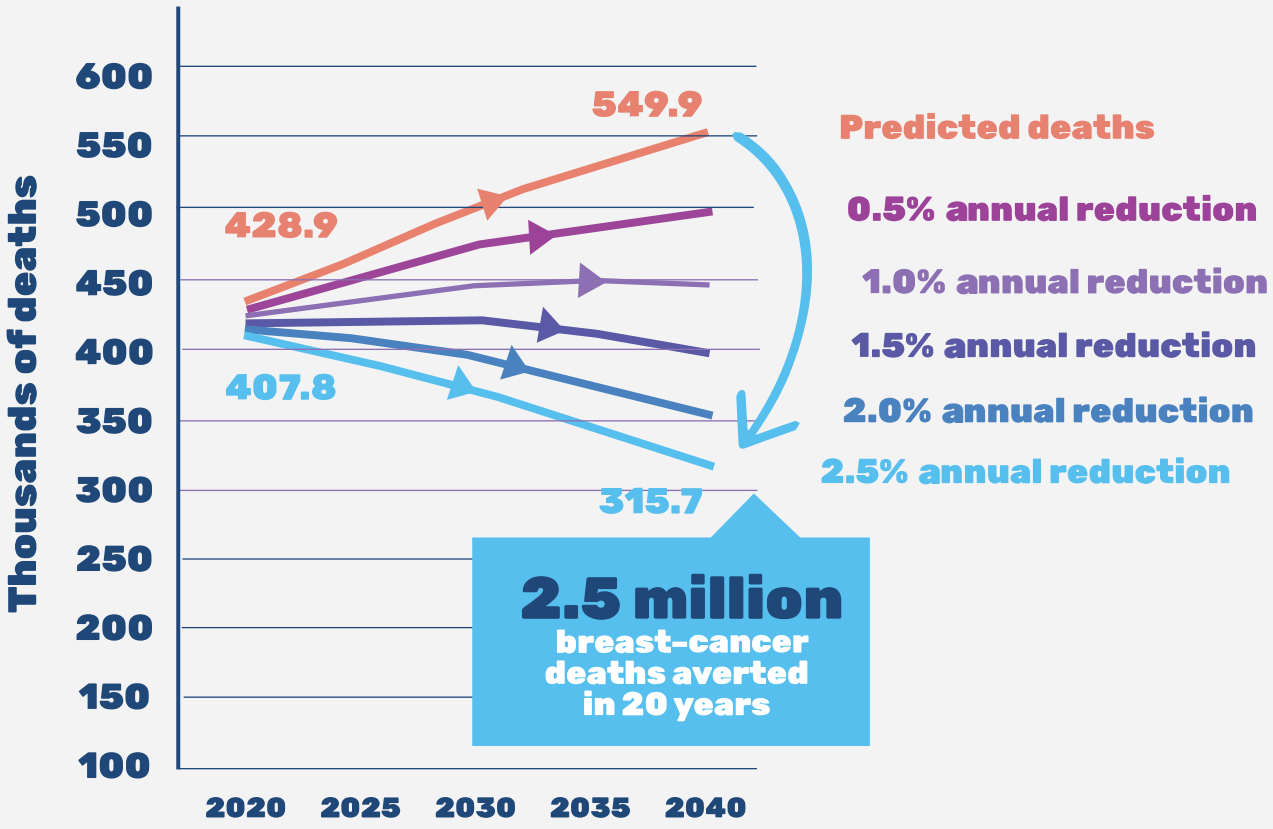
KPI benchmark for Pillar 3: >80% of breast-cancer patients complete their recommended treatment

Access to and the affordability of standard breast-cancer treatment are major obstacles to improving breast-cancer outcomes. One of the most common challenges in LMICs relates to patients who do not complete the treatment initiated or have such significant delays in doing so that the therapeutic benefits are limited *(9)*. Patients might not be able to complete the full course of treatment for a variety of reasons, including inadequate access and unaffordable out-of-pocket expenses. Incomplete treatment leads to poorer patient outcomes, including recurrence and death. Lack of treatment completion also negatively affects quality of life because patients suffer the side-effects of treatment but fail to receive its full clinical benefits.

Predicted impact of GBCI on the improvement of breast-cancer outcomes

Breast-cancer mortality among individuals under age 70 is projected to increase globally by 28% between 2020 and 2040 (Fig. 5) *(10)*. At present, more than 10 million breast-cancer deaths are predicted to occur over this 20-year period (Fig. 5). If the mortality risk could be reduced by 1% annually, this rising breast mortality would plateau (Fig. 5). If breast-cancer mortality could be lowered by 2.5% annually, which is less than decreases occurring in HICs since 1990, the cumulative number of averted breast-cancer deaths would be 2.5 million over 20 years – the aspirational goal of GBCI *(5)*.

Fig. 5. Projected annual global breast-cancer deaths in females under age 70, 2020–2040



Note. Based on current predictions for women under age 70 (top line) and different annual mortality reductions from 0.5% per year to 2.5% per year, using the International Agency for Research on Cancer (IARC) GLOBOCAN 2020 "Cancer over time" risk-reduction model *(5)*.
This figure is reproduced with permission of the publisher, Elsevier Ltd., from Anderson, et al *(5)*.

Investment case for action on breast cancer

Due to the high volumes of breast-cancer patients, **the allocation of budgets must be made with financial sustainability in mind.** It is critical to ensure that expenditure is efficient and effective, and that the focus is on patient outcomes. In determining the services and equipment required to achieve the target outcomes, it is important that the priority-setting process allows for stakeholder input and joint decision making on investment in medical devices and related infrastructure *(11)*. While the generation of complete country-specific cost-effectiveness analyses goes beyond the scope of this framework document, in generating investment cases, it should be recognized that systems supporting breast-cancer care provide a foundation for all oncology care (which also applies to some specific NCDs). **The development of systems to address the breast-cancer burden can contribute to strengthening the health-care system through quality control, technology introduction and human-resources development.** By treating breast cancer (the most common cause of female cancer-related death and disability-adjusted life years lost) as a public health priority, countries can potentially strengthen their entire health systems (Box 5).

In countries where efforts to detect early-stage breast cancer are new, and the diagnosis of late-stage breast cancer is common, **a phased implementation approach is needed to permit the development of programmes and infrastructures that can sustainably support the required early-detection activities.** In the first (preparatory) phase, early-diagnosis services are established while treatment resources are scaled up to prepare for the predicted rise in the volume of breast-cancer patients. The preparatory phase, before the initiation of population-based screening programmes, is essential since the number of patients diagnosed with cancer and requiring treatment based on early-diagnosis efforts alone could predictably double in its 5-year course. In the subsequent phase(s), early-detection efforts can be expanded to include screening, using (i) clinical-detection strategies (clinical breast assessment alongside targeted clinical breast examination (CBE)-led screening), (ii) mammographic (MG) screening of the target population (MG-led screening), or a customized combination of the two based on health-care resources, workforce training, geographic constraints and other country-specific issues identified during an initial country-specific situation analysis.

Box 5. The generation of a breast-cancer investment case

In generating an investment case for breast cancer, country-specific analyses need to be performed for: **(1)** the early detection of breast cancer; and **(2)** the determination of breast-cancer treatment, taking national priorities, health-delivery context, and available resources into account.

Case study
Economic evaluation of breast-cancer control in Kenya, 2022

In 2020, the Kenyan Ministry of Health partnered with the World Bank to create an investment case for combatting NCDs. Working in collaboration with WHO and GBCI, the group developed a health-system model to predict breast-cancer outcomes and related implementation costs. The resulting Kenya model for early detection proposes a 15-year implementation plan, using a phased implementation approach (Box 6, Fig, 6A) and examines outcomes projected to 15-years (Fig. 6A, Table 1A) and 40-years (Fig. 6B, Table 1B) *(12)*.

During the first five years, health-system strengthening focuses on: (i) the establishment of diagnostic services to work-up clinically detectable breast changes, thereby establishing early diagnosis services, combined with (ii) the scaling-up of treatment services, which will be required to prepare for the increased patient volumes that are anticipated to result from these early diagnosis efforts. In years six to fifteen, Kenya plans to establish screening programmes based on a combination of CBE-led screening and MG-led screening, utilizing the infrastructure and programming established during the first five years. The following predictions and cost estimates were projected, using the Kenya model and based on the Kenya-specific baseline data collected through an initial (current status) situation assessment.

Box 6. The Kenya model for early detection

The Kenya model for early detection launched in 2022 includes:

- creation of demand (awareness campaigns through traditional and social media, advocated by community, religious and other leaders);
- training (of health workers to increase breast-cancer awareness, the use of CBE, and of imaging, laboratory and health-records personnel);
- service delivery (eight breast-cancer centres of excellence have been established, imaging services have been set up in 47 counties, and quality pathology services and strong linkage and referral structures are in place);
- monitoring and evaluation (paced, planned assessments) *(12)*.

Short-term (5-year) outcomes

Cancer stage
During the first phase of the Kenya model, when early diagnosis systems are established prior to the introduction of screening, stage shifting is predicted to occur where the fraction of patients diagnosed with invasive breast-cancer disease stages I and II is estimated to increase from 31% prior to implementation (current state) to 50% at five years after implementation (Fig. 6A).

Initial costs
Kenya's annual health expenditure will increase by 0.6% (future costs undiscounted).

Diagnosis
Over the first 5-year period, 8100 more cases of breast cancer will be diagnosed than would have been the case if Kenya had not launched this breast-cancer, early-detection and cancer-treatment programme.

Treatment
The number of women who receive breast-cancer treatment will more than double: 4700 lives saved in the first five years will be attributable to increased rates of late-stage cancer treatment.

Medium term (15-year) outcomes

Costs
According to the model, Kenya's annual health expenditure estimates in the early-diagnosis-only, the CBE-led, and the MG-led screening scenarios (future costs undiscounted) are predicted to increase by 0.7%, 1.3% and 2.3%, respectively. Screening efforts constitute 37% of the total estimated cost in the MG-led scenario, compared to only 5% in the CBE-led scenario.

Diagnosis
It is predicted that, by 2037, 15 years into the programme and with fully-scaled screening programmes in place, a higher share of women will be diagnosed in the early stages: 63% in the CBE-led screening scenario, and 69% in the MG-led scenario (Fig. 6A); in both cases, the results exceed the GBCI KPI benchmark for Pillar 1 (≥60% stage I or II for invasive breast cancers).

Treatment
The total cost of treating breast cancer will increase because more breast-cancer cases will be diagnosed and treated (Table 1A). However, the average treatment costs per person will decrease because more early-stage cases, requiring less-intensive forms of therapy, will be identified.

Mortality reduction
Breast-cancer survival rates improve as late-stage diagnoses decrease and more women receive treatment for breast cancer in the early stages (Fig. 6B). Over the 15-year period of the investment case, the early-diagnosis scenario will prevent over 33 600 deaths from breast cancer. The numbers for the CBE-led scenario and the MG-led scenario will be 44 900 and 50 600, respectively.

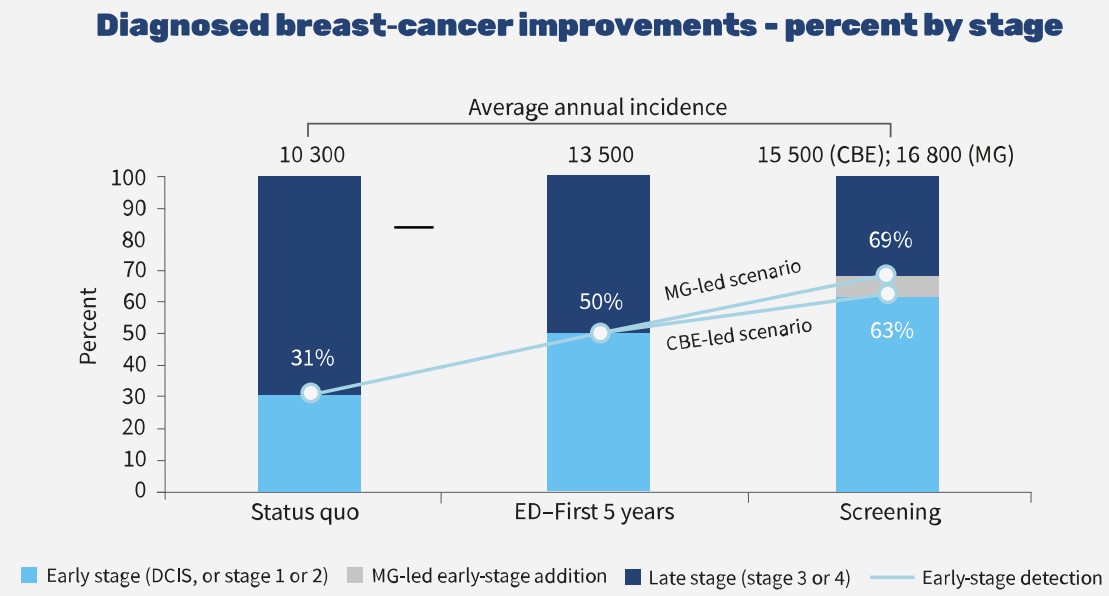
Long-term (40-year) outcomes

Costs
Kanya's annual health expenditure will increase by 1.2%, 2.4% and 4.7% in the early-diagnosis-only, CBE-led, and MG-led screening scenarios, respectively (future costs undiscounted). These predicted increases are based on the growing Kenyan population and projected increased rates of diagnosed breast-cancer and treatment thereof.

Diagnosis
To provide adequate infrastructure for the MG-led scenario, at least 1000 MG machines would need to be in operation throughout the country by 2061, a number that would compare to current machine density in developed countries worldwide today. CBE-led screening would require at least 60 machines to be located at diagnostic facilities, and possibly more to ensure relative availability across regions.

Treatment
Over the 40-year period, the early diagnosis scenario will prevent over 163 000 deaths from breast cancer, 236 000 in the CBE-led scenario and 270 000 in the MG-led scenario, with the associated costs for each scenario increasing in a corresponding fashion (Fig. 6B, Table 1B).

Fig. 6A. The Kenya model for early detection and predicted stage shifting over 15 years (2022–2037), Kenya



Source: reproduced with permission of the publisher from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya (12).*

Fig. 6B. Predicted breast-cancer mortality reductions over 40 years (2022–2062), Kenya

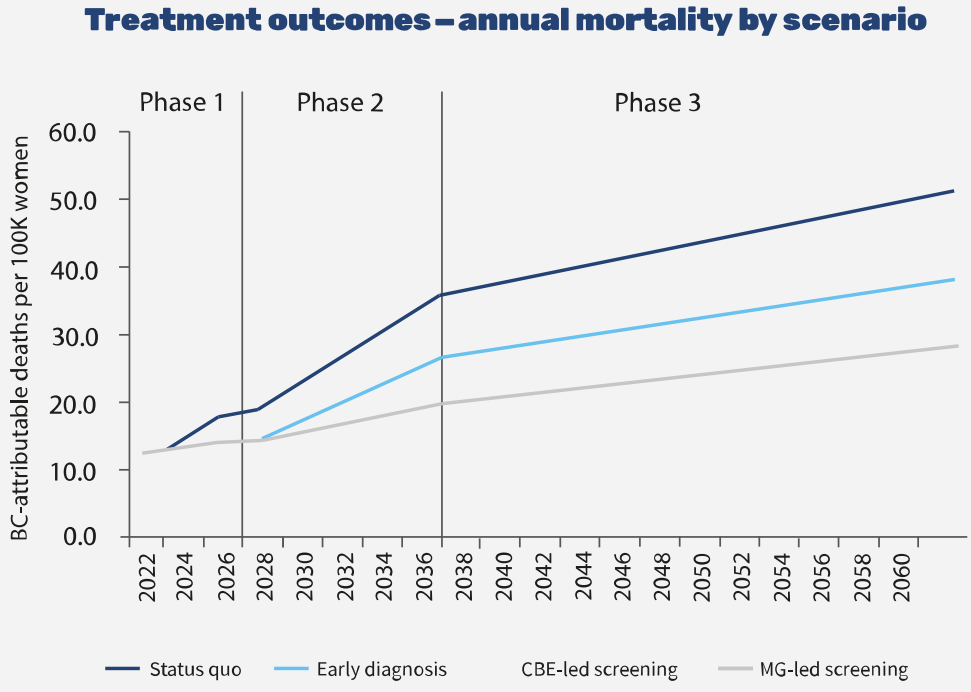


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Table 1A. Predicted breast-cancer-programme and service-delivery costs over 15 years (2022–2037), Kenya

15-year programme- and service-delivery costs (KES (discounted) and approximate US$)			
Cost type	**Early diagnosis only**	**CBE-led total 15-years**	**MG-led total 15-years**
Health-system strengthening	**KES 8.54 billion (US$ 69.99 million)**	**KES 14.56 billion (US$ 118.78 million)**	**KES 15.94 billion (US$ 127.52 million)**
Direct treatment	**KES 11.46 billion (US$ 93.73 million)**	**KES 16.74 billion (US$ 136.95 million)**	**KES 38.41 billion (US$ 311.39 million)**
Screening	—	KES 1.67 billion (US$ 13.66 million)	KES 19.97 billion (US$ 163.57 million)
Diagnosis	KES 1.46 billion (US$ 11.98 million)	KES 3.46 billion (US$ 28. 33 million)	KES 5.34 billion (US$ 43.72)
Treatment	KES 7.42 billion (US$ 60.80 million)	KES 8.77 billion (US$ 71.82 million)	KES 9.77 billion (US$ 80.02 million)
Palliative	KES 2.56 billion (US$ 21.03 million)	KES 2.83 billion (US$ 23.23 million)	KES 2.96 billion (US$ 24.22 million)
Total	**KES 19.99 billion (US$ 163.71 million)**	**KES 31.30 billion (US$ 256.31 million)**	**KES 53.63 billion (US$ 439.12 million)**

Source: based on data from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya* with the permission of the publisher *(12)*.

Interpretation

While the Kenya model projections are based on country-specific data and estimates, certain findings are meaningful to other countries considering investment in breast-cancer early-detection, diagnosis, and treatment programmes. For example, the model illustrates the long-term strategic planning (5, 15 and 40 years) that is required to achieve and sustain improved breast-cancer outcomes. It shows that **multiple approaches can be applied to achieve stage shifting and that choices among these approaches need to be made within countries based upon individual needs and limitations.** It demonstrates that the development of mammographic screening programmes is highly resource-intensive in comparison to clinically based approaches to early diagnosis and is not the initial step in establishing an early-detection programme in a setting where locally advanced breast cancers are common.

Table 1B. Projected long-term cost outcomes, (break-even point) and the overall benefit-to-cost ratio (BCR) for each scenario at 40 years (,2035–2045), Kenya

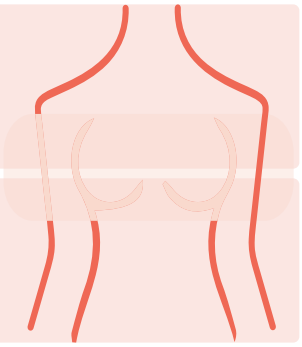
Programmatic scenario	Deaths averted (in thousands)	Break-even point to be achieved by (year)	BCR	Net benefit (in KES/ approximate US$)
Early-diagnosis scenario	163	**2035**	5.0 by end of analysis	**KES 202 billion/ US$ 1.65 billion**
CBE-led screening	236	**2038**	3.7 by end of analysis	**KES 261 billion/ US$ 2.13 billion**
MG-led screening	270	**2045**	2.2 by end of analysis	**KES 221 billion/ US$ 1.81 billion**

Source: based on data from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya* with the permission of the publisher *(12)*.

Pillar 1. The pre-diagnostic interval

Key messages from this chapter

Health promotion for early detection focuses on improving the understanding of the public and health-care professionals of breast-cancer risk factors and symptoms.



Health promotion for early detection focuses on improving the understanding of the public and health-care professionals of breast-cancer risk factors and symptoms.

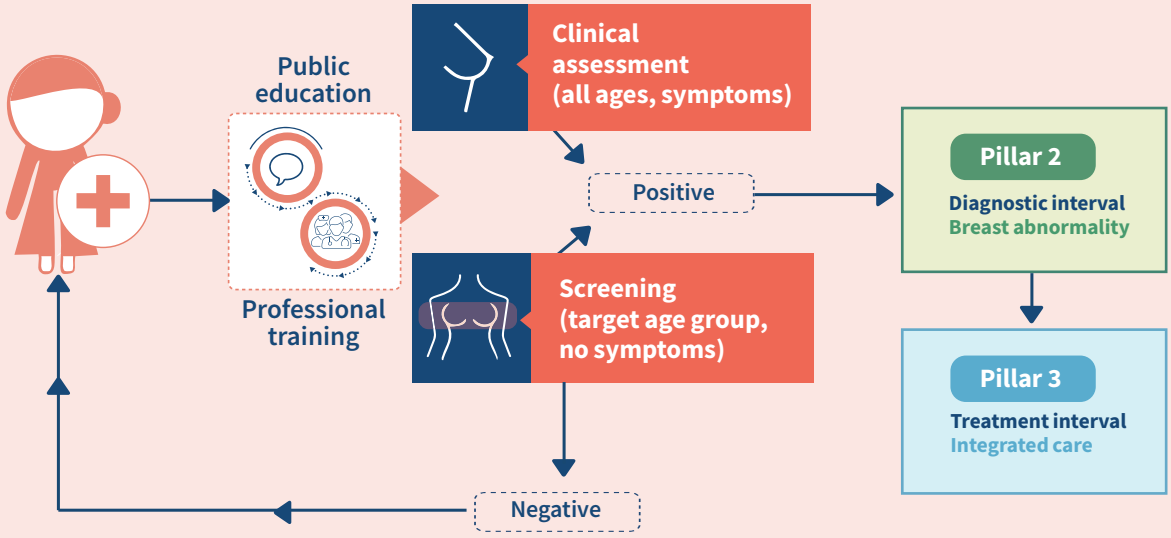
Early detection is founded on breast-health awareness as part of early-diagnosis programmes. These programmes focus on identifying people with signs and symptoms suggesting malignancy and facilitating access to cancer diagnostic services. All health-care systems require the capacity to diagnose symptomatic breast complaints, such as lumps, thickenings, or other clinically detectable abnormalities.

Breast-cancer screening (an alternate early-detection programmatic strategy in which women in a target age group are invited to undergo testing yearly or every other year) may be an aspirational goal once health-system prerequisites have been established. However, organized, population-based screening is not an appropriate or practical initial step in any setting until the required infrastructure and quality-control measures are in place and fully functional.

The KPI for Pillar 1 is >60% of invasive cancers to be stage I or II at diagnosis. No country has achieved a sustained decline in breast-cancer mortality rates of 2% per year or more for at least three consecutive years without also achieving a level of early detection where 60% of patients present with stage I or II disease.

The pre-diagnostic interval (Pillar 1) represents the period before an individual presents to the health-care system with a breast complaint, or for breast screening. This includes individuals with abnormal clinical or radiographic findings who are referred for diagnostic work-up (Pillar 2) (Fig. 7).

Fig. 7. The pre-diagnostic interval



Who is at risk?

Breast cancer is a complex disease (or group of diseases) with multiple risk factors, some resulting from genetic predisposition and others accumulating throughout the life-course. Female sex and advancing age are the strongest risk factors for breast cancer, with over 99% of cases occurring in females. Beyond sex and age, **the primary risk factors for breast cancer include: (i) inherited factors; (ii) hormone-related factors; (ii) environmental and lifestyle factors; and (iv) breast-related factors.**

Inherited factors

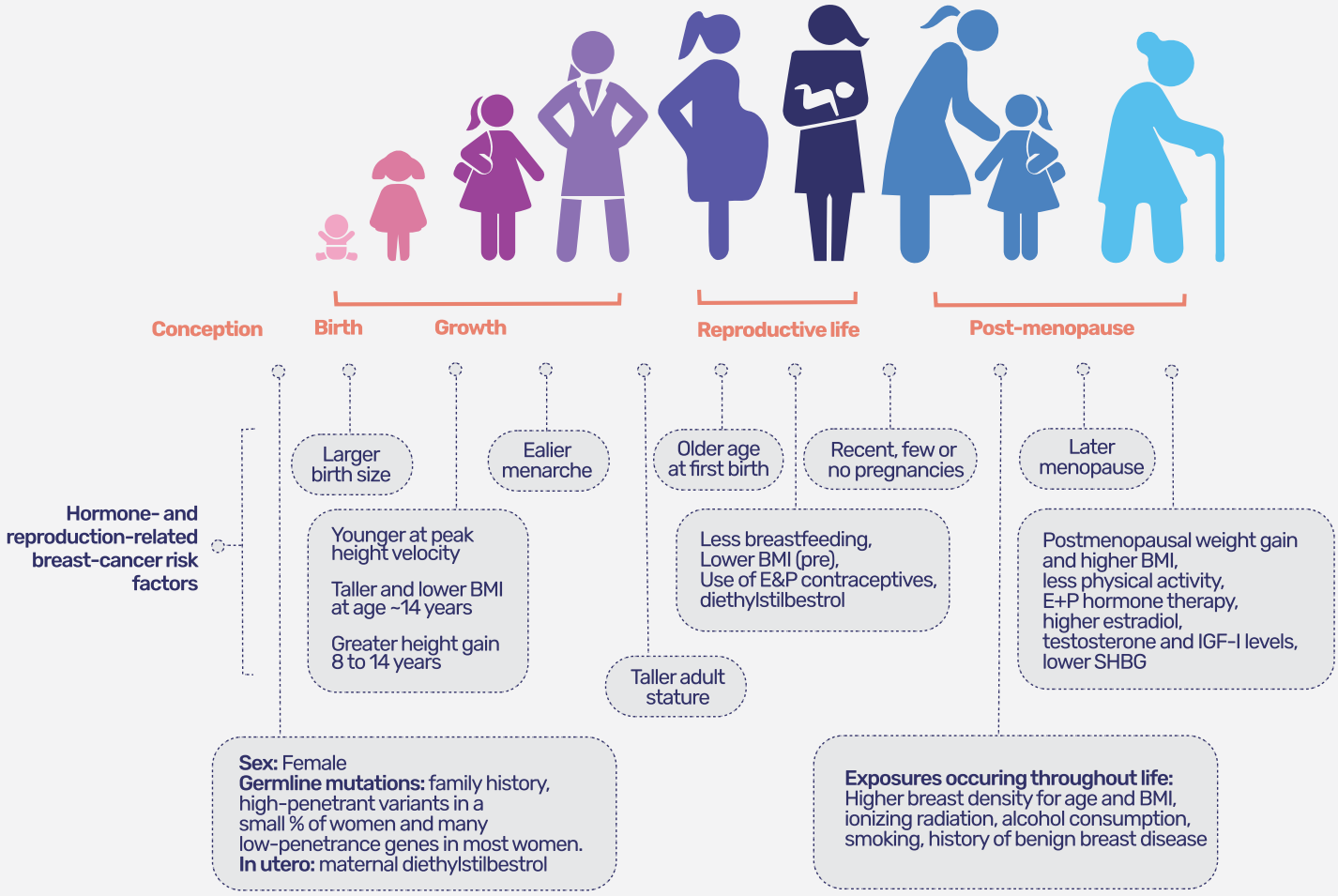
A family history of breast cancer (and, to a lesser extent, ovarian cancer) can represent the presence of **inherited mutations** in moderate to highly penetrant genes (BRCA1, BRCA2, CHEK2, ATM, PALB2, PTEN, TP53, CDH1 and STK11), which increase the risk of breast cancer significantly (up to 80% in a lifetime for BRCA1 and BRCA2). However, **these mutations account for 10–20% of breast cancers** at the population level. Most often, genetic susceptibility results from a combination of multiple low-penetrance gene mutations through interactive processes that are not yet well understood.

Male breast cancer is uncommon, corresponding to less than 1% of breast-cancer cases and representing 0.5% of malignancies in men *(13)*. Pathogenic variants in cancer-predisposing genes are a likely aetiology for 4–40% of male breast-cancer cases, the degree depending on the cohort. In families at high risk for breast cancer, BRCA2 pathogenic variants are responsible for 60–70% of male breast-cancer cases. The estimated lifetime risk of breast cancer is 5–10% among male carriers of the BRCA2 pathogenic variant, compared to a 0.1% risk in the general population *(14)*. Because male breast cancer is uncommon, most treatment options are extrapolated from breast-cancer data related to females. However, because of intense advocacy in recent years, men are no longer excluded from most breast-cancer trials, and data are available regarding newer systemic therapy options. In male patients, breast cancer is virtually always ER+; only about 10% are diagnosed with human epidermal growth-factor receptor 2+ (HER2+) disease (less than 1% have triple-negative breast cancer) *(15)*.

Hormone- and reproduction-related factors

Hormone-related risk factors for breast cancer include early menarche, late menopause, exposure to higher levels of endogenous estrogens, androgens, prolactin, and insulin-like growth factor 1 (IGF-1), and the prolonged use (>5 years) of combined oral contraceptives or estrogen-based hormone-replacement therapy in the post-menopause period (Fig. 8). Other risk factors include reproductive factors, such as lower parity or later age at first birth. The pregnancy period also leads to a transient modest increase in breast-cancer risk, which persists up to 20 years after childbirth before conferring a life-long protective effect. However, risk to mothers can be reduced by breastfeeding.

Fig. 8. Hormone- and reproduction-related breast-cancer risk factors



Notes. BMI = body mass index; E+P = estrogen plus progestin; IGF-1 = Insulin-like growth factor 1); pre = premenopausal; SHBG = sex-hormone-binding globulin
Source: Valerie McCormack, IARC, 2022.

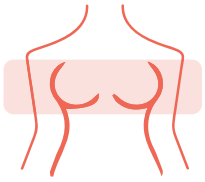
Environmental and lifestyle factors

Known environmental risk factors for breast cancer include in-utero exposure to diethylstilbestrol, a pro-estrogenic drug with a dose–response relationship, and prior chest-wall exposure to ionizing radiation. Lifestyle risk factors include low levels of physical activity, high BMI, and the use of alcohol or tobacco.

Breast-related factors

In addition, a personal history of a benign proliferative breast disease (such as atypical hyperplasia) and higher breast density (as seen on a mammogram) have been linked to an increased risk of breast cancer. The latter may be a tissue-specific marker of several other breast-cancer risk factors, or of ageing breast tissue (Box 7).

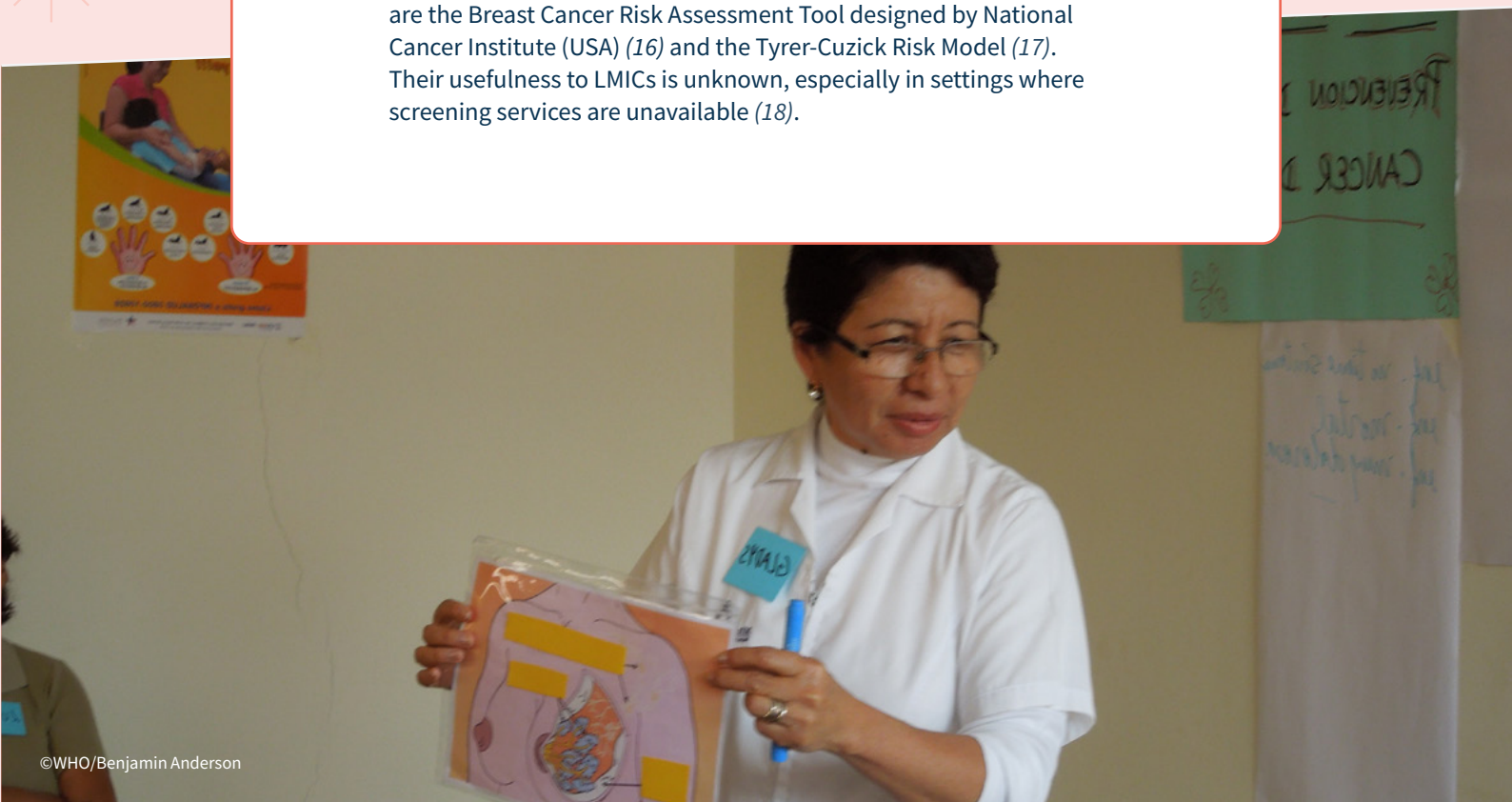
Box 7. Personalized assessment of risk for breast-cancer



Known breast-cancer risk factors include genetic mutations, previous exposure to thoracic radiation, older age, obesity, breast density, and a family history of breast and/or ovarian cancer.

Individuals found to be at increased risk for breast cancer (>20% overall lifetime risk) are candidates for enhanced screening in settings where screening is available and sustainable.

Breast-cancer risk calculators (with strengths, weaknesses and variable efficiency and accuracy impacts) are available for use in the primary-care setting. Two commonly used risk calculators are the Breast Cancer Risk Assessment Tool designed by National Cancer Institute (USA) *(16)* and the Tyrer-Cuzick Risk Model *(17)*. Their usefulness to LMICs is unknown, especially in settings where screening services are unavailable *(18)*.



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Breast-cancer risk reduction

Public education to reduce risk

Education about risk factors is a core component of programmes on breast-cancer awareness. The aim is to positively influence the health behaviour of individuals within communities, as well as to provide guidance on how living and working conditions can negatively influence their health.

Alcohol consumption and breast-cancer risk

One of the strongest modifiable breast-cancer risk factors is alcohol consumption, which in 2016 contributed to 3 million deaths globally and was responsible for 5.1% of the global burden of disease and injury *(19,20)*. The prevalence of alcohol consumption in women aged 15+ varies by WHO region, ranging from 4.3 litres per capita in the European Region in 2019 to 0.1 litres per capita in the Eastern Mediterranean Region. The WHO Global Health Observatory reported that in 2019 the average alcohol consumption in women aged 15 years and older was 2.5 litres of pure alcohol per capita worldwide, ranging from 1.1 litres in low-income countries to 4.7 litres in HICs *(21)*. In 2018, the proportions of breast-cancer risk attributed to alcohol consumption in Asia, North America and Europe were 11.5%, 13.0%, and 20.6%, respectively *(22)*. Compared with non-drinkers, women who drink have an increased risk of breast cancer: 21% higher for hormone-receptor-negative breast cancers and 40% higher for hormone-receptor-positive breast cancers *(22)*.

In the European Union, levels of alcohol consumption described as "light to moderate" (<20g of pure alcohol per day) caused almost 23 000 new cancer cases in 2017, accounting for 13.3% of all alcohol-attributable cancers, and 2.3% of all cases of the seven alcohol-related cancer types, including oesophagus, liver, colorectal, oral cancers, and breast cancers. Almost half of these (~11 000 cases) were breast cancers in females. Also, more than one third of the cancer

ases attributed to light-to-moderate drinking (~8500 cases) resulted from a "light" drinking level of <10 grams per day *(23)*. Cohort studies have shown that even drinking only 1 g of total alcohol per day increases the risk, particularly in postmenopausal women. No "safe" amount of alcohol consumption relative to cancer and health can be established.

Primary prevention for individuals at increased risk

Women at moderate to high risk for developing breast cancer because of non-modifiable risk factors, such as genetic or familial breast-cancer risk, may benefit from specific risk-reduction interventions. The timely identification of increased breast-cancer risk in an individual is key to proposing and enabling the appropriate use of risk-reducing interventions. The two main interventions available to date are: (i) pharmacological therapy, also called chemoprevention (e.g., selective estrogen-receptor modulators (SERMs) or aromatase inhibitors (Ais)); and (ii) risk-reducing prophylactic surgery.

Early-detection programmes

The goal of an **early-detection** breast-cancer programme is to develop and implement strategies for diagnosing >60% of women with early-stage disease (stages I or II) to improve breast-cancer outcomes. In settings where late-stage breast-cancer presentation is common, and women present with cancers that are easily felt or seen, **stage shifting** will be required to increase the fraction of patients initially diagnosed with early-stage disease. Early detection begins with **breast-health awareness** and the establishment of **early-diagnosis** programmes, which focus on identifying people with signs and symptoms of breast cancer (Box 8), suggesting possible malignancy, and linking them to diagnostic services for the correct identification of those with cancer. **Breast-cancer screening**, in which women in a target age-group, without recognized signs or symptoms of breast cancer, are invited to undergo testing yearly or every other year, may be an aspirational goal once health-system prerequisites have been established. However, screening is not an appropriate or practical initial step until the required infrastructure and quality-control measures are in place and have been demonstrated to be fully functional at a clinical level *(24)*.

Box 8. Breast-cancer signs and symptoms

These can vary significantly and may include:

- a painless breast mass or thickening
- thickening, redness or warmth of the skin, or a rash
- enlarged lymph nodes in the armpit(s)
- focal (rather than generalized) breast pain
- nipple discharge or progressive nipple inversion.

Most breast lumps are benign and most breast symptoms are NOT caused by cancer, which is why a diagnostic work-up is required to identify who has cancer and who does not.

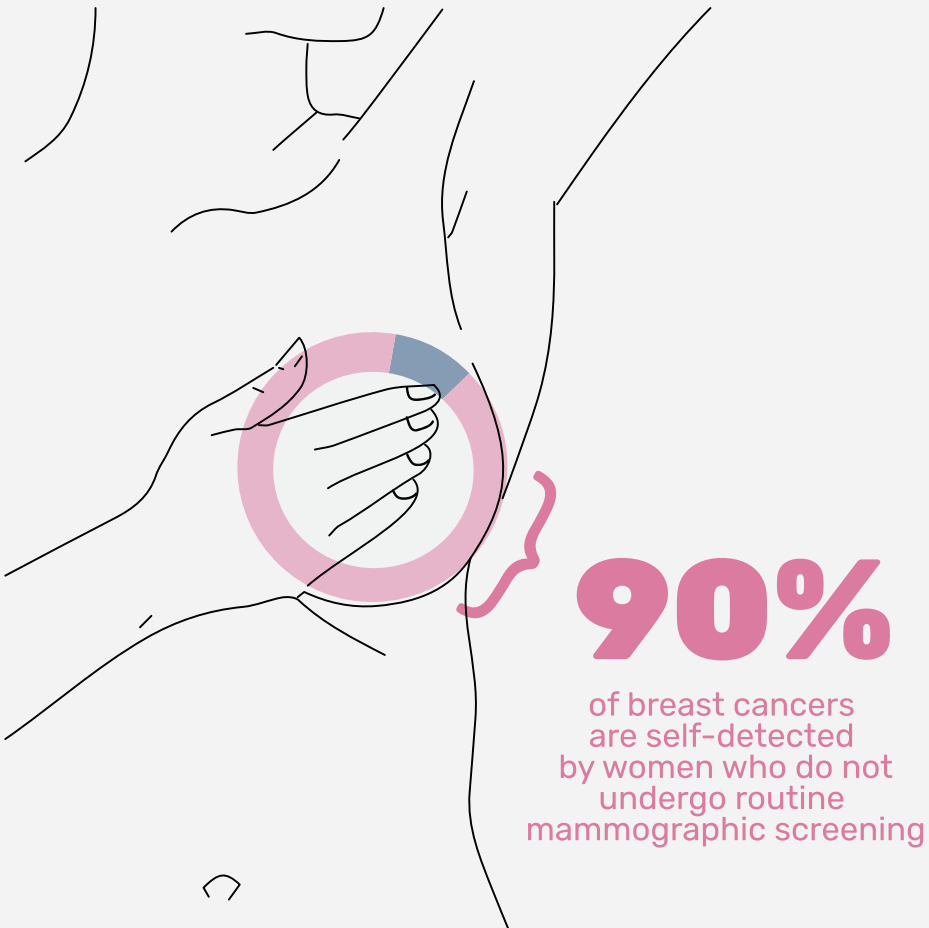
Early-detection strategies: breast-health awareness

Successful early-detection programmes include spreading breast-health awareness among the public. Overall, the goal of breast-health awareness is to improve knowledge about breast cancer in target populations. The development and implementation of breast-cancer awareness and education programmes should involve the participation of patient advocates, family members, peers, medical professionals, media, academic teachers, and cultural and community leaders throughout the process.

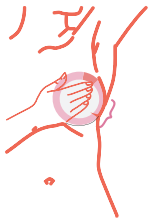
At the individual-level, people must be aware of specific cancer symptoms. To recognize these, **people must know how to conduct a baseline breast self-examination (BSE).** They should be taught the importance of promptly reporting any changes to a health-care worker or health provider (Box 9). In unscreened populations, such as in northern Peru, women self-discover their breast cancers in over 90% of cases *(25)*. **BSE is a valuable tool for awareness education and should not be discourage**d (Fig. 9).

Breast-health awareness can help people overcome the fear, misinformation or stigma associated with cancer. At the individual-level, it should translate into appropriate breast-health behaviour. At the public level, communities should engage community health workers (CHWs), along with religious and traditional leaders, to work with medical teams in developing breast-health-awareness campaigns. CHWs can engage in home visits to raise awareness in communities, give educational talks in health facilities and communities, distribute educational materials, share motivational videos online or to mobile phones, and perform CBEs. **Civil-society organizations (CSOs) can play a significant role in extending the reach of community education and awareness.** When engaging CHWs (and CSOs) in raising awareness, it is essential that they receive the support of the health-care system. For example, it is important that primary-health-care facilities work with CHWs and CSOs on ensuring the availability of affordable and convenient facilities where patients can be evaluated in a timely fashion and informed of any need for follow-up. Engaging breast-cancer survivors in sharing their personal experiences is also a powerful tool for raising awareness *(26)*.

Fig. 9. Sample BSE technique



Box 9. The role of BSE in the early detection of breast cancer



BSE is an examination performed by the individual, which includes inspecting the breast in the mirror and feeling the entire breast and armpits, the arm in use being extended to flatten the breast on the chest wall.

BSE plays a key role in breast-health awareness by helping the individual to know what feels normal. This is a prerequisite for being able to assess where new findings, such as lumps, thickenings, or other persistent changes might represent abnormalities.

While BSE has not been found to improve breast-cancer detection among women who undergo routine mammographic screening, over 90% of breast cancers are self-detected in those who do not.

A randomized study of BSE in Shanghai, China, did not show an improvement in breast-cancer survival in women who had been formally trained in BSE versus those who had not. However, it did show that those in the untrained (control) group were already good at identifying small cancers (less than 2cm) *(27)*.

Breast health awareness should continue to be encouraged. Women who through BSE identify persistent findings that feel abnormal should be supported in seeking diagnostic work-ups.

Clinicians should pay attention to self-identified breast abnormalities and recommend diagnostic work-ups, even if CBE does not reveal what a women describes she feels in her breast and with her fingers *(28)*.

Early detection: clinical breast-assessment skills

The clinical tools essential for the early diagnosis of breast cancer at the primary-care level are history-taking skills and the ability to perform a CBA. Collectively termed "CBA skills", these should be included in medical-school curricula and taught to nurses and clinical health workers who may be involved in primary breast-health care.

Obtaining a medical history

Health-care professionals should know how to take an appropriate medical history and conduct a standardized physical examination in a culturally sensitive manner. Virtual or live workshops with real or simulated patients can teach providers how to take an accurate clinical breast history and perform physical examinations. It is important to ask the women if they had noted any abnormalities in their breasts and if so, to point out in which way they had found the workshops to be helpful in this connection.

Performing a CBE

CBE is a systematic and specific examination of the breasts, nipples, and areolas combined with examination of axillary, infraclavicular and supraclavicular lymph-node beds as performed by a health-care provider (Box 10). First, with the individual in an upright position, the provider visually examines the uncovered breasts to look for asymmetries, puckering, dimpling, or localized skin changes. The clinician then palpates the armpit to feel for enlarged lymph nodes or masses. The individual then lies back on the examining table with her arm above her head, which flattens the breast on the chest wall. The provider then manually examines each breast with one or two fingers of each hand to feel for masses, thickenings, other localized asymmetries or spontaneous bloody or clear nipple discharges.

Abnormal findings on CBE generally warrant diagnostic imaging and may require tissue sampling to make a definitive diagnosis. If advanced disease is suspected, a complete physical examination should be included to check for symptoms of potential metastatic disease (for example, in the form of regional nodes and/or bony tenderness). Although live or virtual workshops (including real patients, simulation-based methodologies, or videos) do have an impact, education in examining real patients is ultimately required to ensure quality of skills in this area *(28)*.

Referral for definitive diagnosis

Well-functioning referral networks and patient navigation are required so that people with breast abnormalities can receive prompt, accurate and definitive diagnoses (Pillar 2).

Early detection: early diagnosis

Early diagnosis in breast cancer is the process whereby individuals with breast complaints and abnormalities undergo prompt diagnostic work-ups to identify the subset of individuals who have early breast cancers. Because breast-cancer early diagnosis requires active patient participation, early-detection programmes begin with public breast-cancer awareness education so that individuals with signs and/or symptoms of possible breast cancer present themselves for CBA and diagnostic work-up. Organized at the population level, early-diagnosis programmes focus on identifying individuals with signs and symptoms suggesting possible breast malignancy and linking those individuals to diagnostic services for the correct cancer diagnosis.

From a health-system perspective, early diagnosis is not an alternative to screening – it is a prerequisite. Systems not yet prepared, or without the resources, for the rapid diagnosis and management of clinically detectable cancers (e.g., those found through visual examination or palpation) should not incorporate image-based screening to find occult cancers (those not detected by clinical examination). Sampling abnormalities seen only on an imaging study is a more complex and resource-intensive procedure than that performed for palpable lesions. Because diagnostic imaging inevitably finds some occult abnormalities that warrant needle sampling, early-diagnosis programmes should include resources for workforce training and equipment and supplies. These will support image-guided localization and the sampling of clinically occult findings, the need for which can be predicted even in the absence of a screening programme (Box 11) *(7)*. **Once early-diagnosis programmes are established, breast-cancer-screening programmes may be considered, recognizing that the resource requirements and costs of effective screening programmes are** prohibitive in the significant majority of LMICs.

Box 10. The role of CBE in the early detection of breast cancer

CBE is required for CBA if the clinician can correlate the findings from the patient's history, BSE, and diagnostic imaging to formulate a differential diagnosis and determine a diagnostic plan for a given breast abnormality.

The goal of breast-cancer early-diagnosis programmes is to correctly diagnose breast cancers early in their course when the signs and symptoms of disease can be subtle. Thus, CBE is the cornerstone for evaluating breast findings in patients who present with self-appreciated breast complaints that could represent cancer.

CBE has not been shown to improve breast-cancer early detection when used in conjunction with mammographic screening. However, CBE has been successfully used as a screening test in previously unscreened populations and has been shown to promote favourable stage shifting *(29)*. One study demonstrated a survival benefit in women aged 50 years and older *(30)*.

Box 11. What is the evidence of a stage-shifting threshold in breast cancer?

IHO performed a population-based analysis to determine the degree of early-stage diagnosis associated with improved breast-cancer survival at the national level.

Among 35 countries with adequate breast-cancer TNM-stage distribution data and longitudinal survival data by year, 20 had achieved sustained reductions in breast-cancer mortality (>2% annual mortality reduction for three consecutive years); 15 had not.

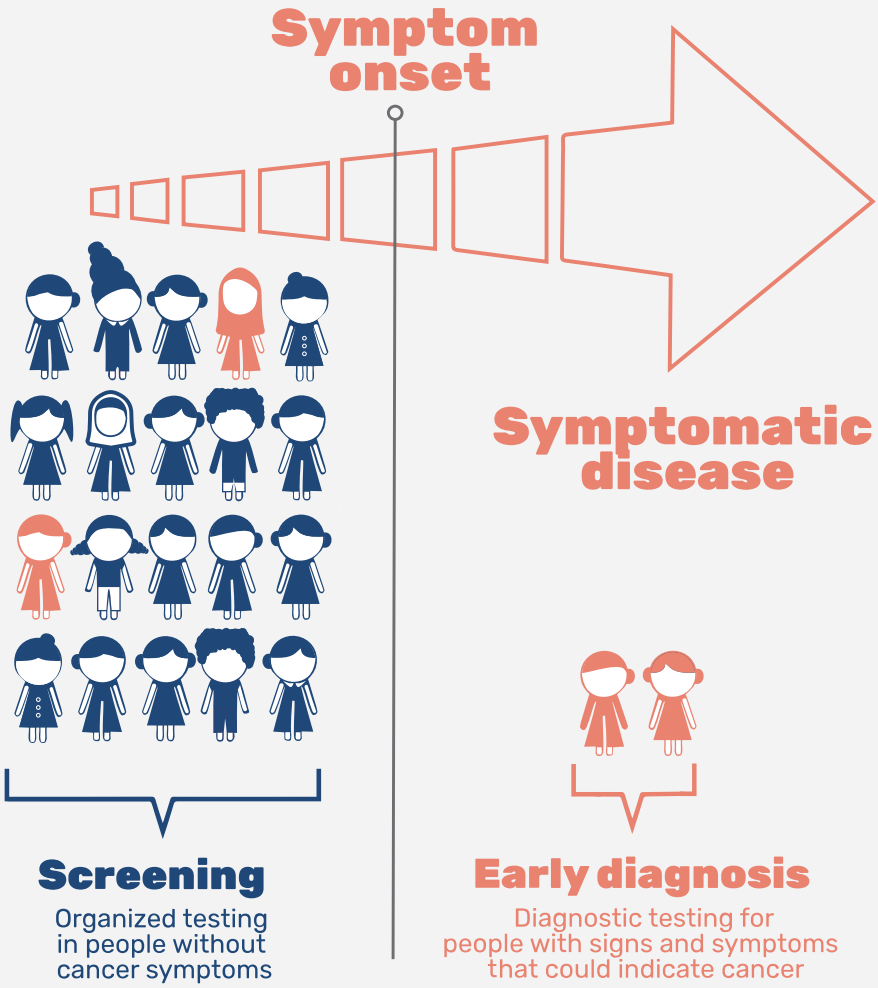
In each of the 20 countries that had achieved sustained reductions in breast-cancer mortality, at least 60% of patients with invasive breast-cancer presented as stages I or II disease. Some of these countries had population-based mammographic screening programmes.

Early detection: screening

In addition to early diagnosis, screening is a tool that promotes favourable stage shifting, but these detection methods differ in resource and infrastructure requirements, impact, and cost (Fig. 10, Table 2).

The goal of breast-cancer **early detection** is for ≥60% of women to have early-stage disease (stages I or II) at diagnosis. The first step is to establish **early-diagnosis programmes** where individuals with early symptoms of breast cancer can come for evaluation and definitive diagnostic work-ups. **Breast-cancer screening** is a more intensive and costly approach whereby women from a target age-group, with no known signs or symptoms of breast cancer, are invited to undergo a screening test. Mammographic screening has been shown to be one method of achieving the ≥60%-early-stage outcome. CBE-screening can approach (but not fully achieve) the **stage-shifting** outcome of mammographic screening. Early diagnosis is a prerequisite for mammographic screening. Systems that are unable to diagnose cancers that can be felt or seen (**symptomatic**) will not have the resources to perform diagnostic studies on individuals without evidence of cancer (**asymptomatic**) and where the cancers are only seen on an imaging study.

Fig. 10. Distinguishing screening from early diagnosis, according to symptom onset



Source: WHO (2017) *(31)*.

Table 2. Early detection: key elements of early diagnosis and screening

Parameter	Early diagnosis	Screening programme
Volume of participants	Limited to those with symptoms suspicious for cancer	Entire target population (can be 50-100 times higher number of participants than early diagnosis)
Test	Diagnostic tests only for those with symptoms	Screening test for an entire target population **AND** diagnostic test for those who screen positive[a]
Health system requirements	Facilities and human resources for timely clinical diagnosis, pathology, radiology, staging, access to prompt treatment	Health system requirements for early diagnosis **AND** significant additional resources for inviting and testing an entire target population **AND** additional diagnostic tests for all people who screen positive with recall mechanism **AND** systematic evaluation
Training and human resource needs	Health-care providers to identify symptoms and signs of early cancer and diagnose, stage and treat cancer	Providers needed for early diagnosis **AND** additional providers, pathologists and/or biomedical laboratory scientists to perform test and interpret results cancer
Public awareness	Attention to signs and symptoms to obtain prompt medical evaluation	Attention to signs and symptoms of cancer **AND** participation in screening programme
Follow-up care	Referral mechanisms to ensure treatment is accessible and affordable	Complex process that includes call-recall mechanism and counselling Increased responsibility for screening programme to ensure follow-up care of screen positive participants. Increased risk of loss to follow-up
Potential benefits	Reduction in stage of disease at diagnosis When linked to treatment reduction in mortality generally evident in three to five years	Potential reduction in incidence in target population if precursor detected and treated by screening (e.g. cervical and colorectal cancers) Reduction in stage of disease at diagnosis in target population (generally earlier stage than early diagnosis) Reduction in mortality when screening delivered effectively and linked to treatment, but not for many years (often >10 years)
Potential for harm	Low: testing limited to only those who have signs and symptoms	Potentially high as test applied to an entire target population[b] Generally, most who screen positive will not have cancer or precancerous abnormalities, but require additional tests and procedures that can potentially lead to complications, psychological distress and utilization of resources Some may be overdiagnosed and overtreated
Applicability and current scientific evidence	Accepted core component of health services to improve timely diagnosis of cancer Relevant for all settings, especially those with weaker health systems	Benefits documented in high-resource settings for limited number of cancers (e.g. cervical, breast) Evidence of harms and significant costs in high- income countries Benefits and harms in LMICs not well established except for cervical cancer screening[c]

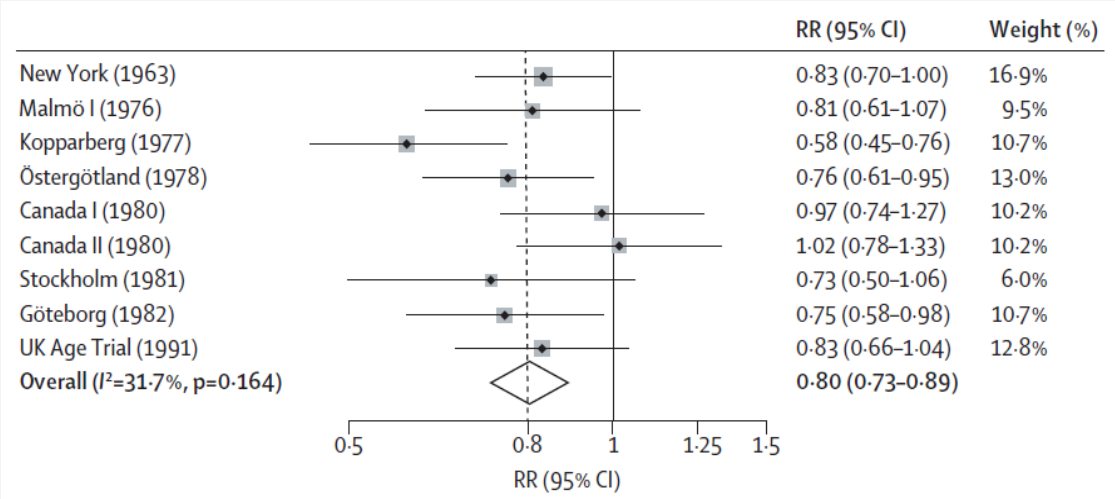
[a] Screen-and-treat approach for pre-invasive cervical cancer does not require a separate diagnostic test for abnormal cells.
[b] Extent of harm depends on the type of cancer screened and quality of the cancer screening programme.
[c] Decision to introduce cancer screening programmes should be based on a careful assessment of disease burden, current health system capacity and available infrastructure, competing health priorities and resource requirement. For example, given the resource requirements and complexities, breast cancer screening with mammography is not recom- mended in countries with weak health systems *(11)*.
Source: WHO (2017) *(31)*.

Mammographic screening is considered the gold standard for the early detection of breast cancer in well-resourced settings. Randomized trials have demonstrated that mammographic screening of women aged 50–69 years can reduce breast-cancer mortality by 23% (Fig. 11). This important finding has promoted the common misconception that mammographic screening is the dominant measure by which women enter the breast-health-care delivery system, and the only one that can lead to adequate stage shifting.

Globally, the majority of breast cancers are first detected by patients themselves and are diagnosed based on clinical symptoms (such as a breast lump, skin thickening, or nipple discharge), a CBE, and diagnostic imaging *(33)*. Women with these symptoms first present for evaluation outside screening programmes, either because they are too young for screening (for example, women under the age of 45) or because screening programmes are not available in their countries or regions. In screening programmes, a fraction of women will present clinically with interval cancers, that is cancers occurring between scheduled screening mammograms. In most LMICs, *over 90% of breast cancers are found initially by the women themselves (25).* **Thus, all health-care systems require the capacity to diagnose symptomatic breast complaints, regardless of whether they can afford and effectively organize mammographic-screening programmes** (Box 12).

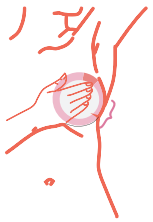
In limited-resource settings where population-based screening by MG is not available, affordable, or feasible, governments have incorporated CBE as another method for detecting palpable early breast cancers (EBCs). **CBE is cost-effective and highly feasible in all resource settings** *(24).* Multiple studies on the use of CBE-based screening have demonstrated successful stage shifting (where the disease distribution weighed more heavily towards early-stage disease). For example, in Peru, women who had a history of undergoing CBE experienced shorter delays between symptom development and presentation. They were also more likely to be diagnosed with early-stage disease compared to women who had never undergone CBE *(25)*.

Fig. 11. Meta-analysis of breast-cancer mortality after 13 years in breast-cancer screening trials



Note. RR = relative risk; CI = confidence interval.
Source: reproduced with permission of the publisher, Elsevier Ltd., from Independent UK Panel on Breast Screening *(32)*.

Box 12. When should a country set up a mammographic screening programme?



The decision to start a mammographic screening programme is a nuanced one that each country must base on an individualized strategic assessment. In appropriately selected countries, it may be necessary to begin screening in urban areas, and subsequently extend it to rural areas where access is more limited.

Having accessible diagnostic imaging and tissue-sampling services (breast ultrasound, diagnostic MG, needle biopsy) in place is mandatory before any breast-cancer-screening efforts can be contemplated (GBCI Pillar 2).

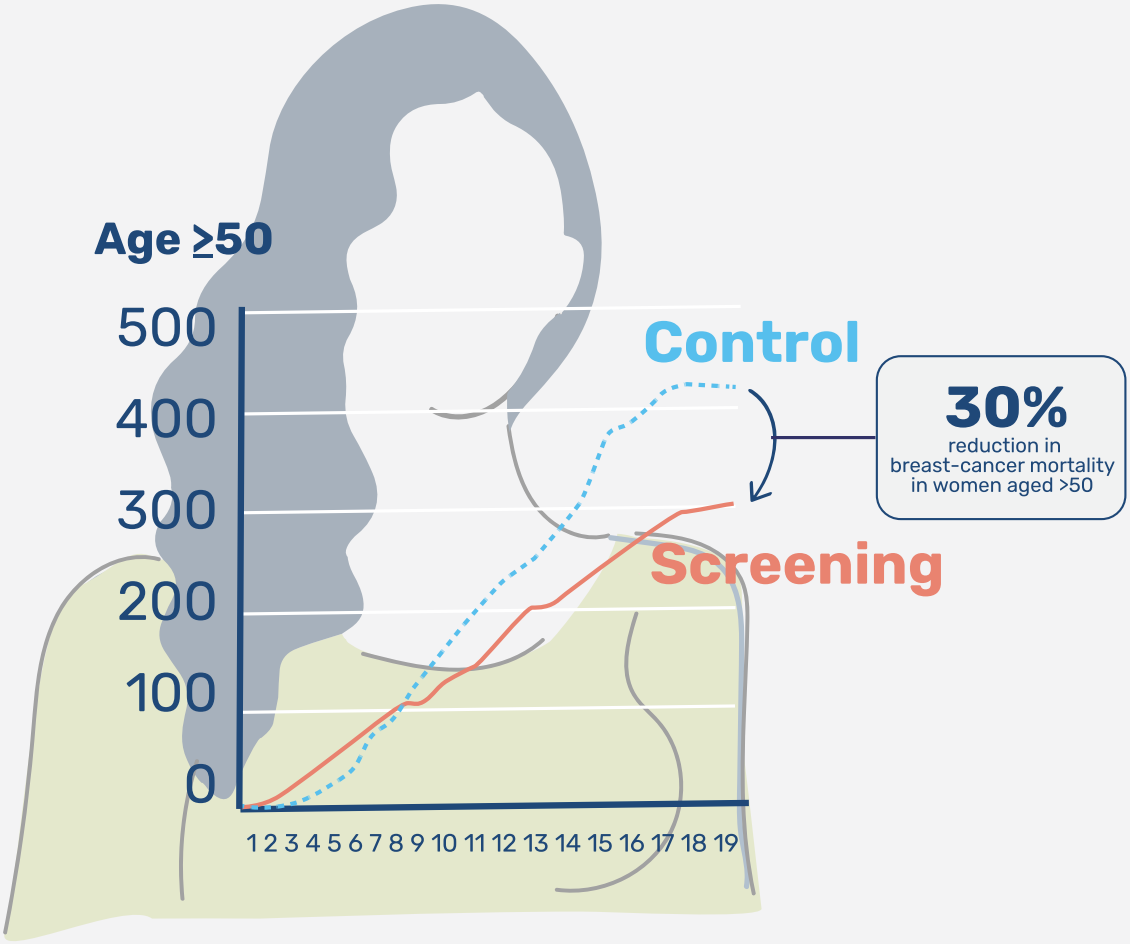
Mammographic-screening programmes are highly resource intensive regarding both initiation and sustainment. Beyond the purchase of MG machines, running effective screening programmes requires a trained workforce, quality-control systems, and data-management systems to keep a track of the patients through repeated mammographic studies over time.

A screen-detected cancer is one that was not seen on a prior mammogram but has become apparent on a current mammogram. Thus, to achieve stage shifting, mammographic screening requires that studies of the same women in the target group be repeated every 1–2 years.

When the majority of breast-cancer patients present with locally advanced breast cancer (LABC) or metastatic breast cancer (MBC) that can be detected through CBE, the focus needs to be on establishing early-diagnosis programmes. This will promote favourable stage shifting at a significantly lower cost *(24,34)*.

A general consensus on population-based screening programmes, using CBE in a target population, particularly in settings where mammographic screening programmes are not feasible, has not yet been achieved. A systematic review of 11 analyses published between 1993 and 2019 found evidence that CBE contributes between 17% and 47% of stage shifting from advanced to early-stage disease *(35)*. This review did not provide direct evidence of mortality benefit from the use of CBE screening, but did note that the inaccessibility and/or unaffordability of treatments for late-stage cancer in LMICs could mask the potential survival benefits resulting from clinically driven stage shifting. By contrast, one subsequently published prospective randomized control trial conducted in Mumbai, India, demonstrated that it is possible to surpass the 60% threshold of diagnosing people with stages I or II disease through improved clinical detection in the absence of mammographic screening. Notably, the Mumbai trial did observe a breast-cancer-mortality reduction of nearly 30% among women aged ≥50 (Fig. 12) *(30)*.

Fig. 12. Cumulative breast-cancer mortality during a 20-year study in a prospective, cluster-randomized controlled study on CBE screening in Mumbai, India.



Source: adapted from Mittra et al *(30)*, licensed under CC BY 4.0 by the Global Breast Cancer Initiative.

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Monitoring and evaluation of the pre-diagnostic interval

Every country with a sustained decline in breast-cancer mortality rates of 2% per year or greater for at least three consecutive years has achieved the KPI benchmark of at least 60% of invasive breast cancers diagnosed at an early stage (stages I or II) *(4)*. No country with higher rates of late-stage breast cancer has achieved this outcome. These findings provide countries with a benchmark for monitoring and evaluating their early-detection strategies. Cancer facilities need to collect and record information related to stage at diagnosis, which is not uniformly the case in LMICs. In some settings, this may be beyond the scope of the cancer registry. Table 2 illustrates the elements considered key to early-stage breast-cancer diagnosis versus those important for screening programmes.

Pillar 2. The diagnostic interval

Key messages from this chapter

Timely breast diagnostics require a series of coordinated services for definitive cancer diagnosis and staging.

The diagnostic interval represents the intermediate period between referral for a diagnostic work-up and the time that a definitive benign or malignant diagnosis is made.

Delays from first presentation to the health-care system to breast-cancer diagnosis (diagnostic-interval delays) are associated with a greater likelihood of late-stage diagnosis and lower chance of breast-cancer survival.

Interventions to promote timely breast diagnostics include organizing services to increase access. If it is not feasible to fully decentralize imaging and pathology services, well-organized sample-transport systems and information systems can effectively decentralize sample collections, while minimizing patient travel and still enabling critical results to be obtained in a reasonable timeframe.

The KPI for Pillar 2 is for breast cancers to be diagnosed within 60 days (two months) of initial presentation to a health-care system.

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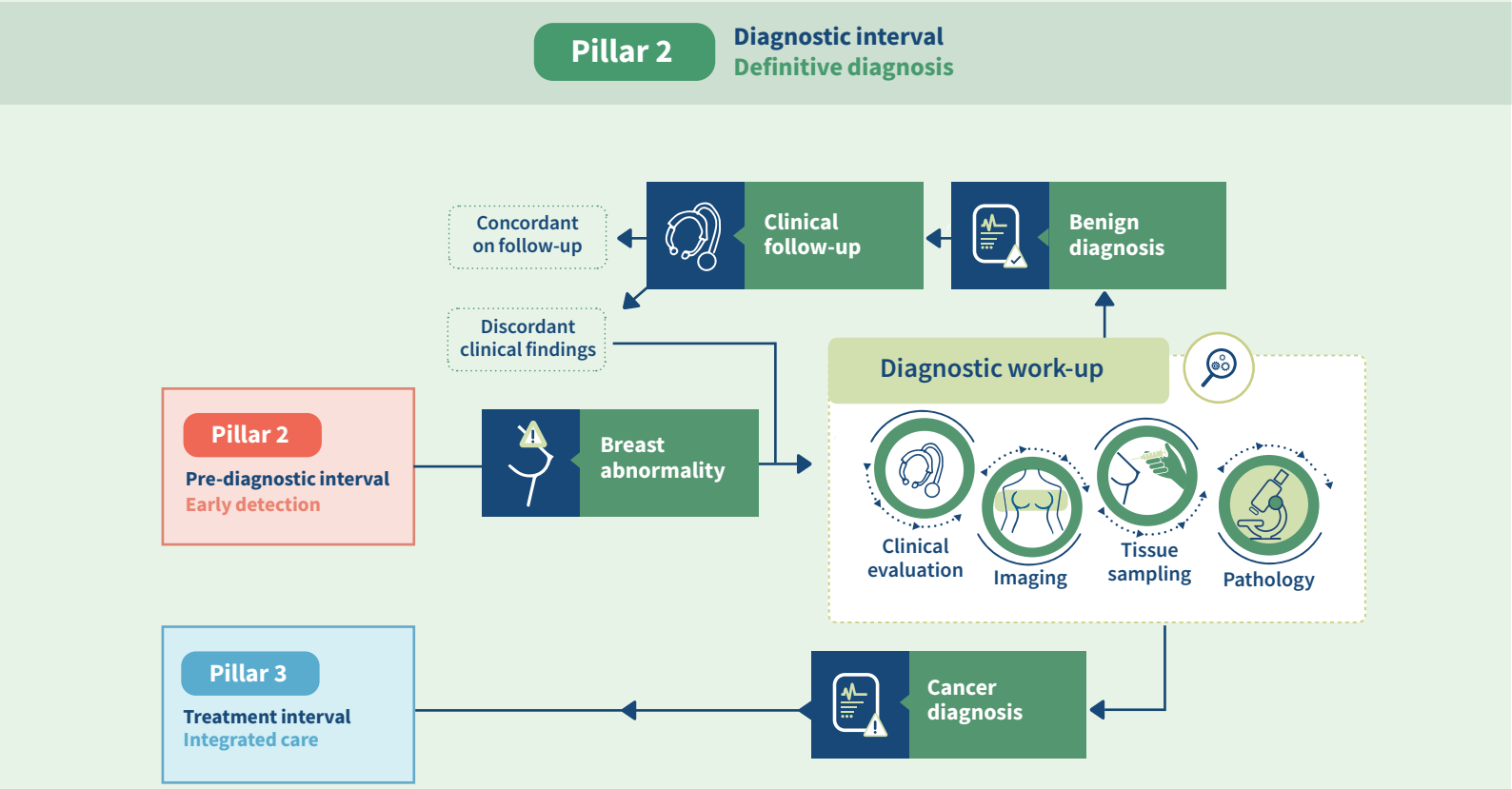
The diagnostic interval (Pillar 2) represents the intermediate period between referral for a diagnostic work-up and the time that a definitive benign or malignant diagnosis is made. Those found to have cancer then need to be referred for definitive treatment (Pillar 3) (Fig. 13).

Fig. 13. The diagnostic interval



Diagnostic imaging and tissue sampling

Patients with a breast abnormality identified through clinical evaluation or an imaging study require diagnostic imaging and, if indicated, tissue sampling at a diagnostic facility capable of delivering these integrated services with an appropriate quality level. Diagnostic imaging (ultrasound with or without diagnostic mammogram) reveals whether a mass (or abnormality) is present. Based on the imaging characteristics, or clinical findings, the mass might be considered sufficiently suspicious to proceed to breast-cancer biopsy. The mass can also appear benign (e.g., simple cyst or lipoma) or probably benign (e.g., a mass likely representing a fibroadenoma). The Breast Imaging Reporting and Data System (BI-RADS) provides a useful lexicon of mammographic and ultrasonographic vocabulary to standardize reporting and minimize unnecessary biopsies and has been successfully utilized in LMIC settings *(36)*. Providers should expect a considerable proportion of benign results when performing CBE (Box 13). In non-cancer cases, the patient can be discharged from the cancer diagnostic pathway and asked to continue annual surveillance or return for short-term follow-up.

Individuals requiring a biopsy need to be guided through the multiple steps necessary to obtain a definitive diagnosis. This patient-navigation process can break down if it requires the patient to travel to another location for a biopsy procedure. Ideally, imaging and biopsy procedures are performed in the same location and during the same visit. The options for biopsy procedures include core-needle biopsy (gold standard), fine-needle aspiration, or incisional biopsy. The optimal sampling methodology will vary, depending on the routine availability of equipment and trained staff to perform the needle biopsies, and pathologists to provide the needle-sampling results *(7)*.

Box 13. How often are benign breast-cancer diagnostic work-ups conducted in unscreened populations?

Among 7573 previously unexamined women in rural Ethiopia who underwent CBE:

- 258 (3.4%) complained of a breast problem
- 49 (19%) were eligible for a needle biopsy
- 5 (10.2%) were diagnosed with cancer

The resulting prevalence in this rural community was in line with the data from the population-based cancer registry in the urban context (which accounts for the small sample) *(37)*.

Pathology and biomarker testing

For a specific breast tumour, pathology laboratories provide the definitive tissue diagnosis (malignant versus benign) that is required to determine if and what type of cancer treatment is required. Histopathologic features are summarized in a standardized written report with the aim of classifying breast tumours *(38)* that, together with standard prognostic factors, can help guide treatment decisions. Tumour size (T stage), lymph-node status (N stage), and whether there is distant metastasis (M stage) are the data required for cancer staging. **Incomplete, non-standard, and poor-quality pathology reports result in insufficient and inappropriate care, which negatively impacts outcomes.**

The pathology laboratory also determines tumour-marker expression for the estrogen receptor (ER), the progesterone receptor (PR), and the human-epidermal-growth-factor receptor (HER2), which defines the subtype of the breast-cancer tumour. This subtyping is essential for breast-cancer treatment since the selection of anti-cancer medication is based on its findings. Tumour-biomarker expression is generally determined by immunohistochemistry (IHC), which uses antibody reagents to determine the molecular expression of a given cancer.

Skilled pathologists, laboratory technicians and diagnostic equipment are often in short supply, and centralized testing may not be available to serve an entire region or country adequately or efficiently. **Centralized testing improves quality and often reduces the cost per assay through high-volume testing; however, it can exacerbate systematic delays in diagnosis** as patients and pathology specimens must often travel/be transported to the testing centre (Box 14). Delays are worsened if biopsy specimens need to be transported again to a more centralized laboratory for biomarker evaluation.

Overall, the goal of histopathology diagnosis is for 100% of patients with breast cancer to receive a confirmed diagnosis with a standard biomarker evaluation (ER, PR, human-epidermal-growth-factor receptor-2/neu oncogene overexpression (HER2/neu)) and a report that describes the breast-cancer features and subtype based on these findings to guide treatment decisions in alignment with WHO recommendations for the selection and use of essential in vitro diagnostics *(40).* In addition, **fast-tracking centralized biomarker evaluation, or utilizing point-of-care testing for biomarker evaluation will shorten the time to diagnosis and the systemic delays typical in LMICs.**

Box 14. Pathology laboratory services

A laboratory serving a catchment population of 1 million people should process 10 000 specimens per year (40 samples per working day) to efficiently utilize its resources, including tissue-processing equipment, consumables, and technical staff.

To achieve this level of centralization, pathology laboratories need to plan strategically to ensure the transportation of an appropriate number of specimens to the facility to meet this benchmark *(39)*.

Centralization versus decentralization of diagnostic services

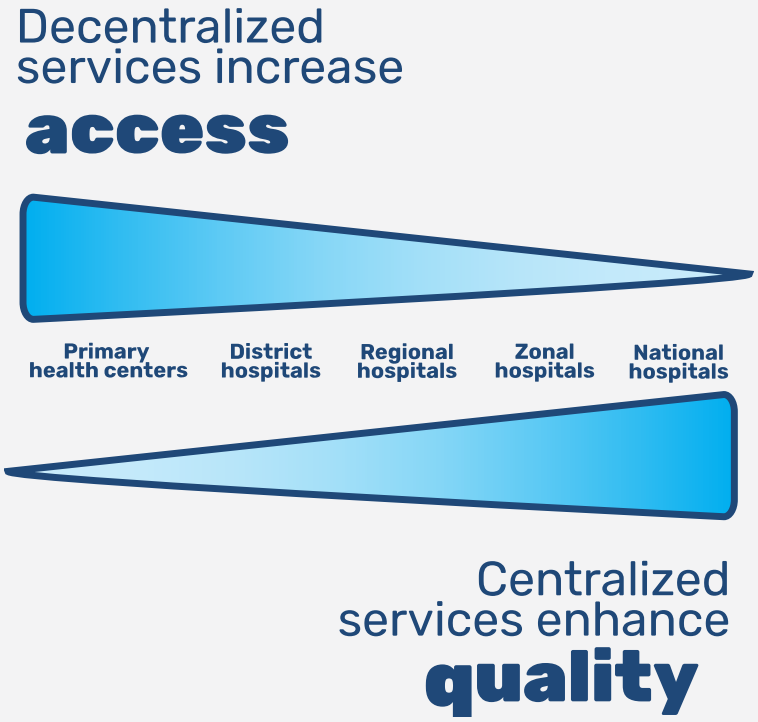
Breast diagnostic services (complete clinical examination, breast imaging, tissue sampling) require a level of expertise and resources that go beyond the primary-care level. **A diagnostic centre needs to be available and accessible to work-up breast abnormalities.** By centralizing the services, quality is better maintained; however, centralized services are less convenient for patients who need to travel to access them, and this can be a source of delay in diagnosis (Fig. 14).

Moreover, it is undesirable to locate all diagnostic services at a tertiary-care facility, since the number of patients requiring services would be many times larger than the number of those who are ultimately found to have cancer. This would create a patient-referral bottleneck that could markedly reduce health-system efficiency. **Secondary-level hospitals may be the best location for breast diagnostic services if they can secure the specialized expertise required to maintain quality, and they are more likely to be geographically accessible.**

Decentralized testing and the use of leapfrog or point-of-care technologies may provide solutions that can minimize systemic delays and improve completion of the diagnostic pathways at similar or lower costs, without compromising quality. The use of fine-needle aspiration instead of core-needle biopsy permits faster tissue processing. Digital imaging and telepathology services can alleviate the need for the presence of a skilled pathologist or cytotechnologist on site. Emerging technologies, such as Messenger RNA (mRNA) biomarker assays, can be used to supplement or replace IHC and in-situ hybridization laboratory techniques, of which the latter can only be used in the most centralized, highly skilled laboratories. The use of mRNA assays where internal quality controls are included may permit testing outside the cancer centre. In addition, it can mitigate some of the quality-control issues and allow the devolution of testing from the centralized test sites to the local sites where tissue blocks are obtained *(41)*.

A balance between centralized and decentralized diagnostic services is generally required. If it is not feasible to fully decentralize the imaging and pathology services, well-organized sample-transport systems and information systems can effectively decentralize sample collections, while minimizing patient travel and still enabling critical results to be obtained in a reasonable timeframe (Box 15).

Fig. 14. Centralization versus decentralization of breast-health services



Box 15. Co-localization of imaging and pathology services

Triple-test evaluation requires the comparison of clinical examinations, imaging, and pathology findings to determine whether the separate test results correlate (are concordant) or conflict (are discordant) with each other.

Discordant findings can be a reason to repeat tissue sampling.

High-quality diagnostic services require the radiology and pathology teams to compare each other's findings to assess how well the imaging level of suspicion is reflected in the actual pathology (concordant versus discordant).

The consolidation and coordination of imaging and pathology services into commonly accessible centres can optimize diagnostic quality.

Cancer staging

Once a cancer diagnosis has been confirmed, the patient should undergo staging to evaluate the extent of disease. Accurate staging is essential to guiding treatment. Staging is based on clinical features, radiological imaging, and surgical findings. Initial cancer staging, based on clinical assessment, is performed at the time of initial diagnostic evaluation (Pillar 2), but definitive cancer staging often requires testing and diagnostic services, which may only be available at the tertiary-care level (Pillar 3).

The clinical stage can also be used to evaluate the effectiveness of cancer-control policies. **Countries that have successfully achieved sustained reductions in breast-cancer mortality in recent years have at least 60% of their breast-cancer cases diagnosed at stages I and II** *(4)*. This high proportion of early-stage diagnoses reflects the capacity of the health-care system to detect cancer early, either through screening or at early symptomatic presentation. It also illustrates access to quality services that allow timely diagnosis and referral for initiation of treatment. **Delays between the identification of symptoms and the start of treatment have been associated with more advanced stages of disease at diagnosis and poorer survival.**

The most widely used classification system for breast-cancer staging is the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumour, node, metastasis (TNM) staging (AJCC /UICC TNM) system, which is based on anatomic features: tumour size (T), nodal status (N), and metastases (M). Despite the ample use of the TNM staging system in clinical care, cancer registries, especially those in LMICs, still face important challenges to collecting these data for all cancer patients. In LMICs, this translates into registries having limited data on breast-cancer stages and, thus, a limited means of comparability. For this reason, use of the Essential TNM Staging System *(42)* has been proposed, as a minimum, to allow population registries to provide staging information when full information on the TNM stage is missing.

AJCC/UICC TNM anatomic staging

The anatomic staging of breast cancer considers tumour size (T), nodal status (N) and metastasis (M) (Fig. 15). Despite the recent development of additional prognostic staging systems, **anatomic staging still provides an accurate prediction of outcome and can be applied to all patients with breast cancer worldwide**, particularly in regions where biomarker tests are not routinely available. In addition, although anatomic staging has evolved over the years, it still can be used for historical comparison, providing a consistent universal terminology for physicians worldwide. Although the anatomy-based staging system provides important insight into a patient's prognosis and global health, the addition of biomarkers refines the prognostic information and leads to better management and, therefore, better outcome.

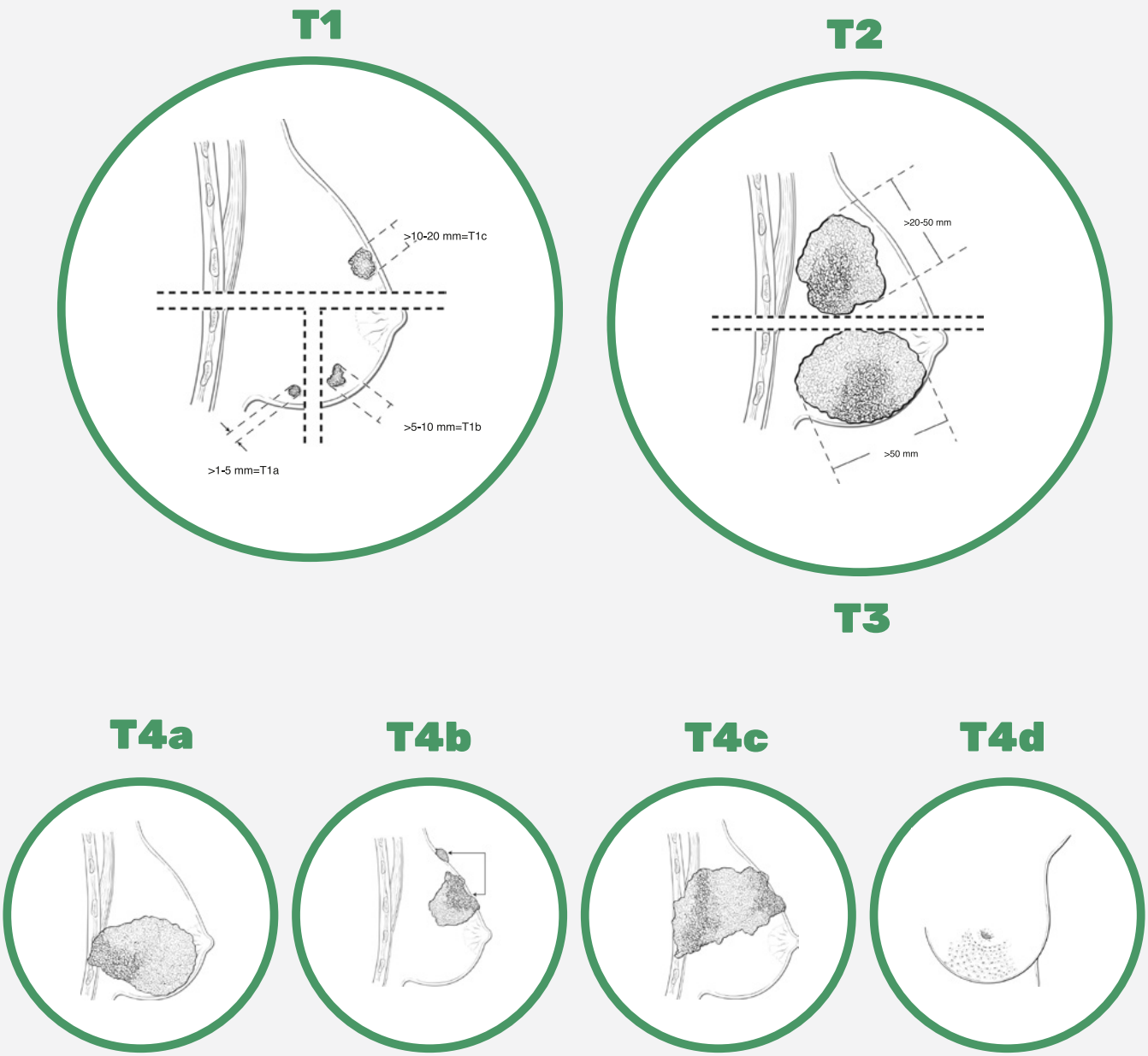
Prognostic staging

Prognostic staging takes anatomic staging into consideration, but also stratifies by biological factors, such as tumour grade, proliferation rate, ER and PR expression, human-epidermal-growth-factor-2 (HER2) expression, and gene-expression prognostic panels *(44)*. These biological factors enable not only an accurate determination of prognosis but also a selection of systemic therapy. At the same time, biological factors are increasingly affecting the locoregional treatment of breast cancer. In consequence, prognostic staging is valuable for predicting outcomes and, in addition, provides a framework for therapeutic targeting.

Essential TNM

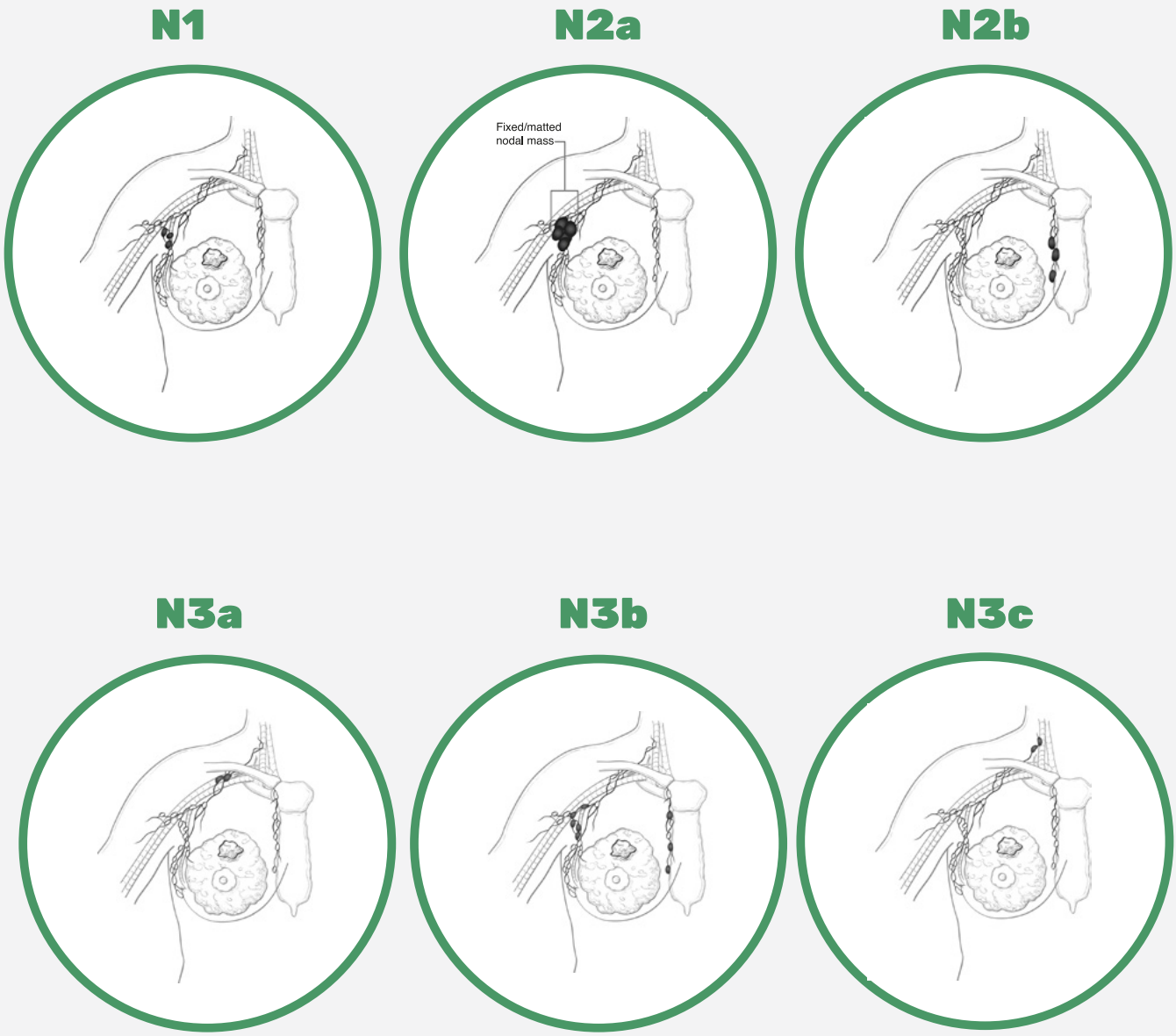
Despite the importance of cancer staging for population-based cancer registries, such data are often incomplete, or too complex to be collected from medical records. To overcome these barriers, simplified staging systems, such as the Essential TNM tool, have been developed. Cancer registrars can use Essential TNM when the individual elements for standard TNM staging have not been accurately recorded. Essential TNM is composed of three key elements that together summarize the extent of cancer in the patient: M – the presence or absence of distant metastasis; N – the presence or absence of regional node metastasis/involvement; and T – the extent of invasion and/or size of the tumour *(42)*.

Fig. 15a. TNM anatomic staging – T stage in breast



Source: reproduced with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the American Joint Commission on Cancer (AJCC) Cancer Staging Manual (8th edition). Springer International Publishing: American Joint Commission on Cancer; 2017 [cited 2023 Feb 18].

Fig. 15b. TNM anatomic staging – N stage in nodal beds



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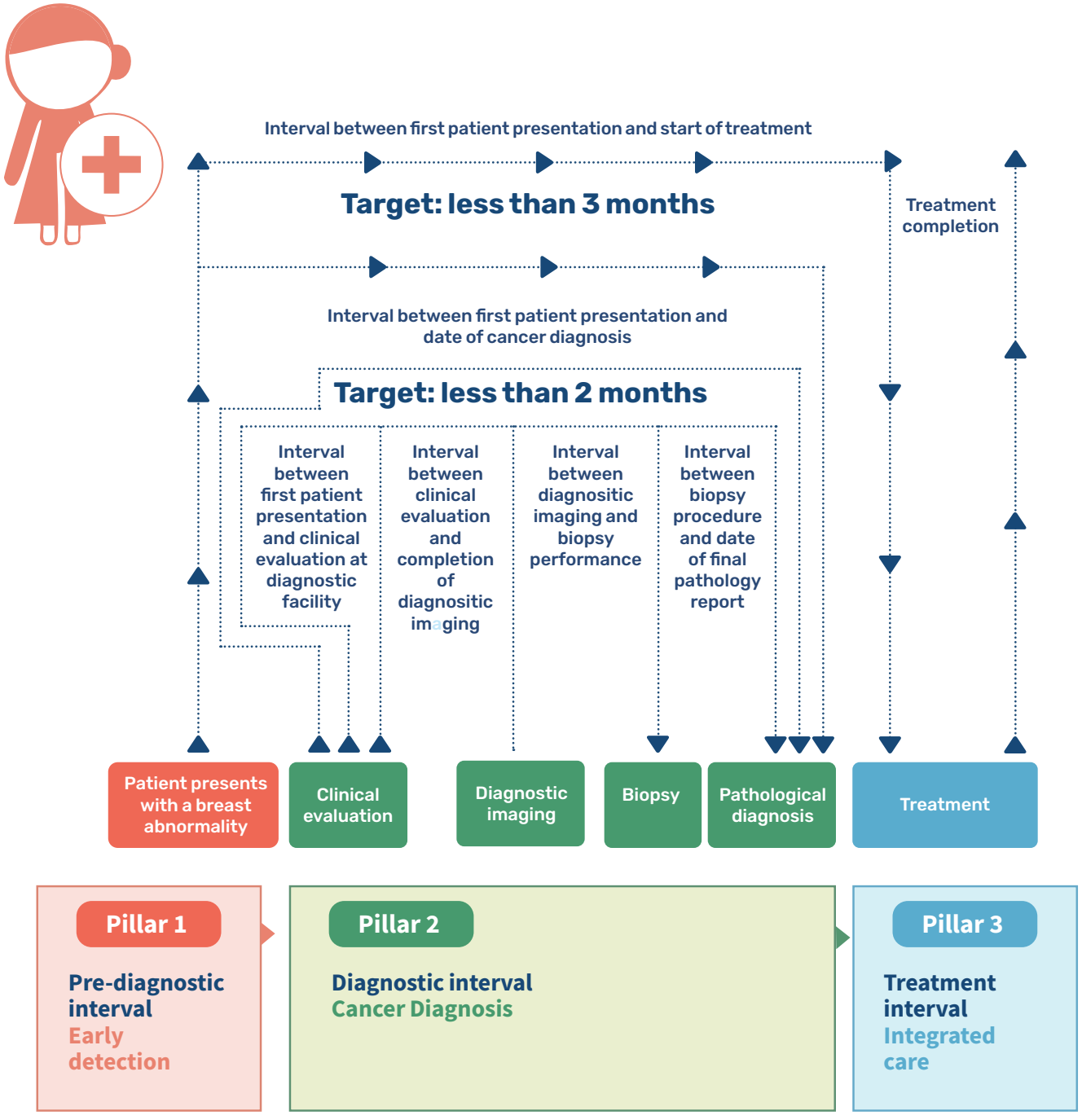
Monitoring and evaluation of the diagnostic interval

Delays from first presentation to the health-care system to breast-cancer diagnosis (diagnostic-interval delays) are associated with a greater likelihood of late-stage diagnosis and lower chance of breast-cancer survival. The **KPI for Pillar 2 is for breast cancers to be diagnosed within two months of initial presentation to a health-care system**. Monitoring and evaluation of this time interval is an important component of maintaining the quality of breast-health care (Fig. 16).

Delays can be experienced across all three intervals (Fig. 16). Long delays to individual presentations may suggest low levels of community awareness of breast-cancer signs, symptoms and treatability, and limited access to or trust in the health care system (Pillar 1). Delays between presentation with a breast mass and diagnosis may result from a lack of clinical expertise in recognizing that the mass is suspicious for cancer. Other reasons for delays include the inability to perform diagnostic imaging and/or a diagnostic biopsy procedure without referral to a larger treatment centre, process a diagnostic specimen locally (necessitating transport of the specimen to a laboratory facility), or send a pathology specimen to another specialized facility to obtain breast-cancer biomarkers (Pillar 2).

Although centralizing diagnostic testing at referral centres may increase quality control, it can also make it difficult for patients to access these services and increase the likelihood of their not be able to complete all the indicated testing in a timely fashion. Cross-facility coordination and patient navigation is critical to minimizing delays.

Fig. 16. Breast-cancer diagnostic timeline and intervals for monitoring



Pillar 3: The treatment interval

Key messages from this chapter

Comprehensive breast-cancer management includes receiving and completing quality-assured cancer-directed therapies (surgery, radiotherapy, and systemic “anti-cancer” treatment), combined with supportive management in an integrated care model.

The treatment interval represents the episode when patients receive definitive care.

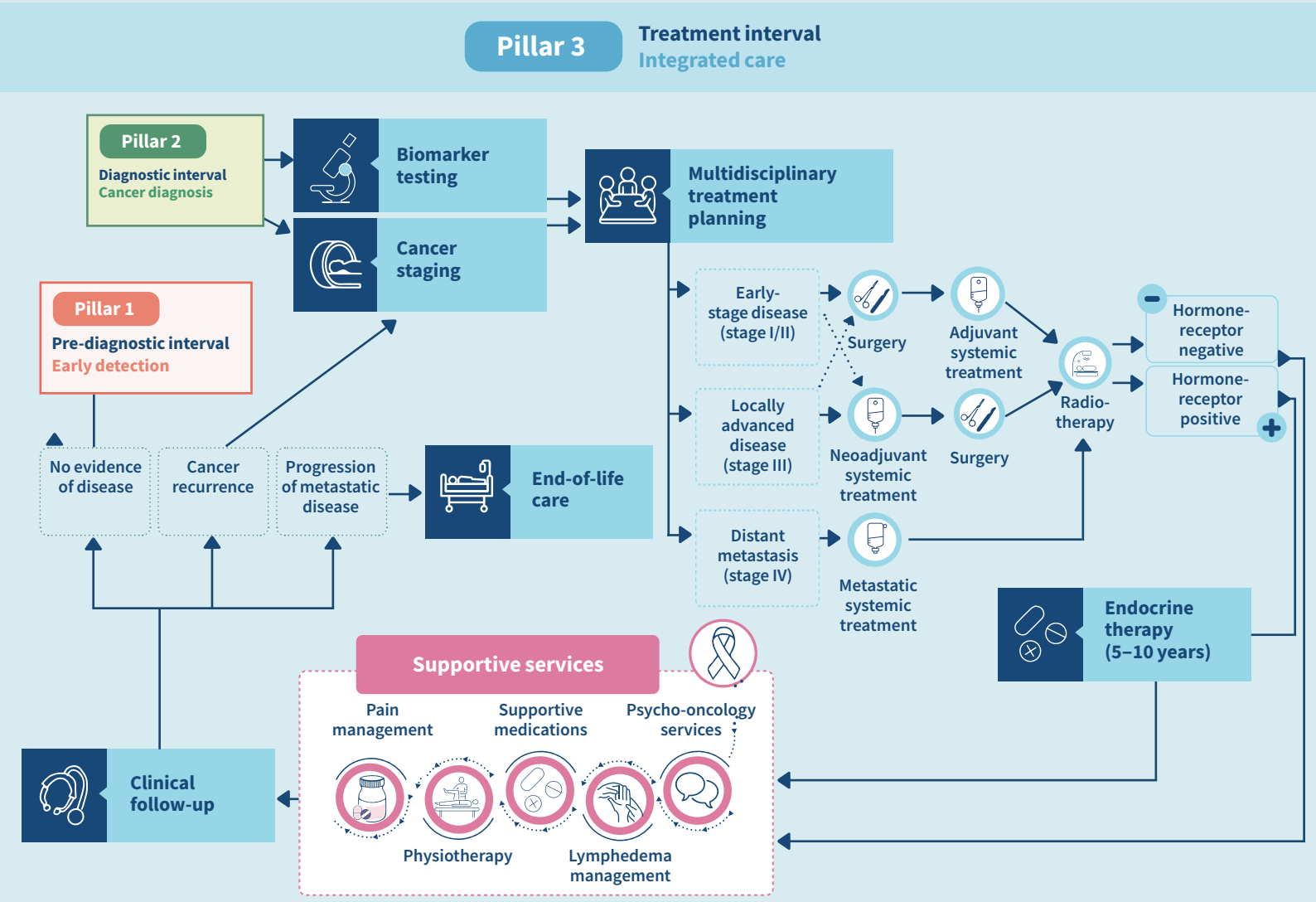
Treatment completion can be defined as the fulfilment of all components or steps of the therapeutic sequence unless there is an interruption for medical reasons. Incomplete treatment can lead to poorer patient outcomes, including worsened survival, and reduced quality of life.

Directed actions can promote treatment completion and reduce abandonment, according to a local context, by addressing patient- and system-related barriers. Provision of guideline-directed and supportive services are essential components of comprehensive breast-cancer services.

The KPI for Pillar 3 is that >80% of patients receive their recommended treatment to completion without abandonment.

The treatment interval (Pillar 3) represents the episode where patients shown to have cancer receive definitive care. Treatment includes cancer-directed therapies (surgery, radiotherapy, and systemic "anti-cancer" treatment, combined with supportive management in an integrated care model) (Fig. 17).

Fig. 17. The integrated-care portion of the treatment interval



Principles of multimodality treatment

Individuals diagnosed with breast cancer can have excellent results when they have access to high-quality, affordable treatment, tailored to the biology of their disease and administered in a timely manner. Effective treatment requires a multidisciplinary approach, often determined by tumour boards with expertise in radiology, pathology, surgical oncology, medical oncology, radiation oncology, and supportive oncology. In well-resourced settings, this approach has achieved 5-year survival rates exceeding 90%. **The optimal effectiveness of breast-cancer therapies depends on treatment beginning within three months of diagnosis and taken to completion without excessive interruption. Optimal results can be anticipated if at least 80% of newly diagnosed patients complete the full course of treatment** *(45).*

Breast-cancer-treatment modalities include surgery, radiotherapy and systemic treatments administered in alignment with evidence-based treatment guidelines tailored to the specific needs of newly diagnosed individuals.

Surgery

Breast surgery, as an essential surgical service (Box 16), is a key component of multidisciplinary breast-cancer care and should be directed at two sites: the breast and the axillary lymph nodes. **There are two strategies for treatment of breast cancer: (i) mastectomy (removal of the breast) with or without reconstruction; or (ii) breast-conserving surgery (lumpectomy).** Lumpectomy is the removal of the tumour and a rim of normal breast tissue around the tumour to ensure the eradication of all microscopic breast cancer. Following lumpectomy, radiation of the remaining breast tissue is required. In both strategies, mastectomy and lumpectomy plus radiation, the survival rates are the same. In resource-limited countries, mastectomy may be used more frequently because the breast cancers presented are larger in size at diagnosis and/or because radiation therapy is not available.

Box 16. Effective breast-cancer surgical services

These require that:

- communities have a sufficient number of surgeons trained in cancer surgery and that anticipated future needs are incorporated in workforce planning;
- policy-makers ensure the availability of the necessary resources (operating rooms, anesthesiologists) to allow patients to receive surgical treatment in a timely fashion;
- cancer-rehabilitation services, such as those for physical therapy, are available to reduce morbidity from breast-cancer surgery, such as lymphedema.

In addition to primary breast surgery, the axillary lymph nodes need to undergo pathologic evaluation since these represent the most common site for the spread of breast-cancer. Axillary staging (determination of the extent of cancer spread) is the single most powerful predictor of distant metastasis in the absence of treatment. **Current surgical recommendations include either complete removal of the axillary-lymph-node bed (axillary dissection) or selective removal of the lymph nodes to which cancer will spread first (sentinel lymph-node biopsy).** Neither breast surgery nor axillary surgery is recommended for patients with stage IV breast cancer (spread to other organs) as an initial step, and likely would not be required except in selected cases where locoregional disease control cannot be managed effectively by nonsurgical means (systemic therapy +/- radiotherapy).

Radiation therapy

Radiation therapy is required to control disease in the breast following breast-conserving surgery and may be required to treat the axillary-lymph-node bed when nodal disease is extensive prior to surgery. Radiotherapy halves the risk of first recurrence in these areas after surgery. Following mastectomy for node-positive cancers, radiation therapy reduces the risk of a recurrence in the mastectomy bed by about one third. In both scenarios, the absolute benefit is greater for patients with higher-risk breast cancers and is dependent on cancer stage and biological features. In some clinical cases, radiation therapy can substitute further axillary-lymph surgery following a positive sentinel lymph-node biopsy. This reduces the need for a second operation (axillary-lymph-node dissection) while reducing the risk of lymphedema, which is the most common surgical complication of axillary-node resection (Box 17) *(46)*.

Box 17. Features of a successful radiation-oncology programme

A successful radiation-oncology programme encompasses:

- technical expertise, including a clinical or radiation oncologist, a physicist/dosimetrist, and radiographers/ radiation-therapy technologists;
- evidence-based clinical regimens on breast radiation that include dosimetric objectives and constraints for target and normal tissues;
- access to regularly maintained equipment for external beam radiation therapy, with back-up in case of service interruptions and breakdowns;
- quality-assurance programmes on radiation therapy to ensure safety and efficacy;
- reimbursement schemes based on treatment indications, not on number of fractions given.

Systemic (anti-cancer medicine) treatments

Death from breast cancer results from the extensive spread (metastasis) of cancer to distant organs. Surgery and radiotherapy control the disease in the breast and lymph-node beds but cannot kill cancer cells that have already circulated throughout the body. The microscopic circulation of cancer cells occurs early in the evolution of a cancer, generally before a diagnosis has been made. Thus, the treatment group that most improves breast-cancer survival comprises anti-cancer medicines given before (neoadjuvant) or after (adjuvant) definitive local therapy (surgery followed by radiotherapy).

As the only therapy that circulates throughout the body, anti-cancer medicines treat cancer cells that have spread beyond the breast and nodes; however, to be effective they must be given in combinations (regimens) correctly chosen, according to the tumour subtype of a given cancer (Box 18).

The three categories of systemic anti-cancer medicines are: (i) chemotherapy; (ii) endocrine (or hormonal) treatments; and (iii) targeted biological therapies. Given in combinations (regimens) in randomized trials, they have been proven to increase breast-cancer survival.

Anti-cancer medication regimens are given in predetermined doses for a set number of cycles between which the patient's body has time to recover before the next round can be safely administered *(47)*. Most standard breast-cancer anti-cancer medicines (and therefore combination regimens) are already included in the WHO Essential Medicines List *(48)* making standard systemic breast-cancer treatment possible (Annex). However, the cost of certain medicines (e.g., trastuzumab) can be prohibitively expensive in some settings. To achieve mortality benefit, complete systemic therapy programmes must be delivered to each patient for the full number of cycles over a defined period.

Box 18. Systemic therapy for breast cancer

The choice of systemic therapy for breast cancer is based on the following:

- tumour biology, mainly breast-cancer subtype (ER, PR and HER2/neu receptor status) (additional factors include histological type, tumor grade, proliferation marker and lymphovascular invasion;
- genomic scores, such as OncotypeDx, also guide systemic-treatment strategies);
- tumour burden, determined by the TNM stage (tumour size, axillary-lymph-node involvement, and the presence/absence of distant metastases);
- patient characteristics (including age, performance status, comorbidities, and patient preferences).

Incomplete systemic therapy will have reduced mortality benefit.

Before initiating systemic therapy, every breast-cancer case should be histologically confirmed. Suspected metastatic disease should also be biopsied to confirm the diagnosis and to evaluate tumour biomarkers, both measures being necessary to correctly guide treatment choices.

Systemic treatment should be started within 8–10 weeks of surgery if given as adjuvant (postoperative) treatment or within 4–6 weeks of diagnosis if given as part of a neoadjuvant (preoperative) treatment regimen. Neoadjuvant regimens are generally preferred for more advanced cancers. The duration of breast-cancer treatment with chemotherapy is generally 3–6 months; anti-HER2 therapy has a duration of up to 1 year although studies of shorter-course therapy are being reported. Endocrine (hormone-based) therapy is oral medication given for 5–10 years following the completion of all other treatments. With metastatic (stage IV) breast cancer, each line of therapy should be given until the disease progresses despite treatment, or if toxicity from the treatment becomes unacceptable.

Categories of systemic-therapy modalities

Endocrine (hormonal) therapy

Endocrine therapy is recommended for most ER+ breast cancers, both in the early and metastatic settings. The main agents are selective *estrogen-receptor modulators/degraders (tamoxifen)* and *aromatase inhibitors*. For some premenopausal women, suppression or ablation of ovarian function is necessary, and for some men with breast cancer a *luteinizing hormone-releasing hormone* agonist might be required. Most of these agents can be administered orally and have a high safety profile. For example, endocrine treatment is effective, available at low cost, and has few side-effects so that it can be managed by trained nurses at first- and second-level hospitals.

Cytotoxic chemotherapy

Several agents have been shown to be effective in prospective randomized trials. They are largely administered as combination regimens, follow specific evidence-based protocols, and should be taken through to completion. For EBCs, the most important agents are anthracyclines and taxanes. For LABCs or MBCs, additional agents, such as capecitabine or vinorelbine, improve efficacy. Platinum salts are also important in advanced-stage disease.

Chemotherapy is necessary for the management of most triple-negative and HER2+ subtypes in both early and metastatic settings. It is also crucial for high-risk ER+/HER2-negative EBC and endocrine-resistant LABC or MBC. In addition to expertise in treatment selection, expertise in managing the cytotoxic chemotherapeutic agents is critical as the side effects can be highly significant and must be well managed to bring patients safely through the complete course of treatment course and avoid early discontinuation.

Targeted therapies

These agents include specific medications or systemic agents that are directed against a specific tumour characteristic. HER2-targeted therapy is based on the use of targeted agents (including antibodies) directed against the HER2 receptor. Several medicines target this receptor, the oldest and most important being Trastuzumab. Used in conjunction with cytotoxic chemotherapy, Trastuzumab reduces breast-cancer mortality by one third in patients with early HER2-positive breast cancer *(49)* and improves disease-free survival in patients with HER2-positive locally advanced or metastatic disease *(50)*. The field is highly dynamic. Ongoing studies are demonstrating new potential improvements. The main limiting factor for targeted therapies is the current high cost of these agents. However, biosimilars have become available at reduced cost and can be used instead of Trastuzumab. In some settings, access to HER2 testing is a critical limiting factor (e.g., <20% of patients get IHC results) as the anti-drug can only be given if the target is known and present (**Box 19**).

Box 19. Successful systemic-therapy programmes for breast cancer

The choice of systemic therapy for breast cancer is based on the following:

These include:

- medical oncologists who can prescribe systemic therapy, manage toxicity and monitor efficacy;
- trained nurses who can administer systemic therapy and help in the monitoring and evaluation of toxicity;
- trained pharmacists;
- access to 24-hour care in emergencies;
- protocols on the preparation for, and the safe handling and administration of, chemotherapy;
- annual (at a minimum) quantification of medicines and volumes;
- procurement mechanisms to avoid stockouts and make full use of generic manufacturers, as appropriate, to reduce costs;
- access to supportive-care medicines for the prevention and management of toxicities;
- tumour biology, mainly breast-cancer subtype (ER, PR and HER2-receptor status plus additional factors, such as histological type, tumor grade, proliferation marker and lympho-vascular invasion, and genomic scores to guide systemic treatment, such as OncotypeDx);
- tumour burden, determined by the TNM stage (tumour size, axillary-lymph-node involvement, the presence/absence of distant metastases):
- patient characteristics, including age, performance status, comorbidities, and patient preferences.

Evidence-based cancer-treatment guidelines

High-quality evidence-based guidelines for breast-cancer treatment provide a framework for treatment planning. Examples of high-quality evidence-based guidelines for the provision of multimodality treatment regimens include those provided by the National Comprehensive Cancer Network (NCCN) *(51)*, the European Society for Medical Oncology (ESMO) *(52)* and the American Society of Clinical Oncology (ASCO) *(53)* (**Table 3**). Such guidelines largely agree on treatment sequencing and preferred regimens, but almost all have been developed based on high-resource settings and the need for them to be contextually adapted. However, a few of them do provide resource-stratified guidance on improving breast-cancer survival in LMICs *(54)*. From the perspective of national cancer-control planning, it is critical to assess and monitor the level of adherence to evidence-based guidelines and the ability of the health-care system to deliver the care recommended in a timely fashion (**Box 20**).

In addition to treatment guidelines, there are various resources available, published by several organizations, which provide standards to guide the development of breast-cancer centres with a focus on optimizing multidisciplinary care *(55,56)*.

Box 20. Why are cancer-management guidelines important?

Providing access to standardized guideline-based management is necessary to improve guideline compliance and reduce breast-cancer mortality.

Cancer guidelines can only help improve cancer outcomes if the care described in the guidelines can be delivered to completion without significant interruption.

High-quality, evidence-based guidelines are available from HICs, but generally need to be adapted to existing services and resources.

Guideline adaptation to existing services and affordable care (resource stratification) is necessary in resource-constrained settings to ensure sustainability over time.

Monitoring the degree to which guideline adherence is achieved at the patient level over time is critical.

Table 3. Examples of high-quality evidence-based guidelines for the provision of multimodality-treatment regimens

Organization	Guideline format	Guideline update frequency	Conflict of interest policy and disclosure
American Society of Clinical Oncology (ASCO)*(53)*	Topic-specific[a]	As scheduled	Yes
American Society for Radiation Oncology (ASTRO) *(57)*	Topic-specific[a], focused on radiotherapy considerations	As scheduled	Yes
Breast Health Global Initiative (BHGI) *(58)*	Topic-specific[a], particularly focused on care in LMICs	As scheduled	Yes
Cancer Care Ontario (CCO)	Topic specific[a]	As scheduled	Yes
European Society of Medical Oncology (ESMO *(52)*	Topic-specific[a] and semi-algorithmic[b] (hybrid) Pan-Asian adaptation available	As scheduled	Yes
National Comprehensive Cancer Network (NCCN) *(51)*	Algorithmic[b] through continuum of care. Resource-stratified adaptation available	At least annually	Yes
Saint Gallen International Consensus Conference *(59)*	Topic-specific[a]	Every 2 years	-

[a]Topic-specific: each guideline individually addresses in depth a specific clinical scenario/question, e.g., chemo- and targeted therapy for patients with HER2-negative metastatic breast cancer, that is either Endocrine-pretreated or hormone-receptor negative, or, radiation therapy for the whole breast.
[b]Algorithmic: low diagram-based composite guideline that addresses multiple decision points along a cancer course.

Treatment completion without abandonment

Treatment completion can be defined as the fulfilment of all components or steps of the therapeutic sequence unless there is an interruption for medical reasons. Incomplete treatment can lead to poorer patient outcomes and reduced quality of life. **The KPI for a breast-cancer programme is that >80% of patients receive their recommended treatment (Box 21).**

The term "abandonment" refers to failure to complete a treatment regimen due to reasons other than medical indications for treatment disruption. In some settings, its use is incorrectly interpreted by patients as blaming them for not following up. In fact, abandonment is often the result of health-system features or failures that are beyond the patient's control. The rates of, and reasons for, abandonment should be tracked with the aim of addressing system failures that may have contributed to it.

Missing one adjuvant chemotherapy cycle or a radiotherapy fraction is not considered abandonment if there is a medical indication for skipping the treatment. **Brief interruptions of treatment due to technical reasons (machine downtime, lack of supplies, lack of personnel) are not abandonment if treatment is resumed in a reasonable timeframe.** However, more extensive delays or treatment interruptions can contribute to patients not completing their regimens according to plan or may cause complete discontinuation. Abandonment should also be distinguished from "loss of follow-up", the latter being used in referring to patients who have completed the prescribed therapeutic schedule but do not return for follow-up.

Box 21. Factors contributing to patient abandonment of prescribed cancer treatment

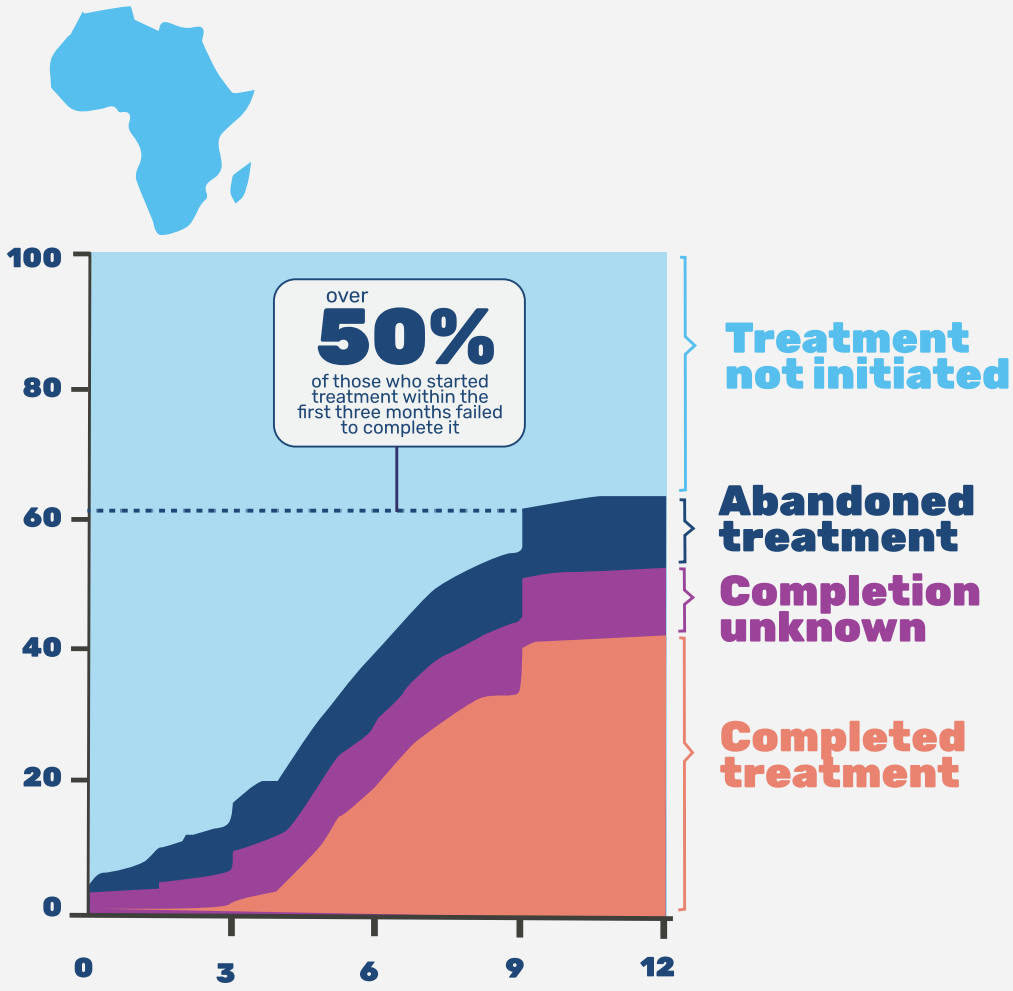
These include:

- patient-related factors: lack of engagement, social pressure, religious beliefs, philosophical attitudes, stigma;
- accessibility-related factors: lack of access to services due to distance to point of treatment;-component delivery; lack of transportation; no provision of lodging/accommodation in or near point of delivery;
- financial factors: unaffordable treatment costs, or costs related to being able to access treatment, such as those for transport and accommodation;
- factors related to failure of the health-care-system: lack of planning, personnel and equipment; overload; structural racism; ageism; gender discrimination; and/or other forms of discrimination.

Monitoring and evaluation of the treatment interval

Access to and the affordability of standard breast-cancer treatment is a major obstacle to improving breast-cancer outcomes. Treatment should start within three months of diagnosis as studies have shown that delays beyond this period of time lead to lower breast-cancer survival rates *(8)*. Moreover, monitoring and evaluating progress towards achieving the KPI of having >80% of breast-cancer patients complete the recommended treatment is critical to improving survival outcomes. **Abandonment rates can reach or exceed 50% in some LMICs** as shown in the African Breast Cancer Disparities in Outcomes (ABC-DO) study, according to which half of the patients who started treatment within three months failed to complete it (Fig. 18).

Fig. 18. Multimodal treatment use (surgery and systemic therapy) in the ABC-DO cohort study in five sub-Saharan African countries



Source: reproduced with permission of the publisher, Elsevier Ltd., from Foerster et al. *(9)*.

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Management of metastatic breast cancer

Metastatic breast cancer (MBC) is the most progressed version of ABC and is defined by the spread of the primary tumour to distant sites and organs, most often bone, lung, liver and brain. When cancer is found at initial diagnosis to have metastatic spread, it is referred to as stage IV breast cancer. Patients with MBC can suffer from cancer-related symptoms and experience a poorer life expectancy *(60)*. When cancers have spread to metastatic sites, the disease is considered treatable but not curable. The timely institution of anti-cancer, high-quality, effective treatments can ixmprove quality of life and overall survival *(61)*. In recent years, with access to multidisciplinary quality care and new targeted anti-cancer agents, the median survival of patients with MBC has increased from 2–3 years to 5 years for two of the three main breast-cancer subtypes, which encompass up to 80% of all patients *(62,63)*. **Access to MBC treatment is fundamental to ensuring equitable health care and avoiding stigma and the exclusion of patients with advanced/metastatic cancers.**

Treatment of MBC/ABC is based on multiple therapeutic modalities. **Since the disease is disseminated at these stages, the main therapeutic approach is systemic therapy.** However, radiotherapy and, in some circumstances, surgery are also indispensable for the adequate treatment of some types of metastases. In some situations, surgery and radiotherapy are also important in the management of de novo metastatic disease *(64)*.

High-quality care is the cornerstone of improvements in short- and long-term outcomes. It is crucial that patients with MBC are discussed by a multidisciplinary tumour board and that a common strategy is defined. No treatment should be initiated without the histological confirmation of malignant disease. For de novo MBC, a biopsy of the primary tumour is needed; for recurrent MBC, a biopsy of one of the metastatic lesions is recommended for confirmation. **Throughout the patient's journey, starting as early as possible, supportive oncology (including palliative care) and psychological support are also fundamental** *(65)*.

The **standardization of patient-centred metrics,** including patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs), regarding access to treatments for MBC is critical (Box 22). Measures of overall survival and breast-cancer mortality, as reported by cancer registries, are generally important to providing an understanding of the impact of treatments. A fundamental indicator for tracking the timeliness of access to cancer treatments is the interval between MBC diagnosis and start of treatment. In addition, it is important to monitor the proportion of patients still on treatment 12 months after its start to track treatment abandonment. **Since MBC is an incurable disease, some form of treatment is almost always necessary.**

Box 22. Metrics useful in the monitoring and evaluation of metastatic cancer

These are:

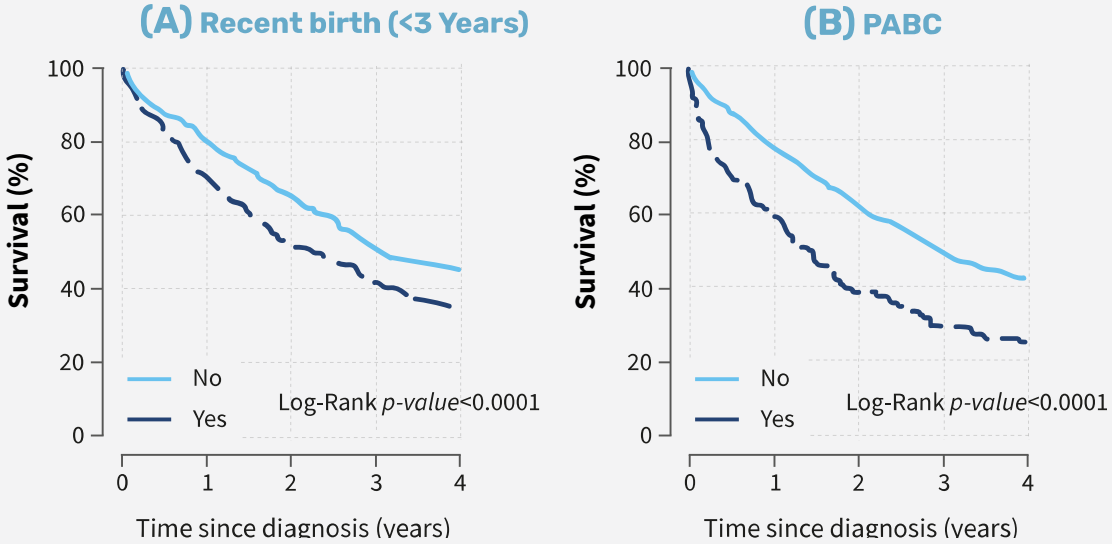
- completeness of the pathology evaluation of prognostic/predictive biomarkers (ER, HER2)
- proportion of patients receiving hormone treatment for ER-positive cancer
- proportion of patients with metastatic cancer whose data have been collected for the last 5 years *(65)*.

Management of breast cancer during pregnancy

Breast cancer during pregnancy is infrequent and commonly presents with more advanced disease (axillary-lymph-node disease and larger primary-tumour sizes). Histologically, the tumours tend to be more poorly differentiated and more frequently ER-/PR-negative than those in non-pregnant women; approximately 30% of them are HER2-positive *(66)*. Because the breast normally changes significantly during and immediately following pregnancy, diagnosis is often delayed because neither the patient nor the physician suspects malignancy. Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during or within one year of delivery, the biological significance of which is that these breast cancers have been exposed to the hormones of pregnancy. The ABC-DO study found that women from sub-Saharan Africa with PABC, and even women who had not long given birth (cancer diagnosed ≤3 years from delivery), had a >50% higher risk of mortality at 4 years than other premenopausal women. This emphasizes the importance of prompt diagnosis and the administration of effective treatment to completion in this patient cohort (Fig. 19) *(67)*.

As with any breast abnormality, the evaluation of the pregnant patient with suspected breast cancer should include a physical examination, paying particular attention to the breast and regional lymph nodes. Diagnostic MG can be done safely with shielding; accuracy is reported to be greater than 80% *(69)*. Ultrasound can be used to examine the breast and regional lymph nodes, assess the extent of disease, and perform a guided biopsy. Ultrasound findings have been reported to be abnormal in up to 100% of breast cancers occurring during pregnancy *(68)*. Biopsies for the cytologic evaluation of a suspicious breast mass may be carried out with fine-needle aspiration of the breast and suspicious lymph nodes.

Fig. 19. Kaplan-Meier survival curves, by reproductive factors in ABC-DO women



Notes. (A) Recent birth (within past 3 years) (yes/no), among premenopausal women. (B) PABC (yes/no), among premenopausal women.
Source: reproduced with permission of the publisher, John Wiley and Sons, from Boucheron et al. *(67)*.

However, **the preferred biopsy technique is core-needle biopsy.** This provides tissue for the histologic confirmation of invasive disease and for hormone-receptor and HER2 analyses and is best for distinguishing cancer from the physiological changes of pregnancy *(69)*.

Cancer-staging studies should be tailored to minimize fetal exposure to radiation. For clinically node-negative T1–T2 (up to 5 cm) tumours, a chest x-ray (with shielding) and blood tests are appropriate. In patients who have clinically node-positive, or T3 (greater than 5 cm) breast lesions, an ultrasound of the liver and magnetic resonance imaging (MRI) of the thoracic and lumbar spine without contrast may be employed. Documentation of the presence of metastases may alter the treatment plan and influence the patient's decision on whether to terminate or continue with the pregnancy.

Assessment of the pregnancy should include a maternal–fetal medicine consultation and a review of the maternal risks, such as hypertension, diabetes, and complications with prior pregnancies.

Documenting fetal growth and the development and age of the foetus through ultrasound is appropriate. An estimation of the date of delivery will help in planning systemic chemotherapy. In addition, a maternal–fetal medicine consultation should include counselling on maintaining or terminating the pregnancy.

Once a cancer diagnosis is confirmed, the initiation of breast-cancer treatment should not be delayed because of the pregnancy. The treatment options are the same as those for a patient who is not pregnant, but the sequence of treatment may be altered to avoid radiotherapy while the patient is still pregnant. The indications for systemic chemotherapy are the same in the pregnant patient as in the non-pregnant patient; however, chemotherapy should not be administered during the first trimester. **Chemotherapy can be given safely during the second and third trimesters**, using agents that do not cross the placental barrier and, therefore, do not directly affect the foetus. Surgery can also be performed safely during pregnancy.

The most common surgical procedure for pregnancy-associated breast cancer is modified radical mastectomy. However, **breast-conserving surgery is possible if radiation therapy can be delayed until the postpartum period** *(70)* When breast surgery is performed at 25 weeks of gestation or later, obstetrical and prenatal specialists must be immediately available on site should the need to deliver a viable fetus arise. Sentinel-node biopsy should not be offered to patients who are under 30 weeks pregnant *(71)*. However, the use of isosulfan blue dye or methylene blue dye in procedures involving sentinel-node biopsy during pregnancy is discouraged because these dyes may cross the placental barrier and their effect on the fetus is unknown.

Supportive services in oncology

The supportive care that breast-cancer patients need includes the management of physical symptoms (pain) and relates to the psychosocial and spiritual aspects of care. **While resource constraints can limit access to these services, the delivery of supportive services should not be viewed as optional.** On the contrary, supportive services are essential to patient compliance and effective care delivery during treatment, as well as to recovery following therapy (Fig. 20)

Supportive services during treatment

During treatment, breast-cancer patients need supportive care, including the management of treatment-related toxicities. In addition, these patients have educational, psychosocial, and spiritual needs *(72)*. Inadequate support services to manage treatment toxicity has serious adverse effects on the patient and can lead to treatment abandonment. For example, antinauseants and antiemetics are essential medications for helping patients to complete chemotherapy with tolerable side effects (Annex).

Supportive services following treatment

The increasing success of breast-cancer therapies means that a large global population of women is impacted by the long-term sequelae of their breast-cancer treatment. Breast-cancer survivors may experience long-term treatment complications and must live with the risk of cancer recurrence *(73)*. addition, they often experience psychosocial complications that require supportive-care services *(74)*. Monitoring and support services should, therefore, be available for and accessible to these individuals. **Direct management may be offered with routine follow-up, usually for five years (Table 4).**

Fig. 20. Supportive services to help breast-cancer patients manage the negative effects of the disease and its treatment

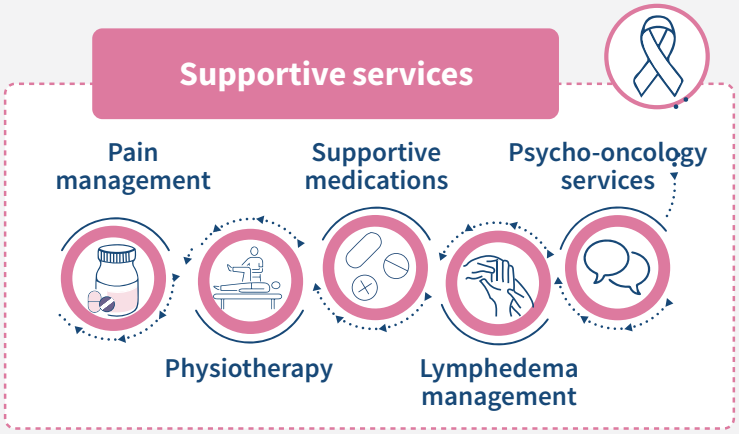


Table 4. Supportive oncology services: common concerns and required support

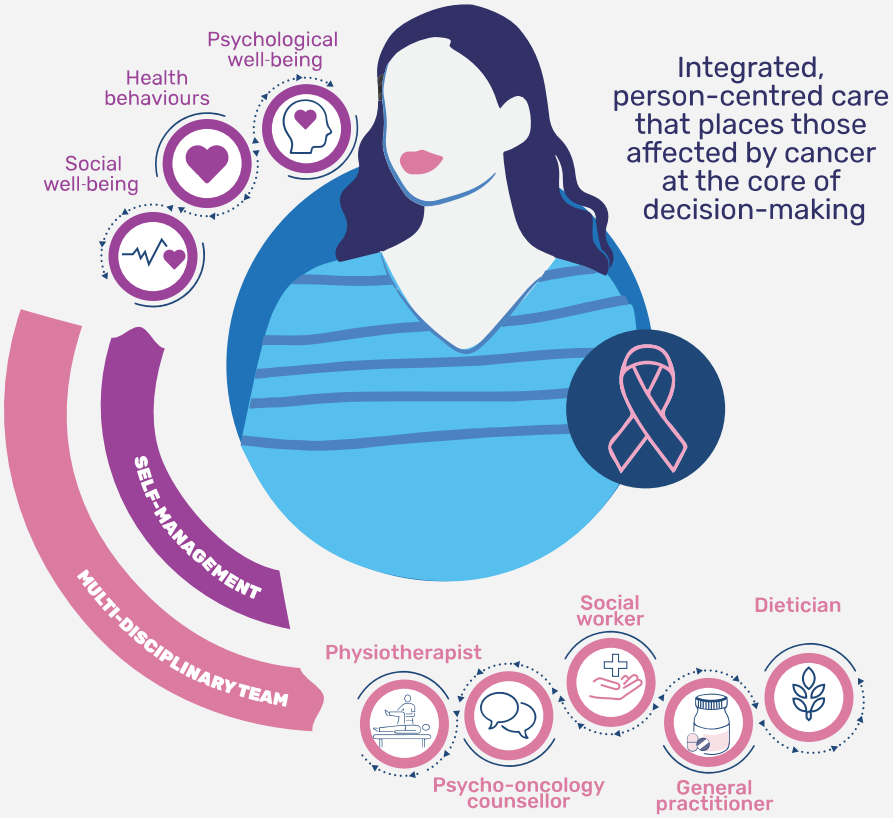
Common concerns	Professional support required	Social support required
• Stress • Depression • Anxiety • Fear of recurrence • Relationships • Intimacy • Quality of life, body image • Anger • Spirituality • Coping	• Physicians • Nurses • Social workers • Psychologists/psychiatrists • Patient navigators • Lay navigators	• Friends and family • Community: support groups, NGOs, spiritual advisors, art and music therapists
• Pain • Fertility • Fatigue • Constipation • Nausea and vomiting • Hair loss • Joint and muscle pain • Menopausal symptoms • Sleep disturbance • Loss of bone density • Lymphedema • Mouth and throat sores • Skin irritation • Surgical complications • Sexual health	• Physicians • Nurses • Pain and palliative specialists • Physical therapists • Pharmacists • Dieticians • Social workers • Patient navigators • Complementary therapists – acupuncturist, massage therapist	• Support groups • NGOs
• Health-system navigation Health literacy • Finances/insurance • Transportation • Lodging • Child/elder care • Employment/return to the workforce • Nutrition • Exercise	• Physicians • Nurses • Patient navigator • Social workers	• Friends and family • Community: support groups, NGOs, religious organizations

Psycho-oncologic needs and services

Psycho-oncology has evolved over the past 60 years into a recognized clinical field in which **the humanistic aspects of cancer diagnoses and treatment are explicitly addressed through interventions to reduce the psychological burden on patients and their caregivers** (Fig. 21).

The expansion of psycho-oncology has been empowered by the movement towards integrated, person-centred care that places those affected by cancer at the core of decision-making, surrounded by a health system oriented to meeting their needs *(75)*.

Fig. 21. Psycho-oncology in breast-cancer management



Palliative care and end-of-life management

Palliative care is an approach that improves the quality of life of patients (both adults and children) and their families who face problems associated with life-threatening illness *(76)*. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual. The holistic palliative-care approach to patient care, which incorporates all domains of the human experience of illness, is traditionally applied to help cancer patients cope with the impact of the disease and its treatment, and to manage symptoms, such as pain, nausea, fatigue, anxiety, delirium, confusion, and depression. At some point, **palliation and support become the central focus of care with the primary aim of addressing the patient's quality of life and supporting the family members.**

The latter are often the informal caregivers with a wide range of care requirements, including physical, psychological, practical, and financial needs. Palliative care is appropriate at any age and at any stage of breast-cancer care, and it can be provided along with curative and life-prolonging treatment.

End-of-life care (EoLC) is palliative care provided as a patient nears the end of life, a period which can last years. While the purpose of EoLC for breast-cancer patients is to enable them to "live well" and with dignity, no matter the condition of their health, the primary goal is to provide them with the assurance that the process up to their death will be compatible with their cultural needs, personal views, and preferences. **This priority is to ensure that the patient will feel comfortable during the end-of-life period and make it easier for the family members to support their loved one.**

Implementation strategies for success

Key messages from this chapter

Major improvements in breast-cancer outcomes can be achieved through directed interventions based on health-system performance, as measured by the GBCI KPIs for each Pillar.

Investing in data systems and embedding monitoring and evaluation into programme implementation allow stakeholders to determine the extent to which a programme or project is on track towards meeting its goals.

Performing a root cause analysis (RCA) to investigate underlying aetiologies relating to the KPI and three-pillar approach enables stakeholders to tailor effective implementation strategies. RCAs can reveal relationships among different variables and underlying causes, leading to process deficits.

The GBCI Framework provides explicit guidance on how RCA can facilitate directed policy and programmatic responses to address specific deficits in health systems for breast-cancer control.

Implementation planning

Major improvements in breast-cancer outcomes can be achieved if it is possible to correct health-system performance as measured by the GBCI KPIs. In the WHO stepwise approach to cancer control, four essential questions need to be asked and answered in implementation planning *(77)*.

Situational analysis

Where are we now?

Before making a plan, an assessment of how the system is required to establish a baseline:

- measure breast-cancer incidence and mortality rates;
- establish the stage distribution of cancers at presentation (early versus late);
- assess gaps in services related to breast-cancer awareness, diagnosis, treatment, and survivorship;
- conduct a fishbone or other root-cause analysis (RCA) to identify possible causes of significant service gaps.

Setting goals and objectives and selecting priority interventions

Where do we want to be?

In implementation planning, consideration should be given to:

- engaging stakeholders across all levels of the health-care system;

  confirming and prioritizing service gaps in the health-care system as seen through a fishbone analysis;
- selecting short- and long-term objectives that are specific, measurable, achievable, relevant and time-bound (SMART);

  determining evidence-based and resource appropriate interventions to address the gaps;
- choosing indicators and setting accompanying targets to measure outcomes;
- developing a monitoring and evaluation plan.

Identify steps needed to implement the interventions

How do we get there?

It is necessary to:

- recruit health authorities/ ministries of health to build support and engagement;
- secure a budget for the implementation of selected interventions by working with local, regional and national financing sources;
- consider integration with other programmes to maximize resources and facilitate implementation;
- develop and disseminate implementation plans;
- define governance structure and responsibilities;
- develop, pilot, and finalize relevant documents, including awareness-raising materials, training resources, data-collection tools and clinical regimens;
- ensure the availability and resourcing adequacy of diagnostic, treatment, and supportive services (in terms of human capacity, competency training, infrastructure and supplies);
- develop and implement a monitoring and evaluation plan;
- scale up interventions with proven benefits and include them in the national cancer-control plan, where it exists.

Continuous programme improvement

How do we maximize the impact on breast cancer?

To do so, it will be necessary to:

- develop a plan for scaling up proven, effective, and sustainable interventions, including timeline and milestones;
- continue routine monitoring and evaluation measures that focus on actionable metrics to ensure iterative programme improvement;
- address long-term sustainability and/or transitioning to the next level of service delivery when more resources become available;
- ensure the continuous availability of funding resources, policy guidance, and training to facilitate intervention maintenance and effectiveness.

Case study from sub-Saharan Africa

In the ABC-DO study conducted in 5 sub-Saharan African countries, 3-year breast-cancer survival varied widely but were low overall, especially in Nigeria, Uganda and Zambia *(45)* (Fig. 22). While the overall outcomes were better in Namibia and South Africa, there were nonetheless significant differences in outcomes based on race (white, mixed-race, black). Some patients presented with very advanced or end-stage disease where prolonged survival would not be anticipated (Fig 22, see A). However, even when considering only those patients who survived for six months following presentation, the same country and racial patterns were persistent (Fig 22, see B).

While the disparities of the ABC-DO data are striking, there is also reason for hope because these same data could be significantly improved by addressing the fundamental approaches developed in the three GBCI Pillars, including: (i) downstaging breast cancer to reduce the high percentage of late-stage presentation; (ii) improving the facilitation of timely diagnosis and treatment; and (iii) carrying treatment through to completion without abandonment (Fig. 22).

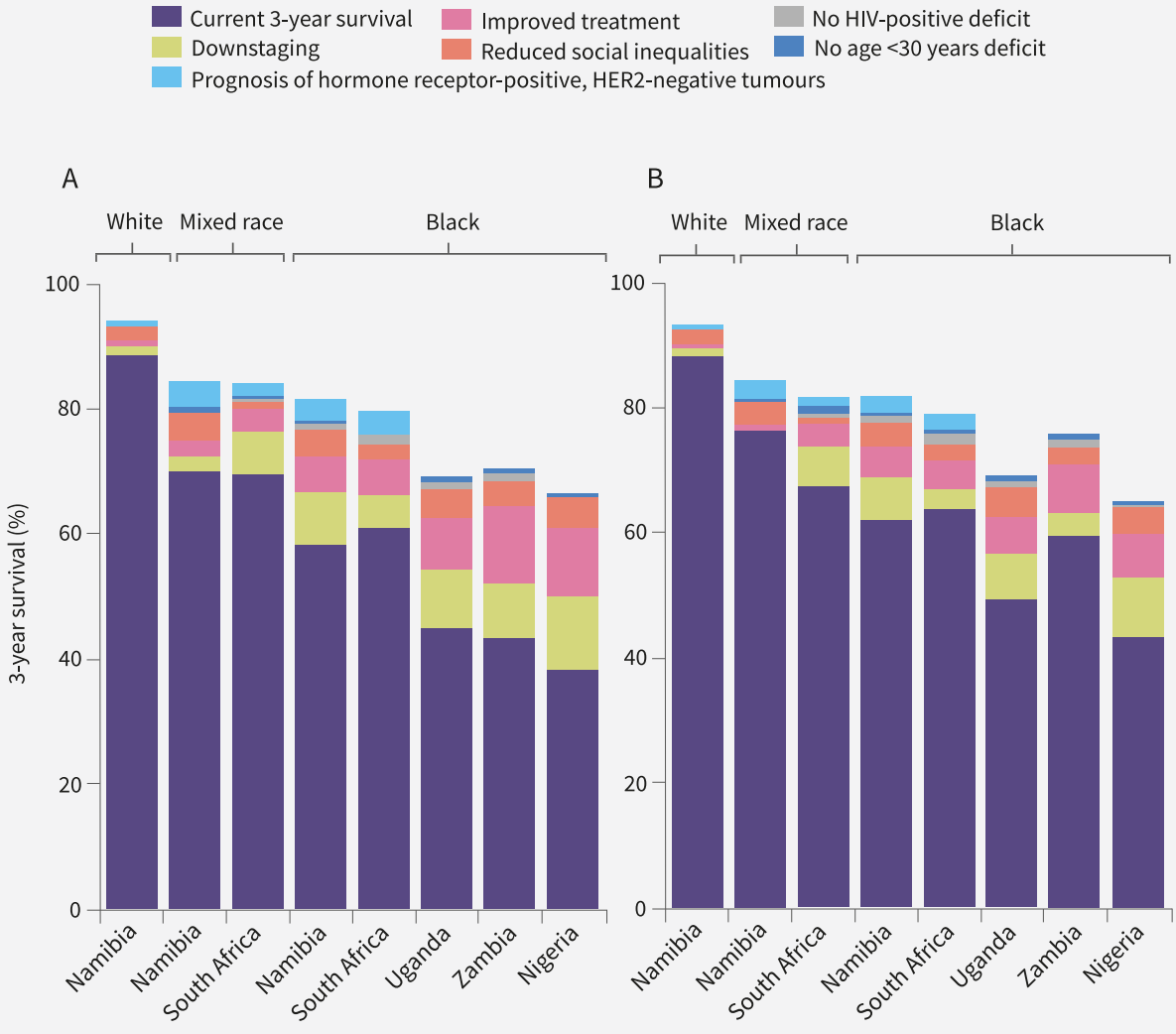
Evaluation of health-care systems

Monitoring and evaluation frameworks

Monitoring and evaluation frameworks allow stakeholders to determine the extent to which a programme or project is on track towards meeting its goals. Where this is not the case, such frameworks can be used to identify underlying problems, define effective implementation strategies, and frame informed decision-making regarding operational management and service delivery. Ineffective strategies, once identified, can be modified or halted to ensure that resources are used effectively and efficiently. Proven strategies should be scaled up and/or disseminated.

The systematic collection and reporting of data (**monitoring**) facilitates the objective analysis and identification of strengths, weaknesses, and areas for improvement (**evaluation**) (Table 5). The goals and objectives of a monitoring and evaluation strategy should be established in a monitoring and evaluation plan, which outlines how to monitor and evaluate health systems or interventions, define KPIs, establish targets, and use evaluation results to plan for project improvement and decision-making.

Fig. 22. Observed and predicted three-year survival from diagnosis (A), and conditional survival to 6 months (B) at observed distribution of prognostic factors and under specific improved scenarios, by site and race, in public hospitals only, sub-Saharan Africa, 2014–2017



Note. The majority of outcome disparities would be addressed by downstaging disease (green), improving access to care (yellow) and improving rates of treatment to completion without abandonment (red).
Source: reproduced with permission of the publisher, Elsevier Ltd., from McCormack et al *(45)*.

Table 5. Monitoring and evaluation (collecting data, monitoring KPIs, and evaluating programme achievement, according to a plan)

What is monitoring?	What is evaluation?
Monitoring is the **continuous assessment** of an ongoing programme or policy. The **monitoring team:** • collects data at predefined intervals, e.g., weekly, monthly, or every 6 months; • provides timely and standardized data collections and reports to the evaluation team.	Evaluation is the **objective and systematic analysis** of an ongoing or completed programme or policy. The **evaluation team:** • reviews data collected through monitoring at predefined intervals, e.g., annually; • uses KPIs with established targets and thresholds to evaluate the success of a programme or policy; • recommends a course of action based on the findings. *For targets not met, the evaluation team:* • identifies the underlying problem, using RCA (fishbone analysis); • recommends a strategy to address the problem. *For targets met, the evaluation team recommends:* • scaling up a successful programme; • continuously improving the quality of an established programme.

In a monitoring and evaluation framework, **KPIs are the first metrics to be evaluated, because assessment of the overall functionality of the care-delivery system, as defined by the three Pillars, is based on these.** The GBCI monitoring and evaluation framework defines health-system functionality in the pre-diagnostic interval (Pillar 1), the diagnostic interval (Pillar 2) and the treatment interval (Pillar 3).

RCA: suggested strategy using a fishbone analysis

RCA is a collective term, describing the wide range of approaches used to investigate a problem and its causes. It is intended to reveal essential relationships among different variables, and underlying causes leading to process deficits. The goal of the RCA process is to identify *what* to fix and not *how* to fix it.

A basic tool used for RCA is the fishbone analysis, developed in the 1960s by Kaoru Ishikawa (Japan) who pioneered quality-management processes in the Kawasaki shipyards. The tool has been used to improve processes in many settings, including health care. In a fishbone analysis, the defect or underlying problem is shown as the fish's head, with the causes extending as fishbones. The ribs branch off the backbone, showing major causes; sub-branches show the root causes (Fig. 23). For each of the three Pillar-related KPIs, different potential causes of underperformance can be identified (Table 6). Specific health-system intervention strategies can be designed based on the core findings from this sort of RCA, using the fishbone analysis tool.

Fig. 23. Using a fishbone diagram to identify underlying causes of underperformance

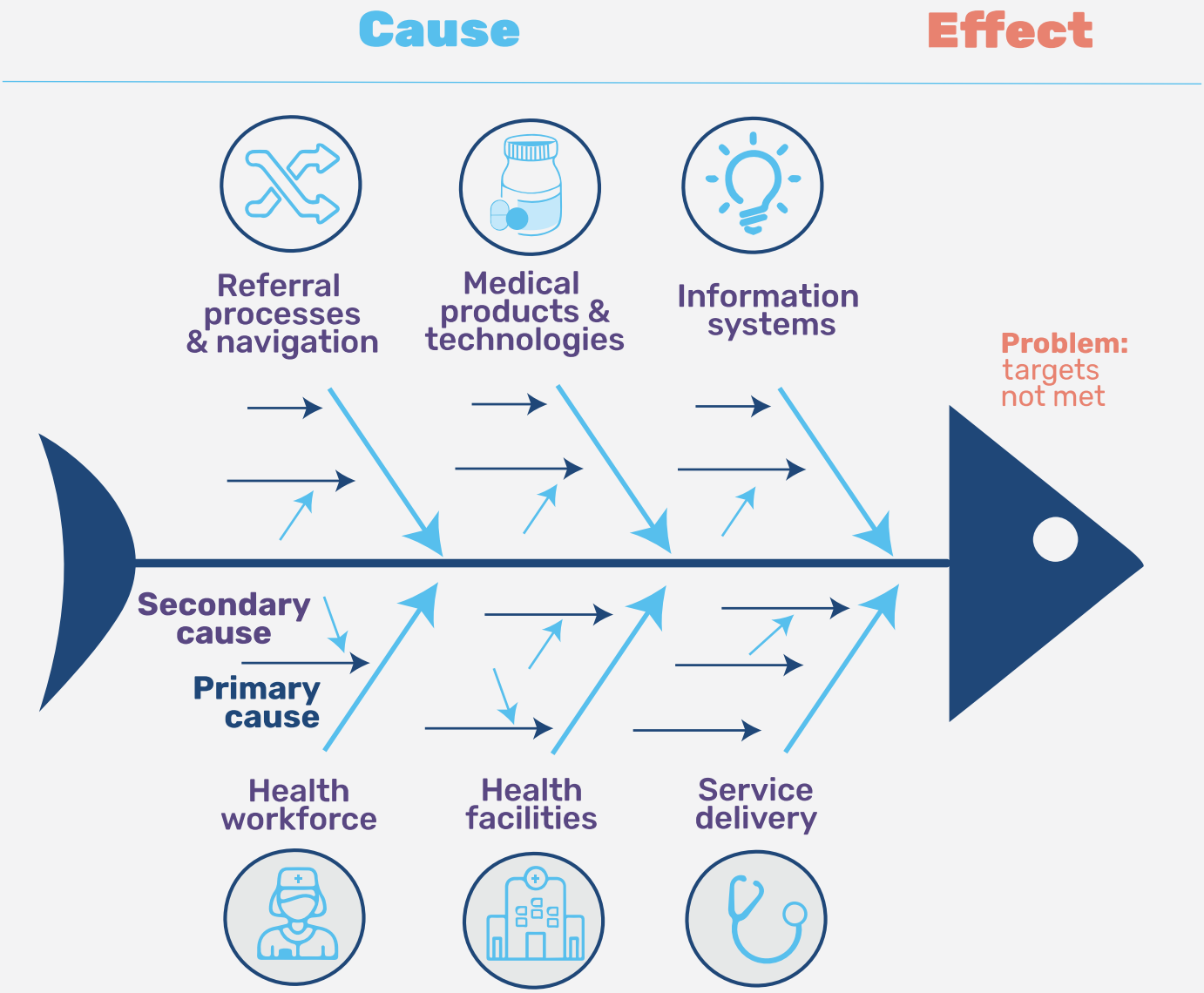


Table 6. Examples of responses to deficits in breast-health systems identified by fishbone analysis

Main underlying cause	Secondary causes	Responses
Pillar 1 Pre-diagnosis		
Lack of training among primary-care providers in how to recognize the signs/symptoms of breast cancer		Train providers to recognize the signs/symptoms of breast cancer
Lack of training among primary care providers in CBA	Low uptake due to lack of confidence	Train providers to conduct CBA Plan training exercises
Patients must travel through multiple levels of the health-care system before accessing diagnostic services		Reduce unnecessary referral steps Train providers to understand the referral pathway
Late presentation of women with signs and symptoms at the primary-care stage	Stigma, fatalism, financial and transport barriers	Educate the public Ensure community-health outreach Support patient advocacy
Poor transfer of information to patients and between the higher levels of the health system		Improve communication
Pillar 2 Diagnosis		
Delays in biopsy	Overutilization of surgical biopsies, causing bottlenecks due to limited operative access; Underutilization of needle biopsies due to inadequate sourcing and/or financing of needles	Develop and implement protocols for needle biopsies Adequately resource needle-biopsy materials; Train selected providers in needle-biopsy techniques.
Reliance on diagnostic mammography	Lack of ultrasound resources because of an insufficient number of trained health staff	Train sonographers to perform ultrasound procedures
Delays in attending diagnostic centres	Transport barriers Diagnostic procedures paid for out of pocket	Work with community, advocates and policy-makers to improve coverage/ decentralization
Pillar 3 Treatment		
Low rates of treatment completion	Surgical service delays Medication stock-outs Out-of-service radiotherapy machines	Examine treatment pathway and patient throughput Identify opportunities to improve efficiency Establish triage protocols when services are unavailable.
Delays in accessing treatment	Unclear referral system	Provide training in use of the referral system across all levels of the health-care system
Long waiting times at cancer centres	Not enough trained staff	Practise task sharing Invest in training more health professionals

Conclusions

Breast cancer has become the most diagnosed form of cancer globally and is the leading cause of cancer deaths among women. No ministry of health can overlook breast cancer if they intend to address cancer as a significant public health issue in their country.

This GBCI Implementation Framework provides national programme managers, policy-makers, and multisectoral actors the guidance they need to assess, strengthen and scale-up services for the early detection and management of breast cancer. Using this Framework, all stakeholders can achieve the Initiative's goal, namely, to assure the feasibility and quality of national health systems by providing countries with evidence-based recommendations for a phased approach to implementing interventions and strengthening health systems towards UHC.

This approach to health-system strengthening should be viewed in the broader context of women's health throughout the life continuum because the services and infrastructure required to manage breast cancer are also needed to deal with other malignancies and NCDs. A health system that can manage breast cancer will find itself better able to address all cancers that depend on early detection, prompt diagnosis and effective multimodality therapy. Because so much is known about the proper management of breast cancer, and because the pathways to tackling it are so well worked out, this provides an opportunity to improve health systems in a resource-appropriate way. Such an approach can be embraced as a tool for improving global health at a level higher than ever before.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Annex. Anti-cancer medicines for breast cancer and WHO Model List of Essential Medicines 2021

Anti-cancer medicine regimens for breast-cancer treatment are selected for individual patients as determined by tumour-marker expression that defines four distinct breast-cancer subtypes (luminal A, luminal B, triple-negative, HER-2+) *(1)*. Standard regimens (Table A1) use predetermined combinations, doses, and sequences of medicines (Table A2) (endocrine therapy, chemotherapy and targeted therapy) based on well-studied combination regimens that have been shown to reduce breast-cancer mortality *(2,3)*.

Principles of anti-cancer medication selection for different breast cancer subtypes

1) **Hormone-receptor positive (ER+) breast cancers (luminal A or luminal B subtypes) are treated primarily with endocrine (hormone) therapies:1**

   a) *Premenopausal*: Tamoxifen, which can be augmented with the addition of a luteinizing hormone-releasing hormone analogue to block ovarian hormone production ;

   Postmenopausal: Anastrozole (aromatase inhibitor) +/- tamoxifen ;

   b) chemotherapy,[2] which is considered in addition to endocrine therapy for advanced-stage, higher-risk premenopausal or postmenopausal ER+ cancers.

2) **Hormone-receptor (ER and PR) negative AND HER-2 negative (triple-negative subtype):**

   a) chemotherapy;[1, 3]

   b) endocrine therapy is **NOT RECOMMENDED** for hormone-receptor negative breast cancers.

3) **HER2+ breast cancer:**

   a) chemotherapy;[1, 2]

   b) endocrine therapy **IS RECOMMENDED** (in addition to chemotherapy) for hormone-receptor positive HER2+ cancers;

   c) trastuzumab-based targeted therapy regimens (in addition to chemotherapy) are preferred but may be cost-prohibitive.[4]

1 Anti-depressants may be needed to relieve hormone-therapy-related side effects, and/or manage symptoms of depression.

2 Chemotherapy regimen selection for non-metastatic cancer (neoadjuvant, or adjuvant) is based on high-level evidence but can be modified in cases of risk of relapse, comorbidities, toxicity profile, and patient preference.

3 Chemotherapy for metastatic disease selection and sequencing (monotherapy or combination regimens) is individualized based on disease presentation (visceral crisis, and/or symptoms), toxicity profile, comorbidities and patient preference.

4 The cost of targeted biological therapies can be prohibitive, making the risk-benefit something that needs to be considered on an individual basis.

Standard chemotherapy regimens

Table A1. Standard chemotherapy regimens using medicines that are included in the WHO essential medicine list, 2021[5]

Combination regimen[a]	Anti-cancer medicines[b]	Interval	Cycles
TC	Docetaxel; Cyclophosphamide	Every 3 weeks	4 cycles
AC-T	Doxorubicin, Cyclophosphamide, Paclitaxel	AC: Every 3 weeks T: weekly or every 3 weeks	AC x 4 cycles followed by T x 12 cycles
CMF	Cyclophosphamide; methotrexate, fluorouracil	Every 4 weeks	6 cycles
FAC	Fluorouracil; Doxorubicin; and Cyclophosphamide	Every 3 weeks	6 cycles
FEC	Fluorouracil; Epirubicin; and Cyclophosphamide	Every 3 weeks	6 cycles
TH	Paclitaxel + Trastuzumab	T: weekly H: every 1 or 3 weeks Concurrent [a]	T x12 cycles H: 12 months
ACT-H	Doxorubicin; Cyclophosphamide; Paclitaxel; Trastuzumab	AC: every 3 weeks T-H concurrent: weekly or every 3 weeks	AC x 4 cycles followed by T x 12 cycles H: 12 months
TC-H	Docetaxel; Carboplatin; Trastuzumab	TC: every 3 weeks H: every 3 weeks	TC: x6 cycles H: 12 months

[a] Well-established chemotherapy multidrug regimens are commonly known by standard abbreviations based on brand names rather than generic names. For example, TC = Taxol (decetaxel) + Cycophosphamide; TH = Taxotere (paclitaxel) + Herceptin (trastuzumab).
[b] Supportive medications are equally important to the anti-cancer chemotherapeutic medicines. Because nausea and vomiting are common side effects of chemotherapy, anti-emetics prophylaxis is considered to be best practice, because they reduce nausea and vomiting, improves quality of life, and potentially reduces treatment abandonment.
Source: NCCN Guidelines *(3)*.

Other supportive medications are considered essential for the management of breast cancer, including filgrastim to stimulate the production of white blood cell when cell counts are low, and zoledronic acid to treat bone thinning (osteoporosis) that can be caused by aromatase inhibitors.

5 World Health Organization model list of essential medicines, 22nd list, 2021 *(4)*.

Table A2. Individual anti-cancer and supportive medicines for breast cancer

Antineoplastic agents	**ATC code (Ref 2)**
A: Adriamycin (doxorubicin hydrochloride)	L01DB01
C: Cyclophosphamide	L01AA01
C: Carboplatin	L01XA02
E: Epirubicin	L01DB03
F: 5-Fluorouracil	L01BC02
M: Methotrexate	L01BA01
P: Paclitaxel	L01CD01
T: Docetaxel	L01CD02
Capecitabine	L01BC06
Vinorelbine	L01CA04
Gemcitabine	L01BC05
H: Trastuzumab	L01FD01
Endocrine therapy	
Tamoxifen	L02BA01
Anastrozole	L02BG03
Leuprorelin	L02AE02
Immunostimulants	
Filgrastim	L03AA02
Medicines for treatment of bone diseases	
Zoledronic acid	M05BA08
Antiemetics and antinauseants	
Ondansetron	A04AA01
Aprepitant	A04AD12
Corticosteroids for systemic use	
Dexamethasone	H02AB02

As measuring units, the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) have become the gold standard for international drug utilization monitoring and research. The ATC/DDD system is a tool for exchanging and comparing data on drug use at the international, national or local levels *(5)*.

Recommendations and advice concerning all aspects of the quality assurance of medicines can be found on the WHO website *(6).*

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* All URLs accessed 23 November 2022.

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