



Expert Task Force: Clinical Practice Guidelines and Public Health Policy for Metastatic Breast Cancer in Latin America

Authors:

Adrián Guzmán Ramírez, Alejandra Bartoli, Alessandra Menezes Morelle, Allan Ramos Esquivel, Bruno Bustos, Brizio Moreno Jaime, Carlos Gallardo, Claudia Arce, Denis Landaverde, Enrique Soto Pérez de Celis, Fancy Gaete, Felícitas Colombo, Fernando Petracci, Geiner Jiménez Jiménez, Gonzalo Gomez Abuin, Ivan Bustillo, Juan A. Fernández, Juan Enrique Bargallo Rocha, Luis Carlos Sarmiento Angulo, Maira Caleffi, Marcelo Cruz, Maria Eugenia Bravo, Mariana Rico, Maycos Zapata, Melissa Juarez, Paula Cabrera, Paula Escobar, Ray Manneh, Raquel Rojas Vigott, Santiago Bella, Sergio Daniele, William Mantilla

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ARGENTINA

Dr. Alejandra Bartoli, oncologist, head of the Oncology Service of the Centenario Hospital of Rosario.

Dr. Santiago Bella, Chief of Oncology at Sanatorio Allende, Cerro, Clínica Universitaria Reina Fabiola and Institute Oulton of Córdoba. Professor of Oncology at the Catholic University of Córdoba. Former President of the Argentine Association of Clinical Oncology.

Dr. Bruno Bustos, oncologist, chief of the Oncology Service of the Hospital General de Agudos Dr. Juan A. Fernández. Oncology auditor for social security and specialist in pharmacoeconomics.

Dr. Sergio Daniele, oncologist, chief of Oncology of the Italian Hospital, of the Breast Clinic of La Plata and chief of the Oncology Department of the Angel H. Roffo Oncology Institute of the City of Buenos Aires.

Dr. Gonzalo Gomez Abuin, clinical oncologist of the Oncology Service and head of the Oncology Research Unit of the Hospital Alemán.

Dr. Fernando Petracci, oncologist of the Breast Cancer Department of the Alexander Fleming Institute, teaching coordinator of the Institute and member of the Ethics Committee

BRAZIL

Dr. Maira Caleffi, MD, Mastologist, Head of the Mastology Service at Hospital Moinhos de Vento, Porto Alegre. President of the Board of Directors of IGCC - Institute of Governance and Cancer Control and FEMAMA - Brazilian Federation of Philanthropic Institutions in Support of Breast Health. Member of the Board of Directors of the Union for International Cancer Control (UICC) and World Health Organization consultant for the Global Breast Cancer Initiative (GBCI).

Dr. Marcelo Cruz, medical oncologist at the Sírio-Libanês Hospital, São Paulo.

Dr. Alessandra Menezes Morelle, medical oncologist at the Oncology Department of Hospital Moinhos de Vento, Porto Alegre. Specialist in breast cancer and gynecological neoplasms.

CHILE

Dr. Maria Eugenia Bravo, breast surgeon, president of the Chilean Society of Mastology.

Dr. Paula Escobar, gynecologist and mastologist of the Luis Tisné Hospital. Former president of the Chilean Society of Mastology.

Dr. Fancy Gaete, medical anatomopathologist, head of the Anatomic Pathology Unit, Hospital Dr. Luis Tisné. President of the Chilean Society of Anatomic Pathology and vice-president of the Chilean Society of Mastology.

Dr. Carlos Gallardo, medical oncologist, head of research at the Bradford Hill Research Center in Santiago.

COLOMBIA

Dr. Ivan Bustillo, internist and clinical oncologist. Director of the Department of Hemato-Oncology of the Portoazul AUNA Clinic in Barranquilla (Colombia).

Dr. Ray Manneh, clinical oncologist, scientific director of the Society of Oncology and Hematology of Cesar (SOHEC).

Dr. William Mantilla, internist specialized in Hematology and Oncology, head of the Breast Cancer Functional Unit of the CTIC Foundation - Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center. Professor of the Medicine Program of the Universidad del Rosario.

Alejandra Toro, Director of Project Management of the Salud Querida Foundation (SQ) and of Projects and Relations of FUNDEM. Founder of the Pink Light Movement and advisor to the international Beyond the Pink Ribbon movement.

Dr. Maycos Zapata, clinical oncologist of the Breast, Melanoma and Soft Tissue Unit of the Institute of Cancerology (Medellín). Professor of the Department of Internal Medicine of the University of Antioquia.

COSTA RICA

Dr. Adrián Guzmán Ramírez, Medical Oncologist, Medical Oncology Service, Max Peralta Hospital, Caja Costarricense del Seguro Social (CCSS).

Dr. Geiner Jiménez Jiménez, Medical Oncologist, Medical Oncology Service, Hospital Rafael Ángel Calderón Guardia, Caja Costarricense del Seguro Social (CCSS). National Coordinator of the Medical Oncology postgraduate course at the University of Costa Rica.

Dr. Melissa Juarez, Medical Oncologist, Medical Oncology Service, Hospital San Juan de Dios, Caja Costarricense del Seguro Social (CCSS).

Dr. Denis Landaverde, Medical Oncologist, Chief of the Medical Oncology Service, Hospital Mexico, Caja Costarricense del Seguro Social (CCSS).

Dr. Allan Ramos Esquivel, Medical Oncologist, Chief of the Medical Oncology Service, Hospital San Juan de Dios, Caja Costarricense del Seguro Social (CCSS). Associate Professor of the Department of Pharmacology and Clinical Toxicology of the University of Costa Rica.

Dr. Raquel Rojas Vigott, Medical Oncologist, Medical Oncology Service, Hospital Mexico, Caja Costarricense del Seguro Social (CCSS).

MEXICO

Dr. Claudia Arce, medical oncologist of the Breast Tumor Service of the National Cancer Institute (INCan).

Dr. Juan Enrique Bargallo Rocha, surgical oncologist, head of the Breast Tumors Department of the National Cancer Institute (INCan).

Dr. Paula Cabrera, medical oncologist, head of the Medical Oncology Department of the National Cancer Institute (INCan).

Dr. Brizio Moreno Jaime, internist, medical oncologist with specialization in breast cancer and clinical researcher, Hospital Regional ISSSTE León.

Dr. Enrique Soto Pérez de Celis, medical oncologist, specialist in geriatric oncology and researcher at the National Institute of Medical Sciences and Nutrition Salvador Zubirán (INCMNSZ).

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Executive Abstract

Breast cancer is the most frequent malignant tumor among women in Latin America (LA). The latest WHO estimates, through the International Agency for Research on Cancer (IARC) published by the Global Cancer Observatory (Globocan), show that in 2020, 210,100 women were diagnosed with breast cancer and around 58,000 died from the disease. It is the leading cause of cancer mortality among women in the region. Almost a third of the women affected are under the age of 50 (32%), a higher percentage than the North American statistic of 19%. Projections indicate that by 2040 the incidence of breast cancer in the region will increase by nearly 50%.

Although there is a lack of accurate data on the prevalence of metastatic breast cancer and estimates vary between countries, they reveal that a significant percentage of patients have metastatic disease at the time of diagnosis, which is largely explained by late detection. Although early-stage breast cancer is potentially curable, breast cancer mortality and incidence rates are significantly higher in low- and middle-income countries than in high-income countries. These high mortality and incidence rates mean that patients diagnosed with breast cancer in low- and middle-income countries are more likely to die from their breast cancer.¹

International recommendations are conclusive in pointing out that the burden of disease generated by breast cancer can be managed in countries with limited resources, such as those in LAC, by strengthening public health policies, implementing effective clinical practice guidelines for diagnosis and treatment, strengthening prevention and early detection programs, and improving access to targeted and innovative therapies.¹

Clinical Practice Guidelines (CPG), developed systematically on the basis of the available scientific evidence, are one of the main instruments for dealing with diseases and making decisions on the most appropriate health care to optimize health outcomes. They also contribute to a more efficient and effective use of resources and to the improvement of public health.

The "Task Force on the impact of public policies on Clinical Practice Guidelines for metastatic breast cancer in Latin America" is a project developed by the Americas Health Foundation (AHF), with the aim of analyzing the current situation of the guidelines in the CPGs for this disease that are applied in the region and how health policies affect their adoption in order to address it and improve its control. The analysis focused on six countries, with the participation and contributions of experts in medical oncology, pathology, mastology, surgical oncology and patient organizations in each country: Argentina, Brazil, Chile, Colombia, Costa Rica and Mexico.

Although in the countries analyzed, which comprise about 70% of the region's population, there has been progress in terms of the implementation of policies focused on addressing breast cancer as a public health problem, the increasing incidence and burden of the disease reflect the significant challenges posed by this cancer today.

¹ Francies FZ, Hull R, Khanyile R, Dlamini Z. Breast cancer in low-middle income countries: abnormality in splicing and lack of targeted treatment options. *Am J Cancer Res*. 2020 May 1;10(5):1568-1591. PMID: 32509398; PMCID: PMC7269781.

Among the major challenges common to all the countries consulted are the need for updated national CPGs, the large gap in national population-based cancer registries, the lack of timely diagnosis and the difficulty of access to treatment.

Given that epidemiological information is a key input to guide the development of public policies and implement specific actions to address the problem, all countries have population-based cancer registries (PBCR) but these correspond to cities, provinces or regions and not all of them are representative at the national level. Moreover, the most recent data - which are those reported by countries and published by Globocan projected to 2020 - date from 2016. Costa Rica is the only country with an RCBP that covers the entire nation, called the National Tumor Registry, cataloged by the IARC as high quality and whose latest reported data are from 2018.

Health systems in the region are fragmented, heterogeneous and present important gaps in access and coverage to health services, with significant differences between social security or public health and the private sector. The latter covers about 10% of the population in the six Task Force countries.

All of them present common barriers of various kinds that have an impact on access to diagnosis and timely treatment:

- **Regulatory barriers**, such as bureaucracy in health systems and gaps in regulations that cause inequities and disparities in their application.
- **Financial barriers**, which particularly affect access to the most recent treatments considered high-cost, and as a consequence, this access has been subject to legal action through *amparos* or *tutelas*.
- **Geographic and infrastructure barriers**, such as the distance to specialized centers, which are generally concentrated in the main cities.
- **Early diagnosis barriers**, given by fragmented and inconsistent screening programs that contribute to an advanced stage at the time of diagnosis.
- **Barriers in health system navigation**, which cause delays leading to advanced stage breast cancer diagnoses.
- **Barriers in the training of health personnel**, especially with respect to primary care professionals on the suspicion of the disease, whose role is fundamental for referral to specialized services.
- **Barriers to raising awareness among the general population** about prevention and the importance of mammography screening.

All the analyzed countries have CPGs for breast cancer and include metastatic disease. These guidelines are generated by institutions at the national, local or provincial level, and from the public and private sectors.

The official guidelines, generally developed within the orbit of national health ministries, have in common that they are not binding because they are recommendations and are not updated periodically. The CPGs that are usually binding are the institutional ones, as is the case of the breast cancer guideline of the Costa Rican Social Security Fund (CCSS), which applies to all its centers. However, it was found that most of the national CPGs are outdated and are between 1-11 year(s) old.

In this regard, in **Argentina** there are three guidelines for metastatic breast cancer made by the National Cancer Institute (INC): "Advanced Breast Cancer: Anti-HER2NEU Therapy", "Metastatic Breast Cancer: Non-AntiHER2 Therapy" - both from 2015 - and the guide "High-cost drugs in the treatment of metastatic breast cancer", from 2018. In **Brazil**, the CPG used in the public system is the so-called "Diagnostic and Therapeutic Guidelines for Breast Carcinoma" (DDT), from 2019, from the Ministry of Health. In **Chile** the most recent

is the "CPG GES, AUGE N°8: Breast Cancer", made in 2021 by the Departments of Health Technology Assessment and Comprehensive Management of Cancer and other Tumors. In **Colombia**, the "Clinical Practice Guide for the early detection, comprehensive treatment, follow-up and rehabilitation of breast cancer" is the CPG at the national level, from 2017, whose development was carried forward by the National Cancer Institute (INC) and the Institute for Health Technology Assessment (IETS). In **Costa Rica** there is the "Clinical Practice Guide for the treatment of breast cancer" of the CCSS issued by its Medical Management in 2012. In **Mexico** there is the "Breast cancer treatment in second and third level of care" guide of the Ministry of Health, from 2017, which was coordinated by the National Center of Technological Excellence in Health (CENETEC) and is the guide of the Mexican Institute of Social Security (IMSS).

Table 1. Updates and recommendations of CPGs for breast cancer in Latin America.

Country	Most relevant CPGs for breast cancer	Institution	Year last updated	Criteria (date) of update
Argentina	Advanced breast cancer: Anti - HER2NEU therapy.	Ministry of Health, National Cancer Institute (INC)	2015	Estimated upgrade in 2 years
	Metastatic breast cancer: Non-AntiHER2 therapy.		2015	
	High-cost drugs in the treatment of metastatic breast cancer.		2018	
	Current recommendations for oncologic treatment 2022-2023.	Argentine Association of Clinical Oncology (AAOC)	2022	Annual
	Guidelines in Oncology. Diagnosis, treatment and follow-up of cancer.	Angel H. Roffo Oncology Institute	2018	Unspecified
	Oncology treatment guidelines.	Association of Clinical Oncologists of Córdoba	2017	Unspecified
	Treatment protocols high-cost drugs: Breast cancer.	Ministry of Health of the Province of Santa Fe	2017	Unspecified
Brazil	Diagnostic and Therapeutic Guidelines for Breast Carcinoma (DDT).	Ministry of Health	2019	Unspecified
	Guidelines for oncological treatments recommended by the Brazilian Society of Clinical Oncology (SBOC).	Brazilian Society of Clinical Oncology (SBOC)	2022	Unspecified
	"Oncologic Treatment".	Unimed	2018	Unspecified
Chile	CPG GES, AUGE N°8: Breast Cancer.	Ministry of Health	2021	National Cancer Law (21258/2020): CPGs should be reviewed every 2 years or as warranted by available scientific evidence.
Colombia	Clinical Practice Guide for the early detection, integral treatment, monitoring and rehabilitation of breast cancer.	Ministry of Health and Social Security, National Institute of Cancerology (INC), Institute for Health Technology Assessment (IETS).	2017	Review every 3 years or earlier, based on available evidence
Costa Rica	Clinical Practice Guideline for the treatment of breast cancer.	Social Security Fund of Costa Rica (CCSS)	2012	Established review for 2015
	Consensus on the pharmacological treatment of cancer.	Association of Medical Oncologists of Costa Rica (ACOMED)	2021	June 2023
Mexico	Treatment of breast cancer in second and third level of care.	Secretary of Health	2017	3 to 5 years after publication
	Mexican Consensus on diagnosis and treatment of breast cancer.	Colima Consensus	2021	2023

The most recent or most frequently updated national CPGs are those developed by local scientific societies, such as the 2022-2023 recommendations of the Argentine Association of Clinical Oncology (AAOC), the 2022 guidelines of the Brazilian Society of Clinical Oncology (SBOC), and the Colima Consensus of Mexico,

the latter in 2021 and whose next revision is scheduled for 2023. The Costa Rican Association of Medical Oncologists (ACOMED) made a consensus on pharmacological treatment of cancer, in 2021, with an update date of June 2023.

In this context, most specialists in all the countries analyzed use the CPGs of local scientific societies and international CPGs such as the breast cancer guidelines of the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO). Their application has the limitation that they include drugs that may not be available in the countries or may not be registered by the local regulatory authority.

Adherence to national CPGs depends on how up to date they are, but also on the field in which the specialists work, as well as on the feasibility of being able to adhere to the proposed recommendations in terms of drug coverage policy and access to treatment.

Regarding this last aspect, it is worth mentioning that most countries have regulations that specifically determine the list of interventions and drugs covered by the public health system for breast cancer care. The private sector also has such regulations. The exception is Argentina, whose regulations generally establish that breast cancer treatments are included in the benefits of the Obligatory Medical Program (PMO).

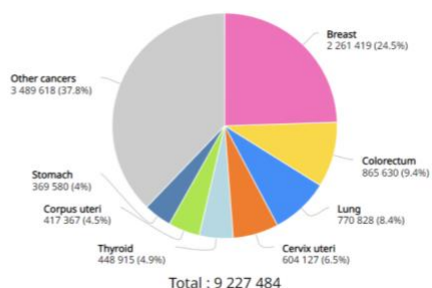
Based on the general overview of the situation in the region, and with the premise of contributing to the improvement of comprehensive care for breast cancer and metastatic disease, the role of the CPGs is highlighted, and the following recommendations are suggested:

1. **Development of evidence-supported CPGs for breast cancer and metastatic disease adapted to the reality of each country. The guidelines should:**
 - Develop with the participation of all stakeholders involved in comprehensive cancer care.
 - Determine the maximum time for access to care across the breast cancer continuum
 - Binding for the delivery of breast cancer care
 - Be periodically updated in a planned manner, at least every two to three years
 - Consider inclusion of innovative diagnostic methods and treatments for breast cancer
 - Be effectively communicated to all health care personnel involved in comprehensive breast cancer care
2. **Ensure consistency between breast cancer CPGs and regulatory decisions that determine the availability of treatment.**
3. **Establish systems to monitor adherence to breast cancer CPGs in LA and evaluate their impact on patient outcomes.**
4. **Implement a comprehensive approach to breast cancer management to address fragmentation in care.**
5. **Create public policies to ensure timely access to treatment after diagnosis for breast cancer patients.**
6. **Governments in the region should continue to explore innovative financing mechanisms that allow for the inclusion of innovative breast cancer treatments in health budgets.**
7. **Establish population-based cancer registries (PRCs) to increase local information on breast cancer in LA and guide public policies for cancer.**

Introduction

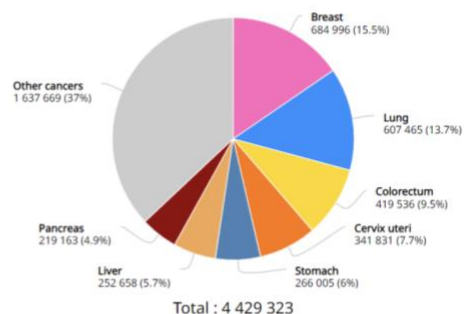
Breast cancer is the most frequent malignant tumor and the leading cause of cancer mortality in women worldwide. In 2020, according to data from the Global Cancer Observatory (Globocan), more than 2.26 million new cases were registered and about 685,000 women died from this cancer, with age-adjusted incidence and mortality rates of 47.8 and 13.6 cases per 100,000 women, correspondingly². Estimates by the World Health Organization (WHO) indicate that almost one in 12 women will contract breast cancer in her lifetime and that this disease causes more disability-adjusted years of life lost than any other malignant neoplasm.³

Estimated number of new cases in 2020, World, females, all ages
Estimated number of new cases in 2020, World, females, all ages



Data source: GLOBOCAN 2020
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)
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Estimated number of deaths in 2020, World, females, all ages
Estimated number of deaths in 2020, World, females, all ages



Data source: GLOBOCAN 2020
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)
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https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key-total&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0

https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key-total&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0

The disease burden of breast cancer is significantly higher in developing countries. In fact, in Latin America and the Caribbean, the proportion of women affected before the age of 50 is higher than in North America (32% versus 19%).⁴

In this region, breast cancer also has the highest incidence: in 2020, according to Globocan data, 210,100 women were diagnosed with the disease (which accounts for 28% of all cancers) and caused almost 58,000 deaths.² In addition, a high percentage of deaths due to breast cancer in Latin America and the Caribbean (50%) occur in women under 65 years of age, compared to the North American statistic (37%).⁴ It is estimated that its incidence in the region will increase by about 50% by the year 2040.⁵

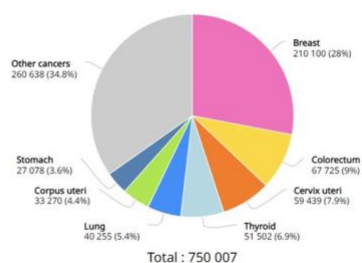
² International Agency for Research on Cancer (IARC), WHO, Global Cancer Observatory (Globocan) 2020. Cancer Today, Fact Sheets Breast: <https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf>

³ World Health Organization (WHO). Breast cancer. (Marzo 2021). <https://www.who.int/es/news-room/fact-sheets/detail/breast-cancer>

⁴ Pan American Health Organization (PAHO) 2020. <https://www.paho.org/es/temas/cancer-mama>

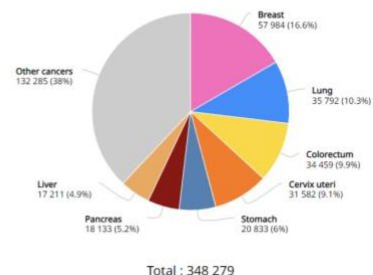
⁵ International Agency for Research on Cancer, WHO, Global Cancer Observatory (Globocan) 2020. Cancer Tomorrow. <https://gco.iarc.fr/tomorrow/en/dataviz/bars?mode=population&cancers=20&sexes=2>

Estimated number of new cases in 2020, Latin America and the Caribbean, females, all ages



Data source: GLOBOCAN 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)
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Estimated number of deaths in 2020, Latin America and the Caribbean, females, all ages



Data source: GLOBOCAN 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)
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https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=904&key=total&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0#collapse-others
https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=904&key=total&sex=2&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0#collapse-group-1-0

As regards the five-year survival rate, in low-income countries it is lower than in high-income countries. In the latter it is 90%-80% while in Latin America it ranges around 70%. This is largely due to late diagnosis of breast cancer, advanced stages and metastatic disease. Early detection and early treatment have a significant impact on improving survival outcomes and decreasing the burden of disease.³⁻⁶

Given these concerning data, the Americas Health Foundation (AHF) carried out a Task Force that included six countries in the region with the aim of reviewing the guidelines for breast cancer care practices in the most advanced stages that are applied in each one of them. The meetings were held during September 2022 and were attended by experts in medical oncology, pathology, mastology, surgical oncology and patient organizations from Argentina, Brazil, Chile, Colombia, Costa Rica and Mexico.

Based on the empirical data collected during the meetings and other bibliographic references, this report has been compiled to analyze and clarify the impact of public policies on the development and implementation of Clinical Practice Guidelines (CPG) for metastatic disease, as well as the barriers that influence their adoption and their impact on actual practices for the care and control of the disease.

To this end, the following aspects were addressed in each of the countries analyzed: the epidemiology and burden of the disease, the general organization of the health system and the main initiatives regarding breast cancer issues, the barriers and gaps in access, the current status of national CPGs for metastatic breast cancer, and the impact of health policies on their adoption.

The purpose of this Task Force is to provide a comprehensive consensus view that contributes to the work of all stakeholders involved in one way or another in decision making regarding clinical practices and public policies on breast cancer in the region.

International guidelines for updating CPGs

CPGs can be described as a set of recommendations based on the evaluation of the risks and benefits of health procedures, aimed at reducing variability in clinical practice and increasing the safety and quality of patient care. A CPG can become obsolete when scientific evidence evolves, when new technologies are

⁶ Cazap E. Breast Cancer in Latin America: A Map of the Disease in the Region. *Am Soc Clin Oncol Educ Book*. 2018 May 23;38:451-456. doi: 10.1200/EDBK_201315. PMID: 30231404.

developed for the diagnosis or treatment of diseases, when there are changes in the socioeconomic context or in the values and preferences of patients.

According to international updating guidelines, it is recommended that CPGs be published with a "revision" date indicating how long the recommendations remain valid. Since there is no gold standard on the periodicity of such updates, it is suggested that the effectiveness of the CPGs be reviewed according to new research findings on the subject, new therapies available, and the possible need for new guidelines based on areas that still lack evidence.

Among the manuals consulted, 25 (71.4%) recommend specifying a time period between the publication of a CPG and the initiation of an updating process, with 2 to 3 years being the most frequently recommended (40%). A minimum of 2 years and a maximum of 5 years is suggested as a review schedule for CPGs.⁷

The frequency of updates to breast cancer CPGs may vary depending on the organization or country issuing the guidelines, or on the availability of new evidence that significantly modifies the recommendation of existing CPGs. Also, some organizations issue interim or specific updates to address urgent clinical issues or emerging therapies.

Nevertheless, despite the diversity in CPG review practices, there are specific recommendations from international reference organizations:

- The World Health Organization (WHO) recommends that CPGs be reviewed and updated at least every 2-5 years, but this may vary depending on the specific context. For example, if new evidence emerges that significantly changes the recommendations of a CPG, an update may be necessary sooner than every 2-5 years.⁸
- The UK National Institute for Health and Care Excellence (NICE) recommends that guidelines be updated every 3 to 5 years, or sooner if significant new evidence becomes available.⁹
- The European Society for Medical Oncology (ESMO) policy states that its guidelines should be updated every 2 years or sooner if new evidence emerges that may significantly modify the recommendations. In addition, ESMO has a "living" guideline specific to metastatic breast cancer, which is continuously updated.¹⁰⁻¹¹
- The National Comprehensive Cancer Network (NCCN) guidelines are continually updated throughout the year, and the NCCN panel meets several times a year to review and update the recommendations based on the latest scientific evidence.¹²

⁷ Vernooij R W, Sanabria A J, Solà I, et al. Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks. *Implementation Sci* 9, 3 (2014). <https://doi.org/10.1186/1748-5908-9-3>

⁸ WHO Handbook for Guideline Development. © World Health Organization 2012. https://apps.who.int/iris/bitstream/handle/10665/75146/9789241548441_eng.pdf?sequence=1

⁹ Developing NICE guidelines: the manual. Published: 31 October 2014. Last updated: 18 January 2022. <https://www.nice.org.uk/process/pmg20/chapter/ensuring-that-published-guidelines-are-current-and-accurate>

¹⁰ ESMO CPG SOP Version 2.2. September 2022. <https://www.esmo.org/content/download/77789/1426712/1/ESMO-Clinical-Practice-Guidelines-Standard-Operating-Procedures.pdf>

¹¹ ESMO Metastatic Breast Cancer Living Guidelines, v1.0.0 May 2022: <https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline>

¹² NCCN: Development and Update of Guidelines. <https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines>

- The American Society of Clinical Oncology (ASCO) updates its guidelines on an ongoing basis as new evidence emerges, with a formal review and update every 12-18 months.¹³
- The International Consensus Conference for Advanced Breast Cancer (ABC) updates the CPG for locally advanced breast cancer and metastatic breast cancer every 2 years. Organized by the ABC Global Alliance, a non-profit platform made up of specialists and organizations working in this field around the world, the Consensus is a forum for sharing best clinical practices and the latest scientific advances in the field. The last Consensus was held in November 2022, with the participation of a panel of 46 experts from 24 countries.¹⁴
- The Institute of Medicine (IOM) of the U.S. National Academies of Sciences, Engineering, and Medicine recommends that clinical practice guidelines be reviewed and updated at least every 5 years to ensure that they reflect the latest evidence and best practices.¹⁵
- The Guidelines International Network (GIN) suggests that the guidelines be reviewed and updated every 2 to 3 years or when new evidence or information emerges that may modify the recommendations.¹⁶

Living CPGs

Within the debates on updating guidelines, there is the perspective of "living" CPGs that, with the support of systematic reviews, are continuously updated. This format seeks to avoid outdatedness, maintaining the permanent applicability of evidence-based clinical practice recommendations, especially in fields where new evidence is continually emerging.

Living guidelines are defined as an optimization of the CPG development process that allows individual updating of recommendations as soon as new and relevant evidence becomes available.¹⁷

Some successful examples have been developed during the COVID-19 pandemic. However, the progress of a living CPG has several challenging requirements, such as maintaining protocols despite numerous update cycles, defining criteria for inclusion of new evidence and modifications of recommendations, and constant review of the scientific literature. On the other hand, the cost of maintaining a CPG is a major challenge when both the systematic review and the planning, elaboration, reporting, dissemination and access processes of living CPG are undergoing continuous updating.

Latin America status

CPGs for breast cancer in Latin American countries need, in most cases, more regular updates. Outdated CPGs cause limitations in access to standard of care treatment and in the incorporation of innovative therapies. As a result, breast cancer patients in Latin America often do not receive the most appropriate treatment and may experience poor outcomes.

¹³ ASCO Guidelines Methodology Manual. © American Society of Clinical Oncology 2022. <https://old-prod.asco.org/sites/new-www.asco.org/files/content-files/practice-patients/documents/2022-Guidelines-Methodology-Manual-9-19-22.pdf>

¹⁴ Wuerstlein R, Cardoso F, Haidinger R. Expert Discussion: Highlights from ABC6: Bridging the Gap and Insights in This First Virtual ABC Conference and from 10 Years ABC Consensus. *Breast Care* 2022;17:107-112 doi: 10.1159/000521342

¹⁵ Institute of Medicine, the National Academies. Clinical Practice Guidelines We Can Trust (2011). <http://nap.nationalacademies.org/13058>

¹⁶ Alonso-Coello P, Martínez García L, Carrasco J M, et al. The updating of clinical practice guidelines: insights from an international survey. *Implementation Sci* 6, 107 (2011). <https://doi.org/10.1186/1748-5908-6-107>

¹⁷ Akl EA, Meerpohl JJ, Elliott J, Kahale LA, Schünemann HJ; Living Systematic Review Network. Living systematic reviews: 4. Living guideline recommendations. *J Clin Epidemiol*. 2017 Nov;91:47-53. Doi: 10.1016/j.jclinepi.2017.08.009

Updates and recommendations of CPGs for breast cancer in Latin America (see Table 1 for reference).

Regular updating of CPGs for breast cancer in Latin America is important for optimizing patient outcomes and ensuring access to innovation. Specifically, updated CPGs help to ensure the following:

- Standardize care: CPGs can standardize the care patients receive, which is important in countries where healthcare delivery lacks uniformity. This can reduce disparities in care and improve health outcomes
- Improve evidence-based care and quality: Updated CPGs provide evidence-based information for the diagnosis and treatment of breast cancer, which can improve the quality of care patients receive. These guidelines also inform changes in treatment recommendations and standard of care.
- Optimizing patient outcomes: By following updated CPGs, physicians can use the most effective, efficient and targeted therapies to treat breast cancer, which can improve patient outcomes and reduce the burden of disease.
- Access to innovation: Regular updates of CPGs help identify innovative new therapies and techniques for breast cancer treatment, guide their use, and ensure that they are available to patients who need them.
- Health policy alignment: Updated CPGs can align health policies with the latest evidence and best practices, which can inform resource allocation decisions and ensure that resources are used effectively and efficiently.
- Medication approval processes: Updating CPGs can inform decisions on the need for approval of new drugs and treatments for breast cancer, ensuring that patients have access to the latest innovations in treatment with safety and efficacy in mind.
- Reimbursement policies: regular updates of CPGs can inform decisions on reimbursement policies for breast cancer treatments, ensuring that patients have access to the most effective treatments while taking into account cost-effectiveness.
- Improving the efficiency of healthcare services: Updated clinical practice guidelines can guide healthcare systems and clinicians in making informed decisions and more efficient use of available resources, improving the accessibility and quality of healthcare while reducing the burden of disease.
- Adherence to CPG: Updated CPGs can increase physician adherence to recommendations and reduce uncertainty about breast cancer treatment by providing clear, up-to-date information on the best methods for treating each disease.

In conclusion, regular updating of breast cancer CPGs is essential to ensure that patients receive the best possible health care, to ensure that access to innovation is effectively integrated into clinical care, and to reduce the burden of breast cancer disease in Latin American countries.

Argentina

EPIDEMIOLOGY AND BURDEN OF METASTATIC BREAST CANCER DISEASE

In Argentina, breast cancer is the most frequent malignant tumor among all types of cancer. According to estimates by the Global Cancer Observatory (Globocan) in 2020 there were about 22,000 new cases of breast cancer in the country, which represented one out of every three malignant neoplasms detected in women and caused 6,821 deaths. The age-adjusted incidence and mortality rates were 73.1 and 18.9 cases per 100,000 women, respectively.¹⁸

The country does not have a national population-based cancer registry. The data come from population-based cancer registries (BCPR) of some cities and provinces, which are those reported to the International Agency for Research on Cancer (IARC) and published by Globocan and are considered to be statistically representative.

There are other registries such as that of the Argentine Society of Mastology, the Breast Cancer Registry (RCM), which details tumor variants and stages at diagnosis. The data come from the Mastology Units and because not all centers have one, the representativeness may be biased. In addition, the National Cancer Institute (INC) implemented the hospital-based Institutional Tumor Registry of Argentina (RITA), which presents some problems in the imputation of data due to methodological issues.

For all these reasons, reliable statistics regarding patients with metastatic breast cancer at the time of diagnosis are unknown. Experts agree that the percentage is estimated at around 10% of cases.

They also point out that in recent years there has been an increase in the incidence of breast cancer in premenopausal patients or those under 50 years of age; in particular, after the COVID-19 pandemic, there has been a higher influx of younger patients and those with locally advanced disease. The impact of the pandemic on cancer diagnosis and treatment is well known due to decreased screening and delays in every instance of care.

THE HEALTH SYSTEM

In Argentina, by law, all individuals are entitled to homogeneous access to health care. It cannot be said that there is a population without health coverage, since the public system has universal coverage. However, it is possible to distinguish two large groups: those who only have access to public services and those who, in addition, have health insurance coverage.¹⁹ These insurances may be mandatory (social security) or voluntary (prepaid medicine).

The Argentine healthcare system is complex and fragmented and results from the coexistence of three subsystems: public, social security and private.

¹⁸ International Agency for Research on Cancer (IARC), WHO, Global Cancer Observatory (Globocan) 2020. Cancer Today, Population Fact Sheets: <https://gco.iarc.fr/today/data/factsheets/populations/32-argentina-fact-sheets.pdf>

¹⁹ Tobar F, Olaviaga S, Solano R. Complexity and fragmentation: the major ailments of the Argentine health system (August 2012). Public Policy/Analysis Document N°108. CIPPEC. Buenos Aires.

The first is made up of public hospitals and primary care centers, which provide coverage to about 37.5% of the population.²⁰ Exclusive coverage, since 100% of citizens are entitled to it. Care is generally free of charge and is financed by the government, mostly with provincial resources, but also by the municipalities and the national government, but with less participation.

Social Security consists of social security funds (OS) -mostly managed by labor unions- and the National Institute of Social Services for Retirees and Pensioners (National Institute of Social Services for Retired and Pensioners), known as PAMI (National Institute of Social Services for Retired and Pensioners). This sector covers 61% of the population and is financed by workers' contributions and employers' contributions. There are the national health insurance companies (33% of the population), provincial health insurance companies (15.6%) that insure public employees in the provinces, and others (2.1%) such as the health insurance companies of the security forces, national universities and the legislative and judicial branches. PAMI covers about 11% of the population.²⁰

The private subsystem is voluntary insurance through prepaid medicine companies or "prepagas", financed by individuals with the payment of a monthly fee that varies according to coverage. Almost 14% of the population opts for these services; 5.3% directly and 8.5% through the transfer of OS.²⁰ The latter is through agreements between the OS and the prepaid companies.

According to the National Household Expenditure Survey 2017-2018 of the National Institute of Statistics and Census (INDEC) in that period, out-of-pocket spending on health represented 6.4% of total expenditure. For households with prepaid coverage this amounted to 11.4%, those with OS coverage was 5.6% and for households that only used public health it was 3.5%.²¹

Law 23.661 of 1989 created the National Health Insurance System with the scope of a social insurance, and established as insurance agents the national HOs, those of other jurisdictions and other entities that adhere to the system.²²

In 1995, Decree 492 of the Executive Power created the Compulsory Medical Program (PMO), which is the basket of medical-health care benefits that the agents of the National Health Insurance System are obliged to provide to their beneficiaries or members, with subsequent regulations that complement or modify it.²³

Oncological treatments are included in the PMO and therefore must be provided free of charge to patients covered by the OS or by the private system, according to Resolution 201/2002 -a complementary regulation of the PMO- which states: "The following will be covered at 100% by the Insurance Agent: ... oncological drugs according to national protocols approved by the application authority". (Annex I section 7)²⁴

In relation to the financing of high-cost drugs, the Superintendence of Health Services - the entity that regulates and controls the Health Insurance Agents - created the Single Reimbursement System (S.U.R.), which manages a fund to support them for medical services of low incidence and high economic impact.²⁵

²⁰ Chamber of Medical Diagnostic Institutions (CADIME). Sectorial Report #19 Health Services. (June 2022). <https://www.cadime.com.ar/newsletter/Informe%20Sectorial%20CADIME%20N%2019%20-%20Junio%202022.pdf>

²¹ National Household Expenditure Survey 2017-2018: Expenditure Report/ 1st ed. National Institute of Statistics and Census - INDEC (2019).

²² Argentina.gob.ar. Regulations. Law 23.661/1989, updated text. National Health Insurance System. <https://www.argentina.gob.ar/normativa/nacional/ley-23661-63/actualizacion>

²³ Argentina.gob.ar. Regulations. Decree 492/1995, updated text. National Executive Power. Social Security. <https://www.argentina.gob.ar/normativa/nacional/decreto-492-1995-27540/actualizacion>

²⁴ Argentina.gob.ar. Regulations. Decree 201/2002, full text. Ministry of Health. Compulsory Emergency Medical Program. <https://www.argentina.gob.ar/normativa/nacional/resolucion-201-2002-73649/texto>

²⁵ Argentina.gob.ar. Regulations. Resolution 1.200/2012, updated text. Superintendence of Health Services. Creation of a Single Reimbursement System. <https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-1200-2012-202779/actualizacion>

Those treated in public hospitals depend on the provision of medicines by the State (for cancer, through the National Oncological Drug Bank and provincial banks). However, despite this legal mandate, timely access and quality of care differ significantly between sectors.

Regarding initiatives to respond to the cancer problem in the country, the creation of the National Cancer Institute (INC) in 2010, under the Ministry of Health, stands out, with the aim of promoting a model of comprehensive and continuous care for oncological diseases, research and human resources training.²⁶ In 2012 the INC launched the hospital-based Institutional Registry of Tumors of Argentina (RITA), in addition to which there were already 7 population-based cancer registries in cities and provinces, which in 2021 totaled 18 -not all are functioning or updated-.

The INC has also implemented, as of 2013, the National Breast Cancer Control Program (PNCM) with the aim of reducing morbimortality by promoting and ensuring quality and equity of care for women at risk, with suspected or confirmed disease.²⁷

ACCESS BARRIERS AND GAPS

Experts agree that the main barrier in breast cancer care in the country is the delay in access to treatment, especially in the advanced stage of the disease. In public hospitals the delay can be from 2 to 4 months, while in the private system it is possible to access the therapy in about 15 days, although there are disparities between prepayments with different levels of difficulty and delay. This is due to economic issues -mainly- as well as bureaucratic ones.

In addition, in recent years, patient care has been concentrated in centers of greater complexity, due to the disappearance of health centers in areas with fewer resources. This concentration causes delays in timely care, leading to detection of the disease in advanced stages.

A retrospective study published in 2019 that collected data from 168 women with breast cancer, 93 treated in private hospitals and 75 in public hospitals in Buenos Aires, showed significant differences regarding the stage at which they reached the diagnosis, the treatment modality and the delay for access. Patients in public hospitals presented more advanced stages compared to those treated in the private sector: stage IV 13.3% versus 3.2%. Adjuvant therapy was administered to 79.6% in private hospitals and 36% in public hospitals. The median time from diagnosis to adjuvant treatment was 130 days in the public sector and 64 days in the private sector. This difference was due to the time to surgery, 50 days in public centers and 18 days in private centers.²⁸

An important gap that hinders access and that experts highlight is education in terms of prevention, as many women do not go for their annual mammogram or medical check-ups.

CURRENT SITUATION OF THE NATIONAL CPG FOR METASTATIC BREAST CANCER

In Argentina there are several locally developed Clinical Practice Guidelines (CPG) that address breast cancer. These are recommendations and are generally not binding on access.

²⁶ Argentina.gob.ar. Regulations. Decree 1.286/2010. National Executive Power. Ministry of Health. Creation of the National Cancer Institute. <https://www.argentina.gob.ar/normativa/nacional/decreto-1286-2010-171762/texto>

²⁷ Argentina.gob.ar. Regulations. Resolution 1.813/2013. Ministry of Health. Create the National Breast Cancer Control Program. <https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-1813-2013-221755/texto>

²⁸ Recondo G, et al. Access of patients with breast and lung cancer to chemotherapy treatment in public and private hospitals in the city of Buenos Aires, *International Journal for Quality in Health Care*. 2019 Nov;31(9):682-690. <https://doi.org/10.1093/intqhc/mzz047>

The National Cancer Institute (INC) has developed various guidelines on prevention, early detection and treatment. The latter, as the entity points out, represents its position after evaluation of the available evidence. For metastatic disease these CPGs are: "Advanced Breast Cancer: Anti-HER2NEU Therapy" (July 2015).²⁹ and "Metastatic Breast Cancer: Non-AntiHER2 Therapy" (October 2015).³⁰ Subsequently also developed the guideline "High-cost drugs in the treatment of metastatic breast cancer" (May 2018).³¹ However, these guidelines should be harmonized with those used by scientific societies and other actors in the system. All of them mention that updating is estimated to take two years.

The Argentine Association of Clinical Oncology (AAOC) has a Clinical Practice Guideline on the different types of cancer; the latest is "Current recommendations for oncological treatment 2022-2023", which includes metastatic breast cancer. It is mainly based on the European Society for Medical Oncology (ESMO) CPG. The update periodicity is annual.³²

On the other hand, there are institutional guidelines such as the Angel H. Roffo Oncology Institute, a reference center in the country, which has its "Guidelines in Oncology" for diagnosis and treatment of cancer, published every two or three years. As well as provincial guidelines, such as the one developed by the Association of Clinical Oncologists of Cordoba called "Oncology Treatment Guidelines" (September 2017)³³, which is the one applied by the provincial social work, and the guide "Treatment protocols high-cost drugs: breast cancer", from the Ministry of Health of the province of Santa Fe (November 2017)³⁴. These guidelines do not detail the update criteria.

In general, in addition to the AAOC guidelines, the most widely used CPGs for breast cancer by specialists in both the public and private sectors are the international ones: those of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN).

THE IMPACT OF HEALTH POLICIES ON THE IMPLEMENTATION OF NATIONAL CPGS

Regarding drug policy and its impact on the application of clinical practice guidelines, as mentioned above, cancer treatments in Argentina are included in the benefits of the Mandatory Medical Program (PMO).

To date, there is no regulation in force that obliges the system's agents to cover a specific list of oncological drugs. Therefore, coverage must be provided according to the indication of the intervening professional, provided that it is appropriate for the patient and that such indication is approved by the National Administration of Medicines, Food and Medical Technology (ANMAT).

New technologies for breast cancer are available for prescription in the country, since local approval is usually granted shortly after they have been authorized by the FDA or the EMA. But such approval does not always replicate the indications of these agencies - based on very delimited inclusion criteria - but can be

²⁹ Advanced breast cancer: anti-HER2NEU therapy, Clinical Practice Guideline (July 2015). National Cancer Institute. Ministry of Health. Argentina. <https://bancos.salud.gob.ar/recurso/cancer-de-mama-avanzado-terapia-anti-her2neu>

³⁰ Metastatic breast cancer: Non-AntiHER2 therapy, Clinical Practice Guideline (October 2015). National Cancer Institute. Ministry of Health. Argentina. <https://bancos.salud.gob.ar/recurso/cancer-de-mama-metastatico-terapia-no-antiher2>

³¹ High-cost drugs in the treatment of metastatic breast cancer: evidence-based recommendations (May 2018). National Cancer Institute. Ministry of Health and Social Development. Argentina. <https://bancos.salud.gob.ar/recurso/drogas-de-alto-costo-en-el-tratamiento-de-cancer-de-mama-metastatico>

³² Argentine Association of Clinical Oncology (AAOC). Current recommendations for oncologic treatment 2022-2023. <https://www.aaoc.org.ar/recomendaciones-actuales-de-tratamiento-oncologico-2022-2023/>

³³ Oncology treatment guidelines. Association of Clinical Oncologists of Córdoba (September 2017). <https://www.aocc.org.ar/wp-content/uploads/2018/02/1-PROTOCOLOS-AOCC2017.pdf>

³⁴ Treatment protocols high cost drugs: breast cancer (November 2017). Cancer Control Agency, Ministry of Health, Province of Santa Fe, Argentina. <https://www.santafe.gob.ar/index.php/web/content/download/243853/1283855/>

broader. And once a drug is approved by ANMAT, it can be prescribed and the patient is entitled to receive it, regardless of the cost, and in general, without a clear cost-benefit analysis.

In this context, in addition to the lack of a defined and unified policy regarding the coverage of high-cost drugs by social security and prepaid health insurance companies - a drug may be financed in some cases and in others, under the same conditions, denied - there are barriers to access, and as a consequence, legal action through *amparos*. Most of these are usually resolved in favor of the patients.

By resolution of the Ministry of Health in 2018, the National Commission for the Evaluation of Health Technologies (CONETEC) was created, an entity in charge of carrying out evaluations and issuing recommendations to the health authority on the incorporation, form of use, financing and coverage policies of health technologies. Its reports are public and freely available for consultation.³⁵

This evaluation instance is eventual, that is to say that the Commission does not prepare reports for all the authorizations of the ANMAT, in addition to the fact that they are subsequent to these. The reports usually have disparities in relation to the regulatory authority's approvals and are not binding.

Experts agree that the entire healthcare system needs to be reviewed and comprehensive changes are required; it has been growing, with the participation of new actors and around 300 social works, each with its own provisions and auditors. There is a need for a single health policy and guidelines regarding what it is possible to cover, and in this sense, to have clinical practice guidelines endorsed by a state entity that are binding.

They also stress that it is essential that the guidelines are backed by cost-effectiveness studies and adapted to the local reality, in order to establish a standard of care based on scientific evidence but also on the capacity of the system. The experience of CPGs for emerging countries that are being developed at the international level can be an important contribution.

They also emphasize that the development of local guidelines should be carried out by oncologists who are specialists in each of the areas covered by the comprehensive approach to breast cancer, with the consensus and support of scientific organizations such as the Argentine Association of Clinical Oncology, the Argentine Society of Mastology and the National Cancer Institute. For this, it is also essential to have data available through a national cancer population registry that will make it possible to measure the reality of the disease.

For the application of the CPG, the experts point out that it is necessary to have an impact on the continuing education of oncologists, expanding access to the training systems of the scientific societies, as well as implementing a mechanism for constant recertification in the specialty.

Brazil

THE EPIDEMIOLOGY AND BURDEN OF METASTATIC BREAST CANCER DISEASE

In Brazil, breast cancer is the most frequent malignant tumor in women. According to data from the Global Cancer Observatory (Globocan) in 2020, 88,492 new cases were registered, representing almost 15% of all cancers and 30.3% of these in women. The age-adjusted incidence rate was estimated at 62 cases per

³⁵ Argentina.gob.ar. Normativa. Resolution 623/2018, updated text. Ministry of Health. Create the National Commission for the Evaluation of Health Technologies (CONETEC). <https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-623-2018-308377/actualizacion>

100,000 women and mortality at 13.8 cases per 100,000 women. This disease caused 20,725 deaths, being the second most deadly malignant neoplasm after lung cancer.³⁶

Data from the National Cancer Institute (INCA) based on the country's Population-Based Cancer Registries (RCBP), mostly from capital cities - 32 in total - indicate that the estimated incidence rate of malignant breast tumors for each year of the period 2020 - 2022 was 43.74 cases per 100,000 women, registering the highest in the Southeast region with an adjusted rate of 57.41/100,000. While the adjusted mortality rate, in 2018, was estimated at 13.84 cases per 100,000 women.³⁷

Regarding metastatic breast cancer, a study published in 2020 that aimed to estimate its prevalence in Brazil using population-based data from four sources and cancer registries (DATASUS, Registro Hospitalar de Câncer, Instituto Brasileiro de Geografia e Estatística and Agência Nacional de Saúde Suplementar) from 2008-2018, showed: almost 45,000 women are living with metastatic breast cancer in the country, representing 1 in 2,409 Brazilian women and 41 women per 100,000. Of these patients, 40% - about 18,000 - were initially diagnosed with stage IV de novo disease and 60% with stage I-III disease and relapsed. The most frequent subtypes of breast cancer were HR+/ HER2 negative (58%) followed by HER2 positive and triple negative. Median overall survival after diagnosis of metastatic disease was estimated at 26.2 months. The study also estimated that in 2023 some 53,000 women in Brazil will be living with metastatic breast cancer.³⁸

THE HEALTH SYSTEM

Brazil's healthcare system consists of the public and private sectors. The former is the Unified Health System (Sistema Único de Saúde - SUS), created in 1988 by the Federal Constitution, which guarantees comprehensive, universal and free access to health care in the country through its own and private services and facilities. About 78% of the population receives health care through SUS, which is financed by general taxes and social contributions collected by the federal, state and municipal governments.³⁹

The private sector is the health insurance sector -called supplementary system- of voluntary affiliation and provided by insurance companies and medical cooperatives. It includes health plans for companies - financed with resources from employers and employees-, for families, individual insurance and plans paid on a per-benefit basis. 25% of the population, more than 49 million people, have some type of private insurance.⁴⁰

The percentage of the population with private health insurance is higher in the Southeastern and Southern States, over 20% and 15% to 20%, respectively, while in the Northeastern States it is 10% to 15% and in the North it is 5% to 10%.⁴¹

The SUS is composed by the Ministry of Health, responsible for the central management of the system and policy development; by the State Health Secretariats (of the country's 26 States), which are in charge of regional governance, participate in policy formulation and support the municipalities; and by the Municipal

³⁶ International Agency for Research on Cancer, WHO, Global Cancer Observatory (Globocan) 2020. Cancer Today, Population Fact Sheets: <https://gco.iarc.fr/today/data/factsheets/populations/76-brazil-fact-sheets.pdf>

³⁷ Instituto Nacional de Câncer (INCA). Informativo Vigilância do Câncer. Nº 8 julho/dezembro 2020. <https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//informativo-vigilancia-do-cancer-n8-2020.pdf>

³⁸ Reinert T, et al. Estimation of the Number of Brazilian Women Living With Metastatic Breast Cancer. *JCO Glob Oncol*. 2020 Feb;6:307-312. doi: 10.1200/JGO.19.00404.

³⁹ OECD (2021), Estudos da OCDE sobre os Sistemas de Saúde: Brasil 2021, OECD Publishing, Paris, <https://doi.org/10.1787/f2b7ec85-pt>

⁴⁰ Agência Nacional de Saúde Suplementar. Acesso à Informação. Dados do Setor: Taxa de cobertura por planos privados de saúde. (Dezembro 2021). [Consultado 8/12/2022]. <https://www.gov.br/ans/pt-br/aceso-a-informacao/perfil-do-setor/dados-gerais>

⁴¹ Agência Nacional de Saúde Suplementar. Dados do Setor. Dados Gerais. Taxa de cobertura dos planos de assistência médica por Unidades da Federação (Outubro 2022). [Consultado 8/12/2022]. <https://www.gov.br/ans/pt-br/aceso-a-informacao/perfil-do-setor/dados-gerais>

Health Secretariats (of the 5,570 municipalities), which organize and carry out the delivery of health services.

In addition to regionalization and decentralization, another organizational principle of the SUS is community participation. This is mainly embodied in the Health Councils, deliberative bodies at the three levels of government. They are composed of community members (50%), health workers (25%) and service providers and administrators (25%).⁴²

The entity that regulates the private health insurance sector is the National Supplementary Health Agency (Agência Nacional de Saúde Suplementar - ANS), which is under the Ministry of Health. Other institutions linked to the Ministry are the National Health Surveillance Agency (ANVISA) and institutions dedicated to research and public health care such as the National Cancer Institute (INCA).

Regarding the response of the health system to the problem of breast cancer, over the years a large number of regulations have been enacted and different initiatives have been carried out, including, at the end of the 1990s, the Viva Mulher Program, which began activities for the early detection of the disease, with the formulation of guidelines and the initiation of the health care network.

Among the most important laws, it is worth mentioning Law 11.664/2008, known as the Mammography Law and referring to the prevention, detection, treatment and control of breast and cervical cancers, which guaranteed mammographic screening to all women over 40 years of age through the SUS. This was recently modified by Law 14.335/2022, which expanded this criterion, establishing that mammography can be performed on all women from puberty onwards, regardless of age.⁴³

Likewise, other laws such as Law 12,732/2012 which instituted the deadline for the start of oncological treatment in the SUS once the diagnosis is received, of up to 60 days; Law 13,685/2018 referred to the notification and mandatory registration of all malignant neoplasms in public and private health services; and Law 13,896/2019 on the maximum period of 30 days for the performance of the necessary tests, upon suspicion of cancer, for diagnosis. These last two amended the previous one, from 2012. All of them have been the result of the effort of the organized civil society and supported by federal deputies and senators.⁴⁴⁻⁴⁵⁻⁴⁶

Currently, the Ministry of Health's Strategic Action Plan for the Treatment of Chronic Pathologies and Noncommunicable Diseases 2021-2030 establishes guidelines for the prevention of risk factors through "the creation and strengthening of intersectoral policies and programs, the organization of network services and the production of information for evidence-based decision making", setting as a goal for breast cancer the reduction of premature mortality in women aged 30 to 69 years by 10% by 2030.⁴⁷

ACCESS BARRIERS AND GAPS

⁴² Conselho Nacional de Saúde (CNS). Ministério da Saúde. Composição. <https://conselho.saude.gov.br/composicao-cns>

⁴³ Lei Nº 14.335/2022. Altera a Lei Nº 11.664/2008, para dispor sobre a atenção integral à mulher na prevenção dos cânceres do colo uterino, de mama e colorretal. http://www.planalto.gov.br/ccivil_03/_ato2019-2022/2022/Lei/L14335.htm#art2

⁴⁴ Lei Nº 12.732/2012. Dispõe sobre o primeiro tratamento de paciente com neoplasia maligna comprovada e estabelece prazo para seu início. https://www.planalto.gov.br/ccivil_03/_ato2011-2014/2012/Lei/L12732.htm

⁴⁵ Lei Nº 13.685/2018. Altera a Lei Nº 12.732/2012, para estabelecer a notificação compulsória de agravos e eventos em saúde relacionados às neoplasias. http://www.planalto.gov.br/ccivil_03/_ato2015-2018/2018/Lei/L13685.htm

⁴⁶ Lei Nº 13.896/2019. Altera a Lei Nº 12.732/2012, para que os exames relacionados ao diagnóstico de neoplasia maligna sejam realizados no prazo de 30 dias, no caso em que especifica. http://www.planalto.gov.br/ccivil_03/_ato2019-2022/2019/Lei/L13896.htm

⁴⁷ Plano de Ações Estratégicas para o Enfrentamento das Doenças Crônicas e Agravos não Transmissíveis no Brasil 2021-2030. Ministério da Saúde. Brasília, 2021. https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/publicacoes-svs/doencas-cronicas-nao-transmissiveis-dent/09-plano-de-dant-2022_2030.pdf/

Experts agree that the main barrier to breast cancer care in Brazil is precisely access to medical care and the delay in both the detection of positive cases and timely diagnosis.

Navigation in the health system is deficient with respect to the time it takes from the arrival at the primary care unit, where it is evaluated if it is a possible case of breast cancer, to the performance of the imaging study, biopsy, diagnostic confirmation and initiation of treatment. Even though in Brazil the regulations establish the deadlines for the oncological diagnosis, which is 30 days, as well as for receiving the first treatment once it has been confirmed, which is 60 days.

In this sense, the biggest time gap they point out is between the identification of the initial symptoms until the biopsy is performed. Delays in the system result in advanced stage disease diagnoses (III and IV).

These barriers are even more significant in the public health system, with important gaps in relation to those who access the private system. There are differences not only in the type of care, but also in access to therapies already approved in the private system and more modern radiotherapy techniques.

There are also access barriers in terms of geography and distances to health facilities and specialized centers, considering that there are localities where people have contact with doctors only once a year, when professionals come to these sites.

Experts point out that the COVID-19 pandemic had a very significant impact on the health system, relegating screening controls. Data from the National Cancer Institute indicate that the number of screening mammograms performed in the SUS in 2020 had a 41% drop compared to 2019 (1,473,277 versus 2,527,833), with a recovery in 2021 - 2,054,881 were performed - but still far from pre-pandemic levels.⁴⁸ In the private sector, information from the ANS shows that 29.5% fewer mammograms were performed in 2020 in women aged 50 to 69 than in 2019 (1,667,069 vs. 2,364,453) and in 2021 11% fewer than in 2019.⁴⁹

THE CURRENT SITUATION OF THE NATIONAL CPG FOR METASTATIC BREAST CANCER

In Brazil, the national Clinical Practice Guideline for breast cancer used in the public health system is called "Diagnostic and Therapeutic Guidelines for Breast Carcinoma" (DDT), established by the Joint Regulation N°5 of the Health Care Secretariat and the Secretariat of Science, Technology and Strategic Inputs of the Ministry of Health, dated 2019.⁵⁰

The DDT, as defined by the Ministry, are documents based on scientific evidence that are intended to guide best practices in oncology and are not limited to the technologies incorporated in the SUS but to what can be offered to the patient, considering that the financing is transferred to the centers for the care of the disease and these have autonomy in the choice of the therapeutic option for each clinical situation.

The guidelines determine the criteria for diagnosis, staging, treatment, post-treatment follow-up and evaluation of the disease, which must be applied by the Ministries of Health of the States, the Federal District and the Municipalities for access to care, authorization, registration and the corresponding reimbursement.

⁴⁸ Instituto Nacional de Câncer (INCA). Controle do Câncer de Mama. Dados e Números. Mamografias no SUS. [Consultado 8/12/2022]. <https://www.gov.br/inca/pt-br/assuntos/gestor-e-profissional-de-saude/controle-do-cancer-de-mama/dados-e-numeros/mamografias-no-sus>

⁴⁹ Agência Nacional de Saúde Suplementar. Dados Assistenciais e Publicações Relacionadas. Dados assistenciais do setor por semestre. Mamografias 2021-2020-2019. [Consultado 8/12/2022]. <https://www.gov.br/ans/pt-br/ acesso-a-informacao/perfil-do-setor/dados-e-indicadores-do-setor>

⁵⁰ Portaria Conjunta N° 5/2019. Aprova as Diretrizes Diagnósticas e Terapêuticas do Carcinoma de Mama. Ministério da Saúde. https://www.gov.br/saude/pt-br/assuntos/protocolos-clinicos-e-diretrizes-terapeuticas/arquivos/2019/ddt_carcinoma_cancerde_mama.pdf

Mammographic screening for early detection is indicated for women between 50 and 69 years of age every two years, although almost half of the new cases in Brazil occur in women before the age of 50.

The guidelines also address aspects related to the care of patients diagnosed with metastatic breast cancer.

On the other hand, there are the "Guidelines for oncological treatments recommended by the Brazilian Society of Clinical Oncology (SBOC)", launched in 2022. Those for breast cancer consist of 4 fascicles referring to: staging, localized disease and adjuvant treatment, localized disease - with neoadjuvant treatment before surgery, and metastatic disease. According to the guidelines, "these are based on predefined levels of scientific evidence and the recommended therapeutic options were evaluated according to their clinical relevance but also for their economic impact".⁵¹

The experts agree that this CPG, being a treatment guide, which is also very rigorous, should include other issues related to the approach to the disease, such as fertility preservation, genetic testing, how to perfect radiotherapy and when it is not necessary to irradiate, among others.

There is also the Unimed guide "Oncological Treatment", whose importance lies in the fact that this entity is the private health insurer with the widest reach: of the population with this type of insurance, approximately 38% corresponds to Unimed.⁵²⁻⁵³

This guideline, as its name suggests, refers to treatments for different types of cancer, including breast cancer - also in metastatic stage. The latest version is from 2018, developed internally. These are recommendations that "guide cancer therapies based on evidence-based medicine and cost-effectiveness studies", basically used by professionals working in the field of this insurer.

The aforementioned Clinical Practice Guidelines and guidelines do not detail the criteria for updating.

Specialists, especially in private practice, in addition to the SBOC guidelines, use the international breast cancer CPGs of the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO).

THE IMPACT OF HEALTH POLICIES ON THE IMPLEMENTATION OF NATIONAL CPGs

Regarding drug policy and given its impact on the possibility of adherence to CPGs, in the Brazilian public health sector, drug coverage for outpatient treatment is guaranteed by SUS and is based on the National List of Essential Medicines (RENAME) of the Ministry of Health; the latest is from 2022.⁵⁴ In the private sector, the National Supplementary Health Agency (ANS) has a list called Health Procedures and Events, which determines the mandatory health care coverage to be guaranteed by private insurance companies.⁵⁵⁻⁵⁶ In the case of high-cost drugs, when they are not financed by these, the SUS is usually used.

⁵¹ Diretrizes de tratamentos oncológicos recomendados pela Sociedade Brasileira de Oncologia Clínica (2022). Mama: doença localizada - neoadjuvância. Mama: estadiamento. Mama: doença localizada adjuvância. Mama: doença metastática. <https://sboc.org.br/diretrizes-publicas/2022>

⁵² Tratativa Oncológica 2018. ©2018 Confederação Nacional das Cooperativas Médicas - Unimed do Brasil.

⁵³ Unimed. Nossos números. [Consultado 8/12/2022]. <https://www.unimed.coop.br/site/sistema-unimed>

⁵⁴ Relação Nacional de Medicamentos Essenciais (RENAME) 2022. Ministério da Saúde. Brasília. https://www.gov.br/saude/pt-br/composicao/secte/daf/renome/20210367-renome-2022_final.pdf

⁵⁵ Agência Nacional de Saúde Suplementar. O que é o Rol de Procedimentos e Evento em Saúde. Brasil. [Consultado el 8 de diciembre de 2022]. <https://www.gov.br/ans/pt-br/assuntos/consumidor/o-que-o-seu-plano-de-saude-deve-cobrir-1/o-que-e-o-rol-de-procedimentos-e-evento-em-saude>

⁵⁶ Resolução Normativa N° 470/2021. Agência Nacional de Saúde Suplementar (ANS). Brasil. <https://www.gov.br/ans/pt-br/assuntos/noticias/sobre-ans/RN470.pdf>

The RENAME is complemented by the National Therapeutic Form (FTN) published by the Ministry of Health, which is an evidence-based guidance document for health professionals, and by the Clinical Protocols and Therapeutic Guidelines (PCDT). The latest version of the FTN is from 2010.⁵⁷

RENAME updates are proposed by the National Commission for the Incorporation of Technologies in the SUS (CONITEC),⁵⁸ a collegiate body of the Ministry of Health created by Law 12,401 of 2011.⁵⁹ While updates to the essential list of the ANS are proposed by the Commission for the Update of the List of Supplementary Health Procedures and Events (Cosaúde), created by Normative Resolution 474 of 2021.⁶⁰

In addition, for a drug to be available in Brazil, it must have the sanitary registration from ANVISA and the maximum price approval from the Drug Market Regulation Chamber (CMED). But the fact that it has regulatory approval does not mean that it is financed by the SUS or by the ANS.

This barrier to access - considering also that not all CPGs contemplate it - has had its correlate in the judicialization through injunctions to obtain coverage for treatments, sometimes with limited proven clinical effectiveness. According to data from 2017, in that year there were around 1,377,000 *amparo* processes in health, of which 340,000 were in relation to medicines.⁶¹

A recent law, dated March 2022, established that the deadline for the ANS to complete the process of including oncology drugs in its list is 120 days, extendable to 60 days. In addition, it must incorporate the technologies recommended by CONITEC to be included in the SUS, within 60 days.⁶²

Given the challenge of expanding access to treatments considered high-cost, the experts suggest that an interesting discussion is the pay for performance alternative, i.e., payment of the technology to the provider based on the patient's positive response within the time established - demonstrated - in the clinical evidence. This type of innovative agreement is a modality already used in countries such as Germany, the Netherlands, Switzerland and the United Kingdom.

The experts stress that improving access to early breast cancer diagnosis and patient navigation in the system for timely care and addressing the disease at early stages is a priority.

They also agree on the need to map the reality of cancer in the country to determine the gaps in access to care, diagnosis and treatment in each of the regions, where it is necessary to have an impact and in what way, in order to establish lines of action and allocate resources accordingly.

⁵⁷ Formulário Terapêutico Nacional 2010. Ministério da Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Assistência Farmacêutica e Insumos Estratégicos. 2a. ed. Brasília. https://bvsm.sau.gov.br/bvs/publicacoes/formulario_terapeutico_nacional_2010.pdf

⁵⁸ Decreto Nº 7.646/2011. Dispõe sobre a Comissão Nacional de Incorporação de Tecnologias no SUS e sobre o processo administrativo para incorporação, exclusão e alteração de tecnologias em saúde pelo SUS. https://www.planalto.gov.br/ccivil_03/_ato2011-2014/2011/decreto/d7646.htm

⁵⁹ Lei Nº 12.401/2011. Altera a Lei Nº 8.080/1990, para dispor sobre a assistência terapêutica e a incorporação de tecnologia em saúde no âmbito do SUS. http://www.planalto.gov.br/ccivil_03/_Ato2011-2014/2011/L12401.htm

⁶⁰ Resolução RN Nº 474/2021. Dispõe sobre a constituição e o funcionamento da Comissão de Atualização do Rol de Procedimentos e Eventos em Saúde Suplementar. <https://www.in.gov.br/en/web/dou/-/resolucao-rn-n-474-de-25-de-novembro-de-2021-362693251>

⁶¹ Acosta A, Falcão M Z, Aith F M A, Vance C (2019). Judicialización del acceso a medicamentos en el contexto suramericano. *Revista De Direito Sanitário*, 20(1), 32-62. <https://doi.org/10.11606/issn.2316-9044.v20i1p32-62>

⁶² Lei Nº 14.307/2022. Altera a Lei Nº 9.656/1998, para dispor sobre o processo de atualização das coberturas no âmbito da saúde suplementar. <https://www2.camara.leg.br/legin/fed/lei/2022/lei-14307-3-marco-2022-792333-publicacaooriginal-164693-pl.html>

THE EPIDEMIOLOGY AND BURDEN OF METASTATIC BREAST CANCER DISEASE

In Chile, breast cancer is the most frequent malignant tumor in women and the second most prevalent in the general population. According to estimates by the Global Cancer Observatory (Globocan) in 2020 there were 5,331 new cases of breast cancer, which represented almost 21% of all cancers in women, and caused 1,674 deaths. The age-adjusted incidence and mortality rates were 37.4 and 10.2 cases per 100,000 women, respectively.⁶³

Chile does not have a national cancer population registry; the data collected by Globocan correspond to the cancer registries of four regions and therefore do not represent the total reality of the disease in the country.

Regarding the incidence of metastatic breast cancer, according to a study published in *Revista Médica de Chile* (2014) that analyzed the medical records of patients diagnosed with breast cancer treated between January 1999 and May 2013 at the Cancer Center of the Pontificia Universidad Católica de Chile, 3.6% had metastatic disease at the time of diagnosis.⁶⁴

Another study of that publication (2017) that had among its objectives to describe the demographic and clinical characteristics of patients with breast cancer diagnosis attended in 6 public hospitals between the years 2000 and 2010 and that analyzed 5,119 records, exposed that 5.1% were in stage IV at diagnosis, while 65.7% in stage I-II and 29.1% in stage III.⁶⁵

A recent study published in the *Revista Chilena de Obstetricia y Ginecología* (2022), a descriptive and retrospective 10-year study that evaluated information on 2,862 women diagnosed with breast cancer treated in the network of the Servicio de Salud Metropolitano Sur Oriente in the period 2006-2015, recorded that 5.1% of patients were diagnosed at stage IV, 56.8% at earlier stages (0, I and IIA) and 3.5% at stage IIIC.⁶⁶

It is worth mentioning that the National Cancer Registry is a project on Chile's public health agenda. There is a pilot plan in the Bio region and in the town of Puerto Montt, oriented mainly to oncology management -it allows the traceability of patients and the stage of treatment they are in- to be observed-

THE HEALTH SYSTEM

The Chilean health system is of a mixed nature: public and private. The former is organized through the National Health Fund (FONASA), the public insurance that provides services through the National Health Services System (SNSS) -with a network of 29 Regional Services and the Municipal Primary Care System-. The beneficiaries are dependent and self-employed workers (they contribute 7% of their monthly remuneration), people who have no resources, pensioners and beneficiaries of the Program of Reparation

⁶³ International Agency for Research on Cancer, WHO, Global Cancer Observatory (Globocan) 2020. Cancer Today, Population Fact Sheets: <https://gco.iarc.fr/today/data/factsheets/populations/152-chile-fact-sheets.pdf>

⁶⁴ Sánchez R, César, et al. Metastatic breast cancer: Characterization of a cohort according to subtypes. *Rev. med. Chile* [online]. 2014;142(4):428-435. <http://dx.doi.org/10.4067/S0034-98872014000400003>

⁶⁵ Castillo César del SM. et al. Impact of the Chilean Explicit Guaranties Health System (GES) on breast cancer treatment. *Rev. méd. Chile* [online]. 2017;145(12):1507-1513. <http://dx.doi.org/10.4067/s0034-98872017001201507>

⁶⁶ Merino Gina F et al. Characterization of breast cancer incidence in a Chilean public health service in the period 2006-2015. *Rev. chil. obstet. ginecol.* [online]. 2022, vol.87, n.3, pp.188-193. <http://dx.doi.org/10.24875/rechog.22000015>

and Integral Attention in Health and Human Rights (PRAIS). Its funds come from the State, from mandatory contributions and co-payments.⁶⁷⁻⁶⁸

The private sector is made up of the 'Instituciones de Salud Previsional' (ISAPRE), which are health insurers that have the power to administer the compulsory contribution of the people who opt for them. They provide services through both private and public facilities.⁶⁷⁻⁶⁸

Citizens are free to choose one or the other. Generally speaking, ISAPREs have more benefits, financed with additional contributions, because they operate according to priced plans that take into account the individual's pre-existing risks.

There are also specific insurance systems for the armed forces (Army, Air Force, Navy), as well as the National Defense Social Security Fund (Capredena) and the Social Security Directorate of the Carabineros (Dipreca).⁶⁸

According to data from December 2021, 77% of the population is affiliated to FONASA and almost 17% is insured by ISAPREs. These percentages are based on the 2017 Census population projected to 2021, which totaled 19,678,363 inhabitants.⁶⁹⁻⁷⁰⁻⁷¹

With respect to the public policies carried out to guarantee access to essential health services and which laid the foundations of the current system, it is worth mentioning the establishment of the Universal Access to Explicit Guarantees Plan (AUGE), also known as the General Regime of Explicit Health Guarantees (GES), through Law 19.966 of 2004.⁷² In addition to updating the previous benefits (Law 18.469/1985), it determined a series of benefits for the population affiliated to FONASA and ISAPRE with enforceable guarantees in terms of access, quality, financial protection and timeliness. Breast cancer was part of the first group of cancers included in the GES (Decree 170/2005 of the Ministry of Health).

In addition, the creation of the Financial Protection System for High-Cost Diagnoses and Treatments, through Law 20,850 Ricarte Soto of 2015, which guarantees coverage for treatments that includes all beneficiaries of the social security health systems. The law contemplated the participation of specialists and civil society organizations in the two commissions it instituted: one to prepare recommendations and the other to monitor the system.⁷³

Currently, the Ricarte Soto Law includes coverage for 27 high-cost diseases, including a therapeutic for HER2+ breast cancer.⁷⁴

As for the GES, to date it guarantees coverage for 87 pathologies. Regarding breast cancer, the maximum times for access to benefits are established: from suspicion to confirmation of diagnosis with mammography and subsequent staging, 45 days respectively; primary treatment from staging, 30 days;

⁶⁷ Superintendence of Health. How the Health System works in Chile. [Accessed 5/12/2022]. https://www.supersalud.gob.cl/difusion/665/w3-article-17328.html#accordion_0

⁶⁸ González C, Castillo-Laborde C, Matute I: [ed.]. Population health series: Structure and functioning of the Chilean health system. Santiago, Chile: CEPS, Fac. of Medicine. CAS-UDD. 2019.

⁶⁹ National Institute of Statistics Chile (INE). Statistical tables. Base projection 2017. Estimates and projections 1992-2050, country. [Accessed 5/12/2022]. <https://www.ine.gob.cl/estadisticas/sociales/demografia-y-vitales/proyecciones-de-poblacion>

⁷⁰ Fonasa Beneficiary Population Dashboard (December 2021). [Accessed 5/12/2022]. <https://public.tableau.com/app/profile/fonasa.estudios.y.estad.sticas/viz/BeneficiariosyCotizaciones3/Portada>

⁷¹ Superintendence of Health. Beneficiary Portfolio 1990-2021. Current beneficiaries of the ISAPRE system in December of each year. [Accessed 5/12/2022]. <https://www.supersalud.gob.cl/documentacion/666/w3-propertyvalue-3757.html>

⁷² Law 19.966. Establishes a regime of health guarantees. Ministry of Health of Chile. Santiago, August 25, 2004. <https://www.bcn.cl/leychile/navegar?idNorma=229834>

⁷³ Law 20.850. Creates a financial protection system for high cost diagnoses and treatments and pays posthumous tribute to Mr. Luis Ricarte Soto Gallegos. Ministry of Health of Chile. Santiago, 01/06/2015. <https://www.bcn.cl/leychile/navegar?idNorma=1078148>

⁷⁴ Chile Attends. Ricarte Soto Law. (Last update: May 25, 2022). <https://www.chileatiende.gob.cl/fichas/38873-ley-ricarte-soto>

complementary treatments from medical indication, 20 days; and follow-up for the first control, 90 days from medical indication; and follow-up for the first control, 90 days from medical indication.⁷⁵

ACCESS BARRIERS AND GAPS

The incorporation of breast cancer into the General Regime of Explicit Health Guarantees (GES) -effective as of July 2005- for access to benefits in relation to diagnosis, treatment and follow-up, meant an important advance in the approach to the disease.

A study that evaluated its impact by analyzing the records of patients diagnosed with breast cancer treated in 6 public hospitals between 2000 and 2010 showed a significant increase in the number of cases diagnosed in stage I, from 8.4% to 24.7% in the post-GES period, as well as an upward trend in overall survival of 1% per year ($p= 0.024$).⁷⁶

However, although oncology care in the country is organized as a network and can be accessed by the entire population, there are barriers and gaps in access.

Experts identify difficulties such as the distance to care centers, the insufficient number of human resources -especially in public hospitals, where most of the population is treated-, infrastructure problems -as is the case of the lack of availability of radiotherapy- and also limitations of financial resources for access to treatment.

Another important gap pointed out is the education of women about prevention. In 2019, about 39% of mammograms were completed in the population susceptible to mammography -in 2020, 34.6%-, and it should be almost 80% to reduce mortality. Access to timely diagnosis is a right; even by law, women can take a day off work to undergo this examination. In Chile, breast cancer screening has been implemented for women between 50 and 69 years of age, which consists of a mammogram every 3 years and, if necessary, an ultrasound scan.

In terms of education, there are also barriers regarding knowledge of the scope and benefits of GES, not only in the general population but even among health professionals.

After the health emergency caused by the COVID-19 pandemic, there was an increase in the demand for care due to the controls that had not been carried out, which led to an overload in the Oncology Services and in the providers. However, experts emphasize that this situation was already present before and the pandemic exposed it in a more evident way.

THE CURRENT SITUATION OF THE NATIONAL CPG FOR METASTATIC BREAST CANCER

In Chile, the most recent national Clinical Practice Guide for breast cancer is the "CPG GES, AUGE N°8: Breast Cancer", developed in 2021 by the Department of Health Technology Assessment and the Department of Comprehensive Management of Cancer and other Tumors of the Ministry of Health. A panel of 18 experts in Medical Oncology, Anatomopathology, Mastology, Breast Surgery, Radiotherapy, Genetics,

⁷⁵ Chile Attends. AUGE-GES Plan. (Last update: November 16, 2022). <https://www.chileatiende.gob.cl/fichas/2464-plan-auge-ges>

⁷⁶ Castillo, César del SM. et al. Impact of the Chilean Explicit Guaranties Health System (GES) on breast cancer treatment. *Rev. méd. Chile* [online]. 2017, vol.145, n.12, pp.1507-1513. <http://dx.doi.org/10.4067/s0034-98872017001201507>

Palliative Medicine and Medical Technology from hospitals, clinics and universities participated in its development.⁷⁷

This guide is an update of the "CPG AUGÉ: Breast Cancer", dated November 2015, whose term of validity was 5 years from the date of its publication.⁷⁸

The development of the Clinical Practice Guide (GES) is based on the review of the effectiveness of the main recommendations of its predecessor and on the definition of a series of questions -some adapted from the European CPG (2018) and from the Chilean Society of Mastology (2017)- that resulted in 27 questions related to screening, diagnosis, treatment, rehabilitation and follow-up. The GRADE methodology was applied, so as to assess the certainty of the evidence and produce recommendations on the 27 topics raised based on the best available scientific evidence.

Among the objectives of this Clinical Practice Guide, besides contributing to improve the detection of breast cancer in early stages and reduce morbidity and mortality, is the standardization of the detection, diagnosis and treatment of the disease.

The guide recommendations also address aspects related to the care of patients diagnosed with metastatic disease.

The experts agree that the recommendations are based on solid, up-to-date evidence, although they do not respond to all clinical issues because they are limited to the questions that were included.

In addition to the GES CPG for breast cancer, the use of which is not mandatory - these are recommendations - the specialists in the country use international guidelines as a reference, especially the CPG of the National Comprehensive Cancer Network (NCCN).

In the event that therapeutics not included in the Explicit Health Guarantees (GES) are indicated, they will not be financed by the system, regardless of whether they have the health registration of the Public Health Institute (ISP), the regulatory authority for drugs in Chile.

Barriers to access to high-cost drugs have led to legal action through injunctions, sometimes on therapeutics with little clinical benefit. Although the injunctions are usually resolved in favor of the patients, the process involves several instances that can take from 3 to 6 months, when time essential in a disease such as breast cancer.

It is worth mentioning that the CPG GES for breast cancer is available on the Ministry of Health's website - on a microsite- in a user-friendly format that makes it possible to navigate through the contents.

THE IMPACT OF HEALTH POLICIES ON THE IMPLEMENTATION OF NATIONAL CGPS

Chile has a national cancer law that was enacted in August 2020 (Law 21.258 of the Ministry of Health), which establishes the framework for the development of public policies aimed at preventing the increase in the incidence of the disease, addressing treatment in a comprehensive manner and the recovery of those

⁷⁷ Ministry of Health of Chile. GES Clinical Practice Guidelines. AUGÉ Health Problem N°8: Breast Cancer. Recommendations GRADE. <https://diprece.minsal.cl/garantias-explicitas-en-salud-auge-o-ges/guias-de-practica-clinica/cancer-de-mama/recomendaciones-grade/>

⁷⁸ AUGÉ Clinical Guidelines, Breast Cancer. Ministry of Health. (November 2015). Santiago, Chile. ISBN: 978-956-8823-55-9. <https://www.minsal.cl/wp-content/uploads/2015/09/GPC-CaMama.pdf>

affected. To this end, it provided for the preparation of a five-year National Cancer Plan, under the responsibility of the Ministry of Health.⁷⁹

One of the main principles of the law is that it incorporated the participation of patients' organizations as a "fundamental component for its enforcement". In addition, it created the National Cancer Commission composed of three representatives from such organizations, five members from scientific associations and three from medical schools.

It also declared cancer to be a notifiable disease (in relation to the national registry) and established that the Clinical Practice Guidelines "must be reviewed every two years, or whenever a favorable evaluation of the available scientific evidence so warrants" (art. 7).

In accordance with this law, the National Cancer Plan 2022-2027 was approved in March 2022.⁸⁰ (Resolution 360 Exempt),⁸¹ based on the plan that preceded it 2018-2028.

Among the initiatives it takes up are the improvement of breast cancer screening coverage, the creation of standards for the provision of equipment and human resources and the promotion of training, the creation of the National Fund for research, the implementation of genetic counseling in the network, the definition of the structure for the National Oncology Network, and the implementation of the National Cancer Registry, among others.

The experts agree that public policies on cancer constitute a State policy in Chile, as shown by the law and the national plan. In addition, progress has been made in improving the benefits of the Explicit Health Guarantees (GES) and there has been an increase in the basket of drugs.

The current public health agenda is aimed at giving the current regulations a greater emphasis on evidence-based medicine, in addition to the gender and multicultural perspective. The latter had not previously been contemplated in the CPGs. It is also focused on improving Health Technology Assessment, which, in the opinion of the experts, would have a positive impact on adherence to CPGs and on access.

The experts stress that the implementation of the National Cancer Registry -unified and integrated into the Digital Hospital platform- is fundamental, as it will make it possible to measure the reality of the disease and to know the resources required to allocate them efficiently. Until it is available, all cancers occurring in the country should be notified centrally, as indicated in the regulations.

They also consider that it is essential to improve the information systems, either by integrating them or by implementing a centralized system or a single, portable clinical record, since each service uses different programs that "do not talk" with each other. Many of the current difficulties, they stress, including the management of waiting lists, are due to the lack of information for decision-making.

On the other hand, they agree on the importance of emphasizing patient education on disease prevention and their rights to access timely care, as well as on dissemination regarding metastatic breast cancer, given that the patients affected are usually those who have the greatest barriers to access to the new technologies that chronicle the disease.

⁷⁹ Law 21.258. Creates the National Cancer Law. Santiago, 26/08/2020. <https://www.bcn.cl/leychile/navegar?idNorma=1149004>

⁸⁰ Ministry of Health. "National Cancer Plan 2022 - 2027." Chile, 2022. <https://leydelcancer.minsal.cl/documentos/Marco-general-del-Plan-Nacional-de-Cancer-2022-2027.pdf>

⁸¹ Resolution 360 Exempt. Approves the National Cancer Plan 2022-2027. Ministry of Health; Undersecretary of Public Health. Santiago, 08/03/2022. <https://www.bcn.cl/leychile/navegar?idNorma=1173910>

THE EPIDEMIOLOGY AND BURDEN OF METASTATIC BREAST CANCER DISEASE

Breast cancer is the most frequent malignant neoplasm in Colombia. According to data from the Global Cancer Observatory (Globocan) in 2020, 15,509 new cases were registered, representing 13.7% of all malignant tumors and 25.7% of these in women. Age-adjusted incidence and mortality rates were estimated at around 48 and 13 cases per 100,000 women, respectively. In absolute numbers, 4,411 deaths were recorded.⁸²

It is worth mentioning that Globocan estimates national data based on four population-based cancer registries (Metropolitan Area of Bucaramanga, Cali, Manizales and Pasto) with a representation of less than 5% of the Colombian population.

There are also other data on this disease in Colombia, such as those of the High-Cost Account (CAC), a non-governmental technical body of the General System of Social Security in Health (SGSSS). These are based on the information that insurers and health service providers report to the CAC. The 2021 report -period 2020- recorded that breast cancer was the most common cancer in women (28% of total new cases), 85,112 women were reported with the disease of which 6,593 were new cases and 3,966 deaths occurred. The median age was 57 years. Ninety percent were staged at diagnosis: in situ 7.95%, stage I 15.52%, stage II 39.97%, stage III 29.09% and stage IV 7.47%.⁸³

The CAC information on cancer refers to the situation of the disease in the population served by the SGSSS insurance system. It is not a population registry and there is surely an underreporting of cases.

On the other hand, the National Institute of Cancerology, a public entity dedicated to patient care, research and health policy advice on this disease, publishes its Statistical Yearbook. In the latest publication, with data from 2021 based on the clinical records of its information system, of the total number of new cases of malignant neoplasms in women (3,102 patients), breast cancer accounted for 16.3%. On admission to the INC, 35.6% of breast cancer cases were in clinical stage III and 16.6% in metastatic stage (IV).⁸⁴ These statistics do not necessarily reflect the behavior of the national population.

The country does not have a national cancer population registry. Therefore, it is not possible to conclusively establish the incidence of metastatic breast cancer, although it is estimated that it could represent between 10% to 15% of breast cancer cases.

THE HEALTH SYSTEM

Colombia's General Social Security Health System (SGSSS), created by Law 100 of December 1993, is a system of social security for health care⁸⁵, comprising the Ministry of Health and Social Protection, the public and private insurance companies (Entidades Promotoras de Salud - EPS), responsible for enrolling

⁸² International Agency for Research on Cancer, WHO, Global Cancer Observatory (Globocan) 2020. Cancer Today, Population Fact Sheets: <https://gco.iarc.fr/today/data/factsheets/populations/170-colombia-fact-sheets.pdf>

⁸³ Colombian Fund for High Cost Diseases, High Cost Account (CAC). Situation of cancer in the adult population served in the Colombian SGSSS, 2021. Bogotá, D.C. 2022.

⁸⁴ National Cancer Institute (INC). Statistical Yearbook 2021. Bogotá, D. C. INC; 2022.

⁸⁵ Law No. 100 of 1993. Whereby the comprehensive social security system is created. Republic of Colombia, National Government. Santafé de Bogotá, D. C., 23/12/1993. https://www.minsalud.gov.co/Normatividad_Nuevo/LEY%200100%20DE%201993.pdf

and collecting contributions as well as guaranteeing the provision of the Health Benefits Plan, and the Health Provider Institutions (IPS), which are hospitals, clinics, laboratories and clinics.⁸⁶

Access to the SGSSS is through two regimes: the contributory and the subsidized, that is, through affiliation to an EPS of one or the other. The former includes salaried and self-employed workers, retirees, pensioners and persons with monthly incomes equal to or higher than one Minimum Legal Monthly Wage in Force. The subsidized regime affiliates people in conditions of poverty or vulnerability (according to the System for the Identification of Potential Beneficiaries of Social Programs - SISBEN), among others.⁸⁶⁻⁸⁷

There is also a special or exempted regime for teachers, the Armed Forces, the Colombian Oil Company (ECOPETROL) and some public universities.⁸⁶

According to data from the Ministry of Health and Social Protection based on the total population of the National Population and Housing Census 2018 projected to December 2021, about 48% of people are affiliated to the contributory regime and almost 47% to the subsidized regime. While the exception and special regime covers 4% of the population. The coverage achieved is 99.03%.⁸⁸

As for the private health sector, a study by the Federation of Colombian Insurers (Fasecolda), the Colombian Association of Comprehensive Medicine Companies (ACEMI) and the Center for Studies on Social Protection and Health Economics (PROESA) shows that in 2019 approximately 9% of the population in Colombia had a voluntary health plan. Among these, prepaid medicine plans accounted for 38%.⁸⁹ This means that just over 3% of the population would have a prepaid policy.

Health expenditure in relation to GDP, according to the Ministry of Health and Social Protection, is close to 8% (year 2021).⁹⁰ Most of this is spent on non-communicable diseases, including cancer, where metastatic disease is estimated to account for about 20% of spending.

But if we analyze health outcomes, in the case of breast cancer, Colombia has the lowest age-standardized 5-year survival rate in the region (72.1%).⁹¹ It is also one of the few countries in the world where mortality associated with this cancer is progressively increasing.

With regard to the response of the health system to the problem of cancer and breast cancer, a series of laws and regulations have been enacted over the years, including, in 2010, the Sandra Ceballos Law 1,384. This law institutes actions for the comprehensive control of cancer by guaranteeing the provision of the required services -by the State and the SGSSS- for the purposes of prevention, early detection, comprehensive treatment, rehabilitation and palliative care.⁹²

⁸⁶ Ministry of Health and Social Protection. General Health System Insurance. <https://www.minsalud.gov.co/proteccionsocial/Regimensubsubsidado/Paginas/aseguramiento-al-sistema-general-salud.aspx>

⁸⁷ User's guide. Step by step on access to health services. Ministry of Health and Social Protection (January 2021). <https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/SG/SAB/AT/guia-usuario-minsalud.pdf>

⁸⁸ Ministry of Health and Social Protection. Health insurance figures. (December 2021). <https://www.minsalud.gov.co/proteccionsocial/Paginas/cifras-aseguramiento-salud.aspx>

⁸⁹ The Voluntary Health Plans Market in Colombia. Center for Studies on Social Protection and Health Economics - Center for Studies on Social Protection and Health Economics - PROESA. Cali / Universidad Icesi. Julio 2021. Año 8. ISSN: 2256-5787 (En línea).

⁹⁰ Ministry of Health and Social Protection. Communications. News. 29/06/2022. <https://www.minsalud.gov.co/Paginas/Colombia-llego-al-aseguramiento-universal-en-salud-al-alcanzar-el-99.6.aspx>

⁹¹ OECD/The World Bank (2020), Health at a Glance: Latin America and the Caribbean 2020, OECD Publishing, Paris. <https://doi.org/10.1787/740f9640-es> (página 155)

⁹² Law No. 1.384 Sandra Ceballos of 2010. Whereby the actions for the comprehensive care of cancer in Colombia are established. National Government. Bogotá, D. C., 19/04/2010. <https://www.funcionpublica.gov.co/eva/gestornormativo/norma.php?i=39368>

In 2012, the National Cancer Information System and the National Cancer Observatory were created (Resolution 4.496)⁹³. That same year, the Ministry of Health and Social Protection promoted the implementation of the Ten-Year Plan for Cancer Control in Colombia 2012-2021, adopted in 2013 with Resolution 1,383, and which positions this disease as a public health problem by proposing a model of care.⁹⁴

More recently, with Resolution 3.280 of 2018, the technical and operational guidelines of the Comprehensive Care Route for the Promotion and Maintenance of Health and the Comprehensive Health Care Route (RIAS) are adopted. The latter is aimed at comprehensive care for risk groups, including breast cancer, and must be adopted and adapted throughout the country.⁹⁵

ACCESS BARRIERS AND GAPS

Experts agree that the main barrier to breast cancer care in the country is the delay in access to coverage, both to reach a diagnosis and to receive timely treatment. In addition, the diagnostic timeliness differs between insurance regimes and even between healthcare centers.

In this regard, data from the 2020 High-Cost Account (CAC) on breast cancer reported that in the country, in that year, the timeliness of diagnosis and treatment in the subsidized regime registered the longest wait (median time of 33 days and 70 days, respectively).⁹⁶ These delays between diagnostic suspicion and the initiation of adequate treatment are indicative of shortcomings in screening strategies.

There are also inequalities in the availability of technology: very high-quality hospitals are located in a limited radius close to the main cities (Bogota, Medellin, Cali, Barranquilla), limiting access to a large proportion of the population to the minimum essential treatment.

An important gap highlighted by experts is the education of women, not only in terms of prevention, but also on how to navigate the health system, as well as what their rights are in terms of enforceable health services.

THE CURRENT SITUATION OF THE NATIONAL CPG FOR METASTATIC BREAST CANCER

The "Clinical Practice Guide for the early detection, comprehensive treatment, follow-up and rehabilitation of breast cancer" is the CPG for this disease at the national level, of the Ministry of Health and Social Protection, whose development was carried out by the National Cancer Institute (INC) and the Institute for Health Technology Assessment (IETS).

The IETS is Colombia's National Agency for Health Technology Assessment. It was created by Law 1,438 of 2011 -on reform of the SGSSS and other provisions- as a non-profit, mixed and decentralized entity of the health sector.

Said CPG was carried out in 2013 with a version also for patients. The second and last edition is from 2017. Regarding the review and update period, the guideline established 3 years or earlier, depending on the

⁹³ Resolution N° 4.496 of 2012. By which the National Cancer Information System is organized and the National Cancer Observatory is created. Ministry of Health and Social Protection. Bogotá, D. C., 18/12/2012. https://www.minsalud.gov.co/Normatividad_Nuevo/Resoluci%C3%B3n%204496%20de%202012.pdf

⁹⁴ Resolution No. 1,383 of 2013. By which the Ten-Year Plan for Cancer Control in Colombia 2012-2021 is adopted. Ministry of Health and Social Protection. Bogotá, D. C., 02/05/2013. <https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/resolucion-1383-de-2013.pdf>

⁹⁵ Resolution No. 3,280 of 2018. Whereby the technical and operational guidelines of the Comprehensive Care Route for the Promotion and Maintenance of Health are adopted. Ministry of Health and Social Protection. Bogotá, D. C., 02/08/2018. <https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/resolucion-3280-de-2018.pdf>

⁹⁶ Colombian Fund for High Cost Diseases, High Cost Account (CAC). Situation of cancer in the adult population served in the Colombian SGSSS, 2021. Bogotá, D.C. 2022.

publication of relevant evidence that may modify the recommendations. In its elaboration participated professional members of the Colombian Association of Mastology, the Colombian Association of Oncological Radiotherapy and specialists from hospitals, clinics, representatives of universities and patient organizations.⁹⁷

The updates refer to recommendations regarding "indications for axillary emptying, adjuvant hormonal management strategies in the premenopausal patient, addition of radiotherapy to conservative surgery in early breast cancer, anti-HER2 therapy in metastatic or progressing HER2-positive breast cancer, combination of carboplatin plus taxanes in neoadjuvant treatment in triple-negative breast cancer, and indications for requesting genomic expression profiles in infiltrating breast cancer."⁹⁷ However, the development and updating of this guide would benefit from a systematic method for the selection of the topics to be reviewed and a more frequent predetermined periodicity.

These guidelines are not binding, as they are recommendations. Nor is it binding with respect to access to medicines, since this depends on the technology with sanitary registration from the National Institute for Drug and Food Surveillance of Colombia (INVIMA). According to experts, one of the important limitations for the development of institutional guidelines is the regulatory restriction to establish recommendations that cannot include drugs without INVIMA authorization and the concordance they must have with the current (2017) guidelines of the Ministry of Health and Social Protection. There may be drugs or procedures available but if these do not have INVIMA registration for use in breast cancer, or go against the Ministry's guidelines, they can generate access difficulties. In other words, the regulations limit the use of treatments to those approved by the local regulatory authority.

In this context, experts recommend that in order to establish the technical criteria for granting drug marketing registrations, the contribution of scientific societies should be considered.

The development of institutional guidelines is not a homogeneous process in the country; for example, the Caesar Oncology and Hematology Society (SOHEC), a reference institution in the comprehensive care of oncology patients, developed its own CPG for breast cancer. It is a hybrid of the guidelines of the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), adapted to the criteria and operation of the institution.

In the process of accreditation and accreditation of cancer care providers, there is the possibility of adherence to international guidelines. There is usually a preference for the ESMO and NCCN CPGs, with the limitation that these include procedures or drugs not available in Colombia or without INVIMA registration.

In Colombia, health is defined as a fundamental right with specific constitutional characteristics. Due to the limitations and barriers to access, which as a consequence have led to legal action through tutela actions, experts agree that international CPGs have become an important tool to support therapeutic decisions, rather than an instrument to aid clinical practice.

THE IMPACT OF HEALTH POLICIES ON THE IMPLEMENTATION OF NATIONAL CGPS

Regarding public health policies, Statutory Law 1,751 of 2015 has been the one that regulated the fundamental right to health in Colombia - it was already enshrined in the country's Political Constitution,

⁹⁷ Colombia, Ministry of Health and Social Protection, Clinical Practice Guide for comprehensive treatment, follow-up and rehabilitation of breast cancer. 2nd edition. Guide N° 19 [GPC on the Internet]. Bogotá D.C.: The Ministry; 2017. https://www.cancer.gov.co/recursos_user/masivos/guias_publicadas_917/GPC_Ca_Mama_v.pdf

as mentioned above - and provided the guidelines for the Ministry of Health to carry out reforms in the SGSSS.⁹⁸

Article 6 defines the principles that comprise this right such as universality, pro homine (implies the interpretation of the rules that is most favorable for its protection), equity, opportunity (health care and technologies must be provided without delay) and sustainability, among others.

Article 15, on health benefits, establishes exclusions in terms of the financing with public resources of services and technologies, basically when "there is no scientific evidence on safety, efficacy and clinical effectiveness" and "their use has not been authorized by the competent authority". Article 17, which refers to professional autonomy, guarantees that it must be exercised "within the framework of self-regulation, ethics, rationality and scientific evidence".

Subsequently, different resolutions were enacted in relation to procedures for defining coverage within the Health Benefits Plan.

However, the persistence of barriers to access brought about the judicialization of the right to health through the tutela as a form of protection. According to a report by the Colombian Ombudsman's Office, in 2018, *tutelas* referring to health accounted for 34.2% of the total for that year.⁹⁹

This judicialization process has possibly led to the visibility of the health system's problems. Patients' organizations have played a key role in providing support and advice to the patient community, as well as in forging alliances with physicians and institutions in favor of equal rights.

In December 2021, the broadest inclusion of medicines in Colombia's history in the Health Benefits Plan took place. Resolution 2.292 updated the services and technologies financed through the Capitation Payment Unit (UPC)¹⁰⁰, which is the annual value that the system recognizes for each member for the coverage of the benefits of the benefit plan. The calculation of the value of the UPC has been the result of discussions since its creation; in general terms it takes into account age, sex, place of residence and historical frequencies of benefit use. One of the most important criticisms is the inability to have prospective data. In cancer, this aspect is very important given the great technological pressure not only from new drugs but also from new indications for existing drugs.

According to the Ministry of Health and Social Protection, with respect to drugs, the number of active ingredients financed with the UPC increased from 459 to 1,059. Among the additions are antineoplastic agents and immunomodulators for different types of cancer, including breast cancer.¹⁰¹

One of the main issues that experts identify as complex is precisely the capitation and prospective global payment contracting model -the payment recognized by the SGSSS to the Health Promoting Entities (EPS) for the financing of health services based on the value they determine annually per member.

This is especially relevant in high-cost diseases since economic resources are allocated regardless of the degree of accident rate. In this way, the risk of insuring patients ends up being transferred to the providers

⁹⁸ Statutory Law 1.751 of 2015. Whereby the fundamental right to health is regulated. Republic of Colombia, National Government. Bogotá, D. C., 16/02/2015. https://www.minsalud.gov.co/Normatividad_Nuevo/Ley%201751%20de%202015.pdf

⁹⁹ Office of the Human Rights Ombudsman Colombia. Tutela and the rights to health and social security 2018. 13th edition. Bogotá, D.C., 2019.

¹⁰⁰ Resolution Number 2.292 of 2021. Whereby the health services and technologies financed with resources from the Capitation Payment Unit (UPC) are updated and established. Ministry of Health and Social Protection. Bogotá, D. C., 23/12/2021. https://www.minsalud.gov.co/Normatividad_Nuevo/Resoluci%C3%B3n%20No.%202292%20de%202021.pdf

¹⁰¹ Ministry of Health and Social Protection. Minsalud updated the Health Benefits Plan charged to the UPC. (28/12/2021). <https://www.minsalud.gov.co/Paginas/Minsalud-actualizo-Plan-de-Beneficios-en-Salud-con-cargo-a-la-UPC.aspx>

who provide the care, which limits medical autonomy -although guaranteed under the Statutory Law- and, ultimately, the effective implementation of the Clinical Practice Guidelines.

For an efficient use of resources to reduce barriers to access and achieve better health outcomes, experts agree that it is necessary to establish the minimum requirements in terms of therapeutics and courses of action. CPGs have a role to play in this regard. And to this end, all the actors involved in their elaboration must be involved: scientific societies, the government, payers and patients.

Costa Rica

THE EPIDEMIOLOGY AND BURDEN OF METASTATIC BREAST CANCER DISEASE

In Costa Rica, breast cancer is the most frequent malignant tumor and the leading cause of death from cancer in women in the country. Data from 2018 from the National Tumor Registry and projected by the Global Cancer Observatory (Globocan) to 2020 indicate that that year there were 1,624 new cases of breast cancer, representing 24.5% of all malignant neoplasms in women, and caused 433 deaths.¹⁰²

The reported age-adjusted incidence and mortality rates are 47.5 and 11.5 cases per 100,000 women, respectively. It is estimated that 25%-30% of all breast cancer cases correspond to metastatic disease.

Data from the National Tumor Registry, under the Ministry of Health, come from the Pathology Services, medical records of public and private health centers and death certificates. It is one of the pioneer cancer registries in Latin America, with international recognition.¹⁰³

THE HEALTH SYSTEM

Costa Rica's National Health System is made up of public and private institutions and facilities whose specific purpose is to maintain and improve the health of the population. It is integrated by: Ministry of Health (MS), Costa Rican Social Security Fund (CCSS), National Insurance Institute (INS), Costa Rican Institute of Aqueducts and Sewerage (AyA), universities, private medical services, municipalities and the community.¹⁰⁴

The CCSS is the public institution in charge of social security in the country; it provides comprehensive health services (universal health insurance), pensions and social benefits. Most of the population, almost 92%, accesses health care through this institution and a very small percentage, about 0.3%, does so through voluntary private insurance.¹⁰⁵⁻¹⁰⁶

The facilities that make up the CCSS are organized into three levels according to the complexity of the services, distributed in seven regions and operate under a network model. At the first level are the Basic

¹⁰² International Agency for Research on Cancer, WHO, Global Cancer Observatory (Globocan) 2020. Cancer Today, Population Fact Sheets: <https://gco.iarc.fr/today/data/factsheets/populations/188-costa-rica-fact-sheets.pdf>.

¹⁰³ Zamora A, Ortiz A, Campos H, Galán-Rodas E, Lajous M. The Costa Rican Cancer Registry: characteristics, evolution and modernization. *Rev Hisp Cienc Salud*. 2017; 3 (3): 95-102.

¹⁰⁴ Executive Decree 19.276-S. General Regulations of the National Health System. 05/12/1989. Costa Rican Legal Information System. http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&nValor1=1&nValor2=10255&nValor3=10974&strTipM=TC

¹⁰⁵ OECD Health Statistics (2022): Social protection, OECD Health Statistics (database), <https://doi.org/10.1787/data-00544-en> [Accessed 18/11/2022]. Costa Rica data from 2020.

¹⁰⁶ OECD Health Systems Surveys: Costa Rica. ©2017 OECD. <https://www.oecd.org/els/health-systems/Estudios-OCDE-sobre-los-Sistemas-de-Salud-Costa-Rica-Evaluaci%C3%B3n-y-Recomendaciones.pdf>

Comprehensive Health Care Teams (EBAIS); the second level comprises the network of regional hospitals and peripheral hospitals for specialized outpatient consultation, outpatient, inpatient and surgical interventions; the third level provides hospitalization and highly complex medical and surgical services, provided by the national general and specialized hospitals.¹⁰⁷⁻¹⁰⁸

Currently, the CCSS has 1088 EBAIS and its 529 sites, 647 periodic visit posts -organized in 105 Health Areas-, 12 peripheral hospitals and 8 regional hospitals. There are 3 national general hospitals and 6 specialized hospitals. In addition, there are the Specialized Centers and Units (6) such as the National Cytology Laboratory and the Human Molecular Genetics Laboratory.¹⁰⁸

Regarding the response of the health system to address breast cancer, in general terms and by way of background: in 1976, mandatory cancer notification was instituted in the country (Executive Decree 6.584-SPPS) creating the National Tumor Registry under the Ministry of Health. The objectives are to collect data on all tumors diagnosed, incidence and prevalence, sex, age, geographic area, distribution and quality of medical care.¹⁰⁹

The National Cancer Council was created in 1983 by Executive Decree 14.370-SPPS, repealed by DE 33.271 of 2006 -with subsequent modifications, the last one being DE 43.076-S of 2021-. It is a body attached to the Office of the Ministry of Health, with the function of advising and defining norms and protocols for the attention of the disease.¹¹⁰

In the late 1990s there was an increase in the incidence of breast cancer.¹¹¹ Therefore, in the year 2000, the use of the "Guía de Atención Integral para el Cáncer de Mama" (Guide for Comprehensive Breast Cancer Care) was made mandatory in public and private institutions (DE 28.851-S), with the aim of standardizing care. The indication of mammography was subordinated to the evaluation of risk factors: in women between 50 and 70 years of age it was recommended every two years, with high risk above 40 years of age, annually, and between 40 and 49 years of age in the face of risk factors.

In 2008, the CCSS began the "Breast Clinics" project to increase early detection, improve diagnosis and management of the disease, especially in the 16 Health Areas where the highest mortality from breast cancer was registered.¹¹²

The clinics were incorporated into the 3 cancer care networks, whose head offices are in the national hospitals Mexico, San Juan de Dios and Doctor Rafael Angel Calderon Guardia.

There are currently 61 Breast Clinics; 93% of them are at levels I and II of care. Its implementation implies that general practitioners carry out an internship of 194 hours in the hospitals of their area of assignment, through the Center for Strategic Development and Information on Health and Social Security (CENDEISSS).¹¹²

This initiative, along with others such as the "Arrive on time" program implemented in 2017 in 5 Health Areas of the Greater Metropolitan Area, to perform mammograms in women aged 45 to 70 years, possibly

¹⁰⁷ Pan American Health Organization. Profile of the Costa Rican health system and services based on the monitoring framework of the Regional Universal Health Strategy. San José: PAHO (2019).

¹⁰⁸ Institutional Report Costa Rican Social Security Fund (CCSS) 2021. <https://www.ccss.sa.cr/arc/memoria-institucional/2021.pdf>

¹⁰⁹ Executive Decree 6.584-SPPS. Declaration of Cancer as a Notifiable Disease. 06/12/1976. Costa Rican Legal Information System. http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&nValor1=1&nValor2=53988&nValor3=59004¶m2=1&strTipM=TC&lResultado=3&strSim=simp

¹¹⁰ Executive Decree 43.076-S. Reforms: Creates National Cancer Council. 17/05/2021. Costa Rican Legal Information System. http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&nValor1=1&nValor2=95384&nValor3=127303&strTipM=TC

¹¹¹ Incidence and mortality of cancer in Costa Rica 1990-2003. Ministry of Health. (July 2005). <https://www.binasss.sa.cr/incidenciacancer.pdf> (página 27).

¹¹² Manual for the Implementation of Breast Clinic in I and II level of care. Code CTC.CM.2020.01. Costa Rican Social Security Fund (2020).

contributed to the fact that in Costa Rica the 5-year survival rate for breast cancer is 86% according to data from the Ministry of Health.

It is worth mentioning that there have been modifications around the indication of mammography as a screening method. In 2014 the "Norma para la atención de personas con cáncer de mama" (DE 38.377-S) stated that it should be performed "between the ages of 45 to 70 years every two years and in patients outside that range according to individual risk". This Decree was repealed by Decree 43.263-S/2021, which declared of public interest the "National standard for the prevention and management of breast cancer" and established that mammography should be performed on women between 50 and 75 years of age every two years and outside that range, based on individual risk.

The last reform, in 2022 (DE 43.728-S), indicates that mammography should be performed once a year in women between 40 and 75 years of age when they do not have risk factors and once a year between 35 and 75 years of age when they do; outside that range, according to individual risk and life expectancy.¹¹³

ACCESS BARRIERS AND GAPS

Experts agree that the main barrier to access to care for metastatic breast cancer is timely diagnosis. There are disparities in access to specialized centers, mostly due to their remoteness. In addition, delays in reporting the results of screening studies and biopsies can take up to six months.

The gap increases significantly in rural areas and communities with indigenous populations -which represent 27.50%¹¹⁴ and 2.4%¹¹⁵ of the population, respectively- where access to health services is geographically difficult.

In small towns, care is usually provided by general practitioners, and depending on training, referral of a suspected case of breast cancer to specialized centers tends to be delayed. In referral hospitals, multidisciplinary teams are available, which allows for more effective patient navigation.

Due to the health emergency of the COVID-19 pandemic, experts stress that patient navigation was more complex. There was a gap from access to the first level of care to specialized oncology consultation that made diagnosis more difficult, and as a result, more cases of locally advanced disease have been observed.

In addition, on May 31, 2022, the CCSS suffered a cyber-attack that forced the preventive deactivation of its computer systems. This caused more than three months of interruption of all digital information and the CCSS had to operate with physical records. The provision of medical services was affected - without access to the Single Digital Health Record (EDUS), where patient information is recorded - causing delays in all care.

In 2008, the CCSS began the "Breast Clinics" project to increase early detection, improve diagnosis and management of the disease, especially in the 16 Health Areas where the highest mortality from breast cancer was registered.

¹¹³ Executive Decree 43.728-S. Reform Officialization and declaration of public and national interest of the national norm for the prevention and management of breast cancer in Costa Rica. 05/10/2022. Costa Rican Legal Information System. http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&nValor1=1&nValor2=98021&nValor3=133059&strTipM=TC

¹¹⁴ National Institute of Statistics and Census (Costa Rica). X National Population Census and VI Housing Census 2011: Territories. Indígenas. 1 ed. San José, C.R: INEC (2013). https://admin.inec.cr/sites/default/files/media/repoblaccenso2011-02.pdf_6.pdf

¹¹⁵ National Institute of Statistics and Census - INEC (Costa Rica). General Household Survey (ENAHO) 2021. General results by subject.

THE CURRENT SITUATION OF THE NATIONAL CPG FOR METASTATIC BREAST CANCER

Regarding the approach to breast cancer, there are regulations and guidelines in Costa Rica. The regulations are those of the Ministry of Health that apply to both the public and private sectors. The latest is Executive Decree 43.263-S/2021, which made official and declared of public interest the "National Standard for the prevention and management of breast cancer", with its updates. It establishes that it must be reviewed every 5 years.¹¹⁶

The CCSS has clinical care protocols and operating manuals for breast cancer, in addition to the Clinical Practice Guide for treatment¹¹⁷ -which includes metastatic disease- and a guide for patients¹¹⁸. All of them are issued by the Health Services Development Directorate, which reports to the institution's Medical Management.

Both guides date from 2012 and were prepared with the participation of panels of experts and with the technical collaboration of the Cochrane Center of Central America and the Caribbean of the Iberoamerican Cochrane Network. In the development of the CPG, the GRADE criteria were applied to evaluate the quality of the evidence and the importance of the recommendations. It was validated by health professionals from different specialties related to oncology, patients and by the Central Committee of Pharmacotherapy of the Medical Management of the CCSS.

The CCSS guidelines are binding for all its centers. The CPG includes general approaches; it is updated in terms of surgical procedures and mentions neoadjuvant and adjuvant treatments in a generic way that were available at the time of its elaboration, in 2012. Therefore, there is a gap with respect to therapeutics. Regarding the date for the next revision, it mentions 2015.

The Costa Rican Association of Medical Oncologists (ACOMED) carried out the "Consensus on the pharmacological treatment of cancer", which was launched in October 2021. This addresses pharmacological management for the most frequent types of cancer, including breast cancer and metastatic disease, and analyzes some drugs that are restricted access in the country. It focuses mainly on antineoplastic drugs. The Consensus specifies June 2023 as the update date.

Specialists usually use the international breast cancer CPGs of the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) as reference guides and the CPG of the Hospital Sírio-Libanês in Brazil.

The main barrier identified by the experts for adherence to breast cancer CPGs is basically access, due to budgetary barriers.

THE IMPACT OF HEALTH POLICIES ON THE IMPLEMENTATION OF NATIONAL CGPS

With regard to the drug policy and given its impact on the possibility of adherence to the CPG, the CCSS has an Official Drug List (LOM) that operates under an "open therapeutic formulary" system, i.e., it contemplates the acquisition and individualized use of drugs for cases of special or exceptional need.¹¹⁹

¹¹⁶ Executive Decree 43.263-S. Officialization and declaration of public and national interest of the National Standard for the prevention and management of breast cancer in Costa Rica. 25/11/2021. Last version 10/28/2022. Costa Rican Legal Information System. http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&nValor1=1&nValor2=95797&nValor3=133617&strTipM=TC

¹¹⁷ Ramírez-Morera A, Tristan-López M, Landaverde-Recinos D, Arce-Lara C, (2012). Clinical Practice Guidelines for the treatment of breast cancer. San José: Costa Rica, CCSS. ISBN: 978-9930-9469-0-9. <https://www.binasss.sa.cr/protocolos/mama.pdf>

¹¹⁸ Ramírez-Morera A, Tristan-López M, Landaverde-Recinos D, Arce-Lara C, (2012). Guide for patients: Breast cancer. San José: Costa Rica, CCSS. ISBN: 978-9930-9469-2-3. <https://www.binasss.sa.cr/protocolos/mama1.pdf>

¹¹⁹ Regulation of the Official List of Medications 2016. Costa Rican Social Security Fund. Directorate of Pharmacoepidemiology. Central Committee of Pharmacotherapy.

The LOM is based on the National Therapeutic Formulary, established by the Ministry of Health, which is also responsible for updating it, with the drugs to be used by the public health services.

The open therapeutic formulary system means that if a prescribed drug is not in the LOM, it is possible to submit the request to the Central Pharmacotherapy Committee (CCF). This is a technical body of the Medical Management of the CCSS, responsible for "drawing up the official list of drugs and approving the purchase of pharmaceutical products that are not included in the LOM", among other functions.¹²⁰

The request can be submitted if the treatment prescription has been previously approved by the Oncology Session, composed of medical oncologists from the referral hospital. It must include the scientific evidence on which the prescription is based and is made using the "Standardized form to manage the request for a non-LOM drug for chronic treatment in the CCSS". The request is sent to the Local Pharmacotherapy Committee and the final approval corresponds to the CCF. The process takes about 3 to 4 weeks, although it may take longer.

In the event that the drug is not approved, some patients proceed with an *amparo* as an option. In this regard, there are an increasing number of patient organizations that play a significant role in supporting and advising patients. The decision to provide the drug is left to the Constitutional Chamber with the support of the Forensic Medicine Department.

The Medical Management, through the CCF, also develops guidelines for the more expeditious availability of drugs in certain scenarios that are not incorporated into the LOM. They may be on a new drug or a specific indication and are generally produced due to repeated requests. This is the case of guidelines for therapeutics indicated for HER2-positive and luminal metastatic breast cancer. The process of developing a guideline takes 2 to 3 years.

The CCF analyzes the drugs through the areas of Pharmacoeconomics and Medicines and Clinical Therapeutics of the CCSS, based on the available scientific evidence, real life evidence and pharmacoeconomic studies.

The experts emphasize that in this process it is important to incorporate the participation of Medical Oncology professionals, as representatives of this discipline in the CCF and with involvement in decision making.

Furthermore, due to the impact of drug policy on access to timely treatment -especially in metastatic breast cancer because of the high cost it demands- experts point out that it is necessary to harmonize a possible standard of treatment, with specific criteria based on the best evidence and cost-effectiveness studies.

To this end, it is essential to have a national agency for the Evaluation of Health Technologies, with the participation of the Ministry of Health and whose decisions are binding for the entire system.

Also, in relation to the country's access to new health technologies, they stress that it could be interesting to consider the regionalization of negotiations with the pharmaceutical industry (Central America as a whole).

¹²⁰ Regulation 8.314. Central Committee of Pharmacotherapy of the Costa Rican Social Security Fund. 15/01/2009. Costa Rican Legal Information System.
http://www.pgrweb.go.cr/scij/Busqueda/Normativa/Normas/nrm_texto_completo.aspx?param1=NRTC&nValor1=1&nValor2=64865&nValor3=77035&strTipM=TC

THE EPIDEMIOLOGY AND BURDEN OF METASTATIC BREAST CANCER DISEASE

In Mexico, since 2006, breast cancer has been the most frequent malignant tumor in women and the deadliest, surpassing cervical cancer. According to estimates by the Global Cancer Observatory (Globocan) in 2020, there were nearly 30,000 new cases of breast cancer in Mexico, accounting for more than 28% of all malignant neoplasms in women and causing nearly 8,000 deaths. The incidence and age-adjusted mortality rates were 40.5 cases and 10.6 cases per 100,000 women, respectively.¹²¹

Since the country does not have a national cancer population registry, it is estimated that there is an underreporting of cases. In this sense, the incidence of breast cancer in its different stages is not accurately known.

According to a retrospective cohort study published in 2017 on the epidemiology of breast cancer in Mexico and which analyzed data from 4,300 patients seen at the National Cancer Institute (INCan) between January 2007 and December 2013, about 70% of the women were overweight or obese, 11% had diabetes, 18% had hypertension, and 5.2% had both comorbidities. Fifty-one percent of the patients were postmenopausal. Fifty-three percent had locally advanced disease at diagnosis and 13% had stage IV disease.¹²²

The National Health and Nutrition Survey 2018-19 (Ensanut) of the National Institute of Public Health indicates that the percentage of women aged 40 to 69 years who went for a mastography -in the 12 months prior to the survey- was 27.5%¹²³ The Ensanut 2021 recorded that 15.6% of women aged 20 years or older had a clinical breast examination in the year prior to the survey. In the 40 to 49 years age group, about 19.3% of women had a clinical breast examination.¹²⁴

It is worth mentioning that in relation to breast cancer prevention, the regulations recommend screening mastography in apparently healthy women between 40 and 69 years of age every two years, as well as clinical breast examination on an annual basis from the age of 25.¹²⁵

A very important challenge is that about 67%, almost 70% of breast cancer diagnoses occur at a locally advanced stage, with a median tumor size at diagnosis of 5 centimeters. Regarding the percentages of hormone-positive, HER2 and triple negative are similar to those reported internationally.

THE HEALTH SYSTEM

Mexico's healthcare system is made up of the public and private sectors. In general terms, the former comprises the social security institutions: the Mexican Social Security Institute (IMSS) -for those working in private companies-, the Institute of Security and Social Services for State Workers (ISSSTE), the Secretariat of National Defense (SEDENA), the Secretariat of the Navy (SEMAR) and Petróleos Mexicanos (PEMEX); and

¹²¹ International Agency for Research on Cancer, WHO, Global Cancer Observatory (Globocan) 2020. Cancer Today, Population Fact Sheets: <https://gco.iarc.fr/today/data/factsheets/populations/484-mexico-fact-sheets.pdf>

¹²² Reynoso-Noverón N, et al. Clinical and Epidemiological Profile of Breast Cancer in Mexico: Results of the Seguro Popular. *J Glob Oncol.* 2017 Dec;3(6):757-764. doi: 10.1200/JGO.2016.007377

¹²³ Shamah-Levy T, Vielma-Orozco E, et al. National Health and Nutrition Survey 2018-19: National results. Mexico: National Institute of Public Health, 2020. https://ensanut.insp.mx/encuestas/ensanut2018/doctos/informes/ensanut_2018_informe_final.pdf

¹²⁴ Shamah-Levy T, Romero-Martínez M, et al. National Health and Nutrition Survey 2021 on Covid-19. National results. Mexico: National Institute of Public Health, 2022. https://www.insp.mx/recursos/images/stories/2022/docs/220801_Ensa21_digital_29julio.pdf

¹²⁵ Mexican Official Standard NOM-041-SSA2-2011. For the prevention, diagnosis, treatment, control and epidemiological surveillance of breast cancer. DOF 09/06/2011. Mexico, D.F. Ministry of Health. https://dof.gob.mx/nota_detalle.php?codigo=5194157&fecha=09/06/2011#gsc.tab=0

the institutions that serve people without social security affiliation: through the Institute of Health for Welfare (INSABI), which in 2020 replaced Seguro Popular. The private sector includes insurance companies and health service providers of private hospitals and clinics.

According to data from the 2020 Population and Housing Census of the National Institute of Statistics, Geography and Informatics (INEGI) the distribution of the affiliated population by health institution showed that 51% corresponded to IMSS, 35.5% to Seguro Popular/INSABI, 8.8% to ISSSTE, 1.3% to PEMEX/ SEDENA or SEMAR and 2.8% to the private sector. Of the more than 126 million inhabitants of the country, around 73% are affiliated with one of the following health services.¹²⁶

The system is highly fragmented, heterogeneous and access to services and care depends on entitlement to one or another of the institutions according to place of work, affiliation and income level.

Heterogeneity is related to several factors, including a very diverse geography - the disparities between Northern and Southern States are significant from a socio-cultural, urban development and infrastructure point of view -, differentiated allocation of budgets in the public health sector, and differences between the institutions themselves in terms of their own regulations and management of their resources.¹²⁷

The incidence of metastatic breast cancer differs between institutions. In the case of ISSSTE it is lower due to better coverage in prevention and early diagnosis. While in the National Cancer Institute (INCan), which attends people without medical services, patients usually arrive with the disease in a locally advanced stage.

Over the years, Mexican governments have implemented several initiatives to address the problem of breast cancer. In addition to the Official Mexican Standard (NOM-041-SSA2-2011)¹²⁵ for the prevention, diagnosis, treatment, control and epidemiological surveillance of breast cancer in force since 2011, which replaced the 2002 standard, the Specific Action Programs were promoted: 2007-2012 for breast cancer and the Prevention and Control of Cancer 2013-2018.¹²⁸ Attempts have also been made to implement a comprehensive cancer program and a population registry for this disease, both at the national level.

Currently, the political agenda is addressing changes in some general aspects of the health field that aim, among others, to homogenize the health system and the institutions that make it up so as to establish a minimum essential treatment, including metastatic breast cancer.

Civil society -third sector organizations, specialists and researchers- together with representatives of the legislative sphere are advancing in the discussion to promote the legal framework by means of a general cancer law, as well as the implementation of the National Cancer Plan and the National Cancer Registry. The latter is considered fundamental by experts, in order to assess the reality of the disease in the country, establish guidelines for action, evaluate and allocate resources according to needs.

In general terms, the National Plan aims to improve primary prevention, detection and timely diagnosis, staff training and access to high quality radiotherapy and surgical services. It also aims to standardize care and therapeutic protocols among institutions, which means less heterogeneity in budgets, actions and access.

¹²⁶ National Institute of Statistics, Geography and Informatics (INEGI), Population and Housing Census 2020. Distribution of the affiliated population by health institution. https://www.inegi.org.mx/contenidos/programas/ccpv/2020/doc/Censo2020_Principales_resultados_EUM.pdf (página 29).

¹²⁷ Soto-Perez-de-Celis E, Chavarri-Guerra Y. National and regional breast cancer incidence and mortality trends in Mexico 2001-2011: Analysis of a population-based database, *Cancer Epidemiology*. 2016;41:24-33. <https://doi.org/10.1016/j.canep.2016.01.007>.

¹²⁸ Specific Action Program for the Prevention and Control of Women's Cancer 2013 - 2018. Health Sector Program. Ministry of Health. <https://www.gob.mx/salud/documentos/programa-de-accion-especifico-prevencion-y-control-del-cancer-de-la-mujer-2013-2018>

ACCESS BARRIERS AND GAPS

According to experts, the main barrier to access in a broad sense is limited budgetary resources. Other significant barriers are the fragmentation of the national health system and the political will to implement the National Cancer Plan.

Hence, a very important challenge is to reach a consensus with all stakeholders on a feasible comprehensive plan, with strategic lines of action that will reduce the gaps in access to early diagnosis and treatment, as well as providing for a minimum essential in terms of therapeutics. In metastatic disease this is especially significant due to the high cost involved.

Institutions such as the National Cancer Institute (INCan) and the National Institute of Medical Sciences and Nutrition Salvador Zubirán (INCMNSZ) have implemented patient navigation strategies and have modeling regarding cost reduction by reducing diagnosis times and the most advanced stages of breast cancer (down-staging).¹²⁹⁻¹³⁰

THE CURRENT SITUATION OF THE NATIONAL CPG FOR METASTATIC BREAST CANCER

In Mexico there are two main Clinical Practice Guidelines for breast cancer, which are the CENETEC (National Center of Technological Excellence in Health) CPG¹³¹ and the Colima Consensus¹³².

The first one, "Breast cancer treatment in second and third level of care" edited by the Ministry of Health and whose last update dates back to 2017, was carried out with the participation of institutions of the National Health System and the coordination of CENETEC. It is the guide of the Mexican Institute of Social Security (IMSS). This CPG provides for its update "when there is evidence that so determines or on a scheduled basis, 3 to 5 years after publication."

The second, "Mexican Consensus on diagnosis and treatment of breast cancer", began in 1994 and is updated periodically; the latest version (ninth) is dated 2021 and the next revision is scheduled for 2023. The Consensus addresses breast cancer in a comprehensive manner: risk factors, primary prevention, early diagnosis, intervention procedures, staging, management recommendations, treatment of metastatic breast cancer, palliative care, psycho-oncological aspects, among other topics, including genetic counseling.

According to a study published in August 2022 in *Clinical and Translational Oncology* whose objective was to evaluate the adherence, attitudes and barriers of physicians with respect to the Colima Consensus, it showed that this is used in a high percentage (40%) as the only guide for breast cancer, especially by surgical oncologists in public hospitals. Among its results, which included 439 respondents, 78% adhered to the Consensus recommendations and 94% believed that it was applicable to their clinical practice. As for attitudes towards the Consensus, 90% considered it a good educational tool and the same percentage mentioned that it improved the quality of care.¹³³

¹²⁹ Chavarri-Guerra Y, et al. Patient Navigation to Enhance Access to Care for Underserved Patients with a Suspicion or Diagnosis of Cancer, *The Oncologist*. 2019 Sep;24(9):1195-1200. <https://doi.org/10.1634/theoncologist.2018-0133>

¹³⁰ Soto-Perez-de-Celis E, et al. Patient Navigation to Improve Early Access to Supportive Care for Patients with Advanced Cancer in Resource-Limited Settings: A Randomized Controlled Trial, *The Oncologist*. 2021 Feb;26(2):157-164. <https://doi.org/10.1002/onco.13599>

¹³¹ Treatment of breast cancer in second and third level of care. Ministry of Health, Mexico City. 16/03/2017. <http://www.cenetec-difusion.com/CMGPC/IMSS-232-09/ER.pdf>

¹³² Mexican Consensus on diagnosis and treatment of breast cancer. Ninth revision. Colima 2021.

¹³³ Martínez-Cannon B, Soto-Perez-de-Celis E, Erazo Valle-Solis A, et al. Physicians' attitudes and perceived barriers to adherence to the national breast cancer clinical practice guidelines in Mexico: a survey study. *Clin Transl Oncol* (2022). <https://doi.org/10.1007/s12094-022-02921-9>. Epub ahead of print. PMID: 35986133.

Both Clinical Practice Guidelines are not binding; they are recommendations based on the evidence available at the time of their preparation. From the normative point of view, the CENETEC CPG is the official guideline. The Colima Consensus, widely used as the study mentioned above showed, bases its recommendations on the treatments available in the country.

There are also inter-institutional guidelines, such as that of the Institute of Security and Social Services for State Workers (ISSSTE), but in this case referring to how to use drugs for the treatment of breast cancer. There is also a large extrapolation of North American and European guidelines such as the National Comprehensive Cancer Network (NCCN) and the St. Gallen International Consensus. In the private setting most insurers, about 80%, rely on NCCN CPGs.

Adherence to Clinical Practice Guidelines depends to a large extent on the context in which physicians work, since their effective application is related to barriers such as lack of resources and logistical problems,¹³³ as well as the availability of multidisciplinary teams.

THE IMPACT OF HEALTH POLICIES ON THE IMPLEMENTATION OF NATIONAL CPGS

Regarding the use of and adherence to the Clinical Practice Guidelines for breast cancer and for metastatic stage disease, one factor to consider is the country's drug prescription policy, due to the impact on their applicability.

In this regard, the Basic List and Catalog of Health Sector Supplies prepared by the General Health Council (CSG) establishes the drugs and other supplies used by the public institutions of the National Health System in order to guarantee access to essential services.¹³⁴ The CSG is a collegiate body with sanitary authority and regulatory powers that reports directly to the President of the Republic, whose provisions are mandatory in the country.

In addition, there are the inter-institutional Basic Charts, based on this catalog. There are also specific mechanisms for accessing high-cost drugs, such as the System for the Analysis and Evaluation of Specific Cases -known as the Control Tower- of the Mexican Social Security Institute (IMSS), and the Program for the Reasoned Prescription of High Specialty Drugs (PEPMAE), of the Institute of Social Security and Services for State Workers (ISSSTE). These imply, for example for breast cancer, that the drugs prescribed must be approved internally by medical oncologists.

Within the scope of the CSG there are also the Technical Protocols, which include interventions, medications, treatments and supplies associated with diseases that give rise to catastrophic expenses. Since their origins, they have evolved, especially in the last ten years, impacting on more access.

At present and in view of the coming year, it is expected that the Technical Protocol for breast cancer¹³⁵ and other neoplasms is expected to determine the way in which the institutions that depend on the Ministry of Health (the National Institutes of Health, including INCan, and others) will be financed. Said Protocol has been updated establishing the interventions and medications indicated -and financed- for each one. Therefore, prescriptions are subject to its provisions.

This form of regulation and ordering of the prescription policy would be aimed at increasing the number of patients who can access high-cost molecules and reducing the differences that exist between hospitals in terms of access to treatments.

¹³⁴ Basic Chart and Catalog of Inputs of the Sector. General Health Council. Mexico. <http://www.csg.gob.mx/contenidos/priorizacion/cuadro-basico.html>

¹³⁵ General Health Council. Commission to define treatments and medications associated with diseases that cause catastrophic expenses. Technical Protocol. Category: Diagnosis and Treatment of Cancer. Title: C50 Malignant breast tumor. March 6, 2018. http://www.csg.gob.mx/descargas/pdf/priorizacion/gastos-catastroficos/protocolos/2018/Tumor_maligno_de_la_Mama_2018.pdf

In this context, experts agree that the development of Clinical Practice Guidelines for breast cancer and metastatic disease based on the best evidence, adapted to the local reality and available resources - as is being done by the World Health Organization (WHO) and the Breast Cancer Global Initiative (BCGI) among other initiatives - would contribute to adherence to the guidelines and wider access to treatments.

Conclusions

As we have observed, breast cancer is a priority public health issue in Latin America because it is the most frequent malignant tumor and the leading cause of oncologic mortality among women in the region. It also affects a large proportion of young women under 50 years of age, with a high prevalence of advanced stages of the disease.

In the countries analyzed in the Task Force, which comprise about 70% of the population of this region, public policies aimed at systematizing breast cancer care and improving early detection have been implemented for more than 20 years. Even before that, regulatory frameworks had already been established in most countries to address this disease as a public health problem.

However, even with these efforts, the growing incidence and burden of breast cancer, as well as the high rates of diagnosis in advanced stages and metastatic stage, continue to show the challenges that persist in order to reduce its impact and morbidity and mortality in the region.

Among the greatest challenges common to all the countries consulted, we find the great lack of national cancer population registries, the lack of timely diagnosis and the difficulty of access to treatment.

As a starting point, the experts point out the need for updated data that reflect the reality of the disease, since this information is a fundamental input for planning and implementing public policies based on needs and evidence. Although all countries have population-based cancer registries (PBCR), these correspond to cities, provinces or regions and therefore not all are statistically representative at the national level.

Costa Rica is the exception, since it has had the National Tumor Registry for more than 40 years, which is classified by the IARC as high quality. It should be clarified that the data has a time lag, because the latest reports published by Globocan are from 2018 projected to 2020.

According to an article published in the International Journal of Cancer at the end of 2020, less than 3% and 10% of the populations of Central and South America, respectively, are covered by high quality population-based cancer registries.¹³⁶

This article also indicates the percentage of the population of Latin American countries that is covered, in each one, by BCPR (all) and by high-quality BCPR: Costa Rica, 100% of the population by both; Mexico, 12.7% by the former; Argentina, 41% and 18.6%; Brazil, 22% and 9.8%; Colombia 25% and 9.1%; Chile, 15% and 7.9%. It should be noted that, in most countries, the latest year of information available is based on 2016 data.¹²⁷

¹³⁶ Piñeros M, Abriata M G, de Vries E, et al. Progress, challenges and ways forward supporting cancer surveillance in Latin America. *Int. J. Cancer*. 2021; 149: 12-20. <https://doi.org/10.1002/ijc.33407>

Country and population-based cancer registries (PCBCR)	Population covered by RCBP (%)	
	All PCBCR	High quality PCBCR
Argentina	41%	18,6%
Brazil	22%	9,8%
Chile	15%	7,9%
Colombia	25%	9,1%
Costa Rica	100%	100%
Mexico	12,7%	

Health systems in the region are fragmented, heterogeneous and present important gaps in access and coverage to health services, with significant differences between social security or public health -even between the institutions that comprise them- and the private sector. The latter covers around 10% of the population in the six Task Force countries. Also, according to OECD data, in 2017 almost 26% of all health spending in these countries was paid out-of-pocket, which is above the OECD average of 21%. The high level of out-of-pocket spending exposes weaker health systems and lower levels of service coverage.¹³⁷

In this context of fragmentation and heterogeneity in health systems, the following barriers are identified as having a direct impact and hindering access to timely diagnosis and treatment of breast cancer:

- **Regulatory barriers:** such as bureaucracy in health systems, gaps in regulations (for example, regarding coverage of treatments, which causes inequities in access), disparities between regulations and their actual application (as in the case of compliance with timeframes for access to diagnosis and treatment in countries where they are established), delays in updating lists of essential drugs or vademecums (including the coexistence of different interinstitutional drug and supplies catalogs, as in the case of Mexico).
- **Financial barriers:** which affect disease care in general, but particularly for access to high-cost treatments, as in the case of metastatic breast cancer. This has led to the fact that in the countries analyzed this access has been judicialized through *amparos* or *tutelas*, procedures that can take from weeks to months, when time is a priority in a disease such as cancer. Hence, in the opinion of the experts, the CPGs have become tools to justify therapeutic decisions rather than instruments to homogenize clinical practice.
- **Geographic and infrastructure barriers:** distance to health centers, especially specialized centers with multidisciplinary teams. In Brazil and Costa Rica, the gap increases significantly in rural areas and indigenous communities. In Colombia, most of the high complexity hospitals are concentrated near the main cities. In Argentina, during the last few years, some health centers in more disadvantaged areas have disappeared and care has been concentrated in centers of higher complexity. In Chile there are shortcomings in the availability of radiotherapy. The insufficient number of human resources in public hospitals affects all countries. This results in greater travel and delays in care.
- **Barriers in patient navigation:** this delays the time it takes to confirm a diagnosis and start treatment. The biggest time gap is usually between identifying symptoms and performing the biopsy and even in reporting the results. These delays lead to advanced stage disease diagnoses.

¹³⁷ OECD/The World Bank (2020), Health at a Glance: Latin America and the Caribbean 2020, OECD Publishing, Paris, <https://doi.org/10.1787/740f9640-es>.

- **Barriers to training of health personnel:** especially with respect to primary care professionals on suspicion of the disease, who are usually the first point of contact of patients with the health system and whose role is key to referral to specialized services.
- **Awareness barriers in the general population:** barriers in terms of education about prevention and the importance of mammography screening. WHO estimates that for mammographic screening to have any impact it must reach at least 70% of the female population. However, in almost all Latin American countries, mammography coverage is nowhere near that figure; in Colombia it reaches 54% but Argentina, Chile and Costa Rica it is between 32% and 46%, while in Mexico it is only 22%.¹³⁸

Given the health reality and the regulatory context analyzed in this report, we must emphasize the role of Clinical Practice Guidelines for breast cancer and their relevance at the national level as reference tools for clinical decision making, improving health outcomes and the efficiency of health systems.

All the countries analyzed have several Clinical Practice Guidelines for breast cancer, which include the approach to the disease in its metastatic stage. These guidelines are generated by various institutions at the national, local or provincial level, and from the public and private sectors.

The official guidelines, generally developed by the Ministries of Health (Secretariat of Health in Mexico), are not binding because they are recommendations - with the exception of the CPG of the Costa Rican Social Security Fund, which applies to all its centers, as well as other institutional guidelines. Most of them date back several years and are not updated periodically according to pre-established deadlines. The most recent is the Chilean GES guide for breast cancer, dated 2021.

Other CPGs at the national level are those developed at the initiative of local scientific societies, such as the 2022-2023 recommendations of the Argentine Association of Clinical Oncology (AAOC), the 2022 guidelines of the Brazilian Society of Clinical Oncology (SBOC), as well as the consensus of Colima (Mexico), the latest of 2021, and that of the Costa Rican Association of Medical Oncologists (ACOMED) also of 2021.

Most specialists use the guidelines of local scientific societies and international CPGs, mainly the breast cancer guidelines of the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO).

In conclusion, adherence to national Clinical Practice Guidelines depends on how up to date they are and the context in which physicians work, since their effective application is directly related to the professional's ability to adhere to the protocols proposed by the guideline. In this sense, CPGs should be oriented to standardize the diagnosis, treatment, complementary care and follow-up of the disease, adapted to the reality of each country.

¹³⁸ Pinto JA, Pinillos L, Villarreal-Garza C, et al. Barriers in Latin America for the management of locally advanced breast cancer. *Ecancermedalscience*. 2019 Jan 22;13:897. doi: 10.3332/ecancer.2019.897.

Recommendations:

An estimated 626,000 women and men die of breast cancer every year, with metastatic disease the cause of nearly all these deaths. Despite advances in breast cancer management that result in a dramatic improvement in overall survival, particularly in metastatic disease, this outcome does not necessarily translate into reality in Latin America, particularly in low-resource settings. (1,2) Breast cancer outcomes in low- and middle-income countries correlate with the degree to which 1) cancers are detected at early stages, 2) newly detected cancers can be diagnosed correctly, and 3) appropriately selected multi-modality treatment can be provided properly in a timely fashion.(3)

High mortality-to-incidence ratios (MIRs) in Latin America indicate poor survival, partly because of the late stage at diagnosis and poorer access to treatment. Approximately 30-40% of breast cancer diagnoses in Latin America are metastatic disease. In Mexico, an estimated 50-60% of all breast cancers were diagnosed in advanced stages and the overall mean time from symptom onset to treatment was 8.4 months. By contrast, 61% of women in the US are diagnosed with localized breast cancer, 31% with regional spread, and only 5% with metastatic disease.(4)

The Task Force proposes the following recommendations to provide sustainable solutions in the rapidly changing environment of the era of personalized medicine that both improve quality of care for patients with metastatic breast cancer and can be implemented in varying settings. These recommendations are according to the regional analysis and based on the premise of contributing to the improvement of comprehensive care for breast cancer and metastatic disease, highlighting the role of CPGs.

1. Develop clinical practice guidelines for breast cancer and metastatic disease led by a government entity with governance capacity to ensure access, that are backed by evidence, and tailored to the realities of each country.

These guidelines should establish the standard of care for breast cancer based on scientific evidence as well as the capacity of the healthcare system in each country. This is especially relevant in the context of metastatic disease due to the significant economic burden it represents.

The guidelines should:

- Be developed with the involvement a broad range of stakeholders involved in integral care, including breast cancer patient organizations, medical and scientific societies, policymakers, health technology assessment agencies, regulators, researchers, and payers. The involvement of these stakeholders can help ensure that the guidelines are tailored to the needs of patients and reflect the realities of the healthcare system in each country.
- Determine maximum time to access care throughout the cancer continuum, from symptom appearance to diagnostic confirmation (times to results of screening and biopsy), staging, medical and surgical treatment initiation, monitoring and control.
- Be binding to ensure that healthcare providers adhere to the recommendations and that patients have access to the best possible care. Binding guidelines can help to standardize breast cancer care across different healthcare settings, ensuring that all patients receive high-quality care regardless of where they receive treatment. Guidelines effectiveness depends on standardization of care; when patients receive some but not all the essential interventions, improvement in cancer outcomes cannot be expected to occur.(5)
- Be updated on a regular basis, at least every two to three year, to ensure that they reflect the latest scientific evidence and best practices in breast cancer care. Partial updates may be conducted in specific cases, as practice-changing evidence emerges.

- Incorporate recommendations on innovative treatments for breast cancer, such as targeted therapies and immunotherapies, as they become available. This can help ensure that patients have access to the latest and most effective treatments and can improve outcomes for those with breast cancer. However, it is important to balance the inclusion of innovative treatments with considerations of cost-effectiveness and the capacity of the healthcare system to deliver these treatments.
- Be effectively communicated to all healthcare providers involved in the integral care of breast cancer, including medical and surgical oncologists, gynecologists, general practitioners, nurses, and therapists. This can be done through medical societies, government-led initiatives, and through care-providing institutions and should include comprehensive training initiatives to ensure the care providers understand how to use and implement recommendations.

2. **Ensure coherence between clinical practice guidelines for breast cancer and regulatory decisions that determine treatment availability.** There is consensus that clinical practice guidelines play a key part in the harmonization of cancer care and the advancement toward equality in access to excellent care. However, there is still a significant disconnect between clinical guidelines and regulatory decisions, often hindering patient access to the standard of care.(3,4) It is important to improve the regulatory process for breast cancer treatments in the region to ensure that effective and safe drugs are approved in a timely manner and are accessible to patients. This can be achieved through the implementation of efficient regulatory pathways and greater transparency in the regulatory process.

Regulatory agencies must also work closely with healthcare providers and medical societies to ensure that regulatory decisions are aligned with the latest clinical practice guidelines for breast cancer treatment. Additionally, it is important to engage in ongoing dialogue and consultation with stakeholders, such as medical oncologists and patient advocacy groups, to ensure that regulatory decisions consider the latest evidence-based practices and patient needs.

3. **Establish systems to monitor adherence to clinical practice guidelines for breast cancer in Latin America and evaluate their impact on patient outcomes.** Phased implementation is an evolutionary process requiring ongoing adaptation as systems improve. As implementation takes place, ongoing monitoring is required to assess the degree to which the system is improving so that next steps in each critical phase in breast cancer diagnosis and treatment can be identified and re-prioritized.(5) This involves collecting data on patient outcomes and analyzing the relationship between adherence to the guidelines and these outcomes. The purpose of this recommendation is to ensure that healthcare providers are following recommended best practices and delivering high-quality care to patients with breast cancer, and to identify areas where the guidelines may need to be revised or updated to improve patient outcomes. These systems can be used individually or in combination to effectively monitor adherence to guidelines and evaluate their impact on patient outcomes. The specific systems used may depend on factors such as available resources, the complexity of the guidelines, and the local healthcare system infrastructure.

Examples of systems to monitor adherence to clinical practice guidelines and evaluate their impact on patient outcomes for breast cancer in Latin America

Electronic medical record systems that can track and report on adherence to specific treatment protocols and identify patients who may require additional care or follow-up.
Clinical audit systems that review patient records to assess adherence to guidelines and identify opportunities for improvement in care.
Patient outcome tracking systems that collect data on patient outcomes, such as survival rates and quality of life, and analyze the relationship between adherence to guidelines and these outcomes.
Regular surveys of healthcare providers to assess their knowledge and use of guidelines, as well as identify barriers to adherence and opportunities for improvement.
Feedback mechanisms that allow patients to provide input on their care and experiences, which can be used to identify areas for improvement in adherence to guidelines.

4. Implement an integral approach to breast cancer management to address fragmentation.

Breast cancer management involves prevention, early detection, diagnosis, treatment, rehabilitation, and palliative care. In LA, most cancer care is carried out in a fragmented and sequential manner, which contrasts with the contemporary standard of cancer care with a multidisciplinary team approach. A study in Colombia revealed that, patients had passed through an average of 6 service providers who intervened in the care of their disease. As a consequence of fragmentation, people diagnosed with cancer lose the continuity of their treatment, reducing the efficiency and quality of care. This problem increases the risk of dying by 33% in those with breast cancer.(6)

The lack of coordination in these models is aggravated by disparities in the distribution of resources. Specialized units are disproportionately located in main cities, leaving large geographic areas underserved and limiting access to innovative therapies and technologies. In this fragmented route, coordination problems are frequent and delays in diagnosis and treatment are common. These may be due to several problems such as the absence of a structured process where patients receive support in their transit through the healthcare system and undergo proper monitoring, as well as the lack of education programs for first contact physician and patients. Frequent difficulties also exist regarding the quality of radiology and pathology reports and adherence to optimal standards of breast cancer care. The patient journey is further complicated by reimbursement issues that obstruct access to medical care.(7)

A centralized approach to breast cancer management ideally involves bringing specialists together in one location and minimally, coordinating and optimizing patient care between the different providers. Centralized services can improve the quality of breast cancer care by providing timely access to diagnostic tests, consultations with specialists, and treatment options. These services can also help reduce healthcare costs by avoiding duplication of services and improving efficiency. Clinical practice guidelines are necessary to streamline care and could result in cost and time savings, optimal use of resources, and improvement in the quality of patient care. The implementation of Breast Units was recommended as a solution streamline precision medicine for breast cancer in Latin America. In Breast Units, the multidisciplinary management approach involves radiologists, pathologists, radiation, surgical, and medical oncologists, nurses, plastic surgeons, psychologists, geneticists, and primary care physicians, among others.(8)

- 5. Create policies that ensure timely access to treatment after diagnosis for patients with breast cancer.** There is consensus in the literature that a shorter time between diagnosis and treatment initiation results in better prognoses and greater chances of survival for the patient. In the more advanced stages of breast cancer, fast intervention is fundamental to treatment efficiency.(9,10,11) Providing timely access to treatment for breast cancer is crucial because it directly impacts the patient's chances of survival and overall health outcomes. Delays in treatment can result in metastasis, aggressive and invasive treatments, higher healthcare costs, and extended hospital stays, which can adversely affect the patient's quality of life and increase the disease burden for the health system. These policies should prioritize high-quality and accessible treatment for all patients with breast cancer, irrespective of socioeconomic status or geographic location, and focus on creating an effective network of oncology care and treatment centers.

Brazil's National Oncology Care Policy (PNAO—Política Nacional de Atenção Oncológica) passed in 2005 through the Ordinance GM/MS 2439 recognizes cancer as a public health problem and enabled the creation of the Oncology Care Network. In 2012, a milestone in the treatment of cancer took place with Law No. 12,732, which ensures patients with malignant neoplasms initiate medical treatment within 60 days after diagnosis.(12) Peru's Law No°31561, has the objective of establishing complementary measures aimed at preventing cancer in women, especially breast and cervical cancer, the two most frequent oncological pathologies. With this, it is sought that the most vulnerable population receives an early diagnosis, treatment, rehabilitation regardless of socioeconomic conditions or social vulnerability. In particular, Law No. 31561 specifies a requirement to update the technical guidelines for cancer, the Petitorio Nacional Único de Medicamentos Esenciales (PNUME), the Petitorio Nacional Único de Dispositivos Médicos Esenciales (PNUDME) y and the national cancer prevention and control plans. The modifications must be in accordance with international guidelines.(13)

- 6. Governments in the region should continue to explore innovative financing mechanisms that enable the inclusion of innovative breast cancer treatments in healthcare budgets.** Stakeholder perception of innovative treatments must pivot to appreciate the solutions that these technologies can provide for the inequities of cancer care in the region. By exploring new approaches to financing and investing in a robust healthcare infrastructure, governments can help to ensure that breast cancer patients in the region have access to the best possible care. The new era of precision medicine brings significant challenges for healthcare systems to adapt their infrastructure, methodologies, and reimbursement policies to enable wide access to these type of drugs for patients. As a result, there is a significant gap between advances in anticancer drug development and delivery of these drugs to patients. This gap risks increasing health disparities in society owing to unequal access to the technology and a lack of knowledge on how to implement advances in clinical practice. According to the Breast Health Global Initiative, government intervention is needed to address drug-delivery problems relating to high cost and poor access.(3) Therefore, it is necessary to optimize dialogues between public and private sector stakeholders to develop country-specific sustainable funding mechanisms that support shared interests and satisfy both payer and patient reimbursement needs.

Managed entry agreements are agreements between pharmaceutical companies and healthcare payers that help to manage the introduction and reimbursement of new drugs. Innovative financing mechanisms can play a crucial role in improving access to breast cancer drugs. A few examples of these are:

Outcomes-based agreements between pharmaceutical companies and payers that link reimbursement to the clinical performance of the drug. For example, a company may agree to

provide a drug at a reduced cost or with a refund if it does not meet predetermined clinical outcomes.

Subscription models are being used in some countries to fund access to high-cost cancer drugs. In a subscription model, a government or health insurer pays a fixed fee to a pharmaceutical company in exchange for access to its cancer drugs. This allows for predictable and stable pricing, while also ensuring access to innovative treatments.

Risk-sharing agreements allow pharmaceutical companies and payers to share the financial risk associated with a new drug. For example, a pharmaceutical company could agree to provide a breast cancer drug at a reduced cost for a limited time period, and then reimburse the payer for any excess costs that result from the use of the drug.(8)

Establish and strengthen population-based cancer registries (PBCR) to increase local data on breast cancer in Latin America and guide policy. PBCR are important because they provide a systematic and comprehensive way of collecting and analyzing data on cancer incidence, mortality, and survival rates within a defined population. They are a fundamental part of any national cancer control plan. Incidence data, which is dependent on the data generated by PBCRs, are necessary for cost efficiency analyses and has a determining impact on public policies. In Latin America, healthcare resource allocation decisions are often based primarily on upfront cost, which is insufficient within systems with finite resources. During the last five years, there has been important progress in the establishment and improvement of existing cancer registries in Latin America. Currently, there are 84 PBCR in the region with a population coverage of 23.3%.(14)

Cancer Control Programs and Policy: PBCR provide valuable information on the effectiveness of cancer control programs. By tracking the number of cancer cases and mortality rates over time, cancer registries can help evaluate the impact of cancer prevention and control strategies.

Burden of disease: PBCR can help understand the burden of cancer within a population and identify trends over time as well as identify disparities in cancer incidence, mortality, and survival rates among different population groups, which can help target resources for prevention and treatment efforts.

Resource allocation: The data collected by PBCR can inform resource allocation for cancer prevention and control. By understanding the burden of cancer in a particular region, policymakers can allocate resources appropriately. Furthermore, PBCR can help identify emerging cancer trends, such as an increase in a specific cancer type or demographic group. This information can help guide regulatory and reimbursement decisions.

Tracking Treatment Outcomes: PBCR can track treatment outcomes, including response rates, progression-free survival, and overall survival. This information can help identify the most effective treatments and guide the incorporation of innovative treatments into clinical practice.

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