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# **Improving Outcomes in the Treatment and Management of Metastatic Colorectal Cancer in Latin America**

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A Report Based on a Latin American Expert  
Summit for Metastatic Colorectal Cancer  
Convened in Buenos Aires, Argentina,  
January 2014

# Key Points

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1. In Latin America, colorectal cancer is the fourth most frequently diagnosed cancer in men and the third most frequently diagnosed cancer in women.
2. Most colorectal cancer deaths are preventable with early screening and detection. Yet, although most Latin American countries have national guidelines for colorectal cancer screening, such programs are infrequently implemented.
3. New drugs developed during the past decade, particularly targeted antiangiogenesis therapies, have produced a paradigm shift in the treatment of metastatic colorectal cancer (mCRC). Patients with mCRC now have treatment options that may extend their lives by many months or even years.
4. Many barriers exist, however, to ensuring that all Latin Americans receive timely and optimal colorectal cancer screening and care. These barriers include:
  - Widespread unawareness and misinformation about colorectal cancer among the general public, the media, primary care providers, and policymakers
  - Scarce financial resources for screening, treatment, and research
  - Insufficient infrastructure within healthcare systems for enabling a screening program to be successful
  - A geographic maldistribution of resources
  - A shortage of physicians trained to screen and treat colorectal cancer
  - A lack of access to mCRC drugs
  - A lack of epidemiological data about colorectal cancer in Latin America
  - Ineffective and uncoordinated patient advocacy
  - A fragmented and “silo” approach to medical care
5. As a result of these and other barriers, most Latin Americans do not undergo regular colorectal cancer screening. The cancer is therefore often diagnosed at a late stage.
6. The barriers also impede the ability of many Latin Americans to access timely and optimal care after diagnosis.
7. Overcoming the current challenges to the early diagnosis and effective treatment of colorectal cancer will require the concerted efforts of all Latin American stakeholders, including patients, caregivers, patient-advocacy groups, healthcare providers (including primary care physicians, surgeons, and oncologists), researchers, scientists, industry leaders, regulators, policymakers, the media, and society at large.

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# Introduction

## What Is Metastatic Colorectal Cancer?

Colorectal cancer is cancer of the large intestine (or bowel), which includes the colon and the rectum. The overwhelming majority of colorectal cancers (95%) are adenocarcinomas, which originate in cells that make and secrete mucus and other fluids in the innermost lining (epithelium) of the wall of the large intestine. Other types of cancers (lymphoma, sarcomas, melanoma, and carcinoid tumors) can also appear in the large intestine, but they are rare. As the cells of adenocarcinomas grow, they can invade some or all of the other layers of the wall, eventually penetrating into adjacent organs and structures. The malignant cells can also reach the capillaries (tiny blood vessels) or lymph vessels (small channels that transport tissue fluids) that serve the large intestine. Once in these blood or lymph vessels, malignant cells can travel to nearby lymph nodes, the small, bean-shaped structures that play an important role in the body's immune response, or to even more distant parts of the body, such as the liver. When the cancer has spread to those distant parts, it is called metastatic colorectal cancer (mCRC).

### Causes and Risk Factors

The exact cause of colorectal cancer is unknown, but several factors are believed to increase the risk of developing the disease.<sup>1</sup> A leading risk factor is age (most colorectal cancers are diagnosed in persons aged 50 or older). Other risk factors include benign colorectal polyps, especially adenomas; a personal or family history of colorectal cancer or, in women, a personal history of ovarian, endometrial, or breast cancer; a personal history of an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease; a diet high in animal fat and/or low in calcium, folate, and fiber; and smoking. Two genetic disorders, hereditary nonpolyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP), also increase the risk of developing colorectal cancer, although these disorders are rare and account for less than 5% of all colorectal cancer cases.<sup>2</sup>

### Incidence and Mortality

Globally, colorectal cancer is the third most common cancer among men and the second most common among women.<sup>3</sup> Each year, an estimated 1.2 million people are diagnosed with the disease around the world and about 608,000 individuals die from it. Colorectal cancer is most prevalent in developed regions of the world, where about 60% of cases are diagnosed. The disease's country-by-country incidence rates vary by tenfold. They tend to be highest in Australia, New Zealand, Europe, and North America, lowest in South-Central Asia and Africa (except southern Africa), and intermediate in Latin America.

Incidence rates have stabilized or declined in some historically high-risk countries, such as New Zealand, Canada, and the United States.<sup>4</sup> In the United States, for example, the incidence rate per 100,000 persons has decreased from a high of 66.3 in 1985 to 40.5 in 2010.<sup>5</sup> Incidence rates have recently begun to increase, however, in historically low-risk countries, such as Japan, Korea, China, and several Eastern European countries.<sup>4</sup> The increasing incidence rates have been linked to changes in dietary and lifestyle factors, including obesity and smoking; the decreasing rates are believed to be the result of more widespread colorectal cancer screening and the subsequent removal of precancerous lesions.<sup>6</sup>

Colorectal cancer's country-by-country mortality rates also vary widely. The highest mortality rates in both sexes are in Central and Eastern Europe, and the lowest are in Middle Africa. Mortality rates have decreased in several areas of the world, primarily due to earlier diagnosis through screening and more sophisticated and effective methods of treatment. In the United States, for example, the colorectal cancer mortality rate has fallen by an average of 2.8% per year in men and 2.6% per year in women since 1998.<sup>7</sup>

In Latin America, colorectal cancer is the fourth most frequently diagnosed cancer in men and the third most

Generic Name	Brand Name	Drug Type
Fluorouracil (5-FU)	–	Chemotherapy
Irinotecan hydrochloride	Camptosar®	Chemotherapy
Oxaliplatin	Eloxatin®	Chemotherapy
Capecitabine	Xeloda®	Chemotherapy
Bevacizumab	Avastin®	Targeted therapy
Cetuximab	Erbitux®	Targeted therapy
Panitumumab	Vectibix®	Targeted therapy
Ziv-Aflibercept	Zaltrap®	Targeted therapy
Regorafenib	Stivarga®	Targeted therapy

**Table 1.** Five approved “targeted” therapies for the treatment of colorectal cancer.

frequently diagnosed cancer in women.<sup>8</sup> The incidence of colorectal cancer is expected to rise in Latin America in the coming years due to growing economies and rising standards of living. Such changes tend to be accompanied by increases in sedentary lifestyles and unhealthy dietary habits, both of which are associated with a higher risk of colorectal cancer. The rapid aging of the region's population will also play a role in higher incidence rates. Colorectal cancer is primarily a disease of older people, and it is estimated that more than 100 million people aged 60 years and older will be living in Latin America and the Caribbean by 2020.<sup>9</sup> The disease's incidence and mortality rates are also increasing, however, among younger age groups, both in Latin America and around the world. These young-onset cases are more likely to be aggressive and diagnosed at advanced stages.<sup>10</sup>

## Treatment Options

Treatment options for colorectal cancer include surgical resection (with or without colostomy), radiation therapy (internal or external), and chemotherapy (systemic or regional). Treatments are recommended based on a variety of factors, including the type, location, and stage of the cancer; treatment toxicities; and the patient's overall health.

Nine drugs have been approved for the treatment of metastatic colorectal cancer in various countries around the world (see Table 1), including five "targeted" therapies, which are drugs that target the specific genes, proteins, or other factors in the large intestine's tissue environment that contribute to the growth and survival of the cancer. Antiangiogenesis drugs are a type of targeted therapy. They work by inhibiting the formation of new tumor blood vessels, thus denying tumors the blood, oxygen, and nutrients they need to grow.

## Paradigm Change

Antiangiogenesis-focused research, which began in the early 1970s, made dramatic advances in the late 1990s. Those advances culminated in the identification of specific antiangiogenic-related approaches to treating a variety of diseases, including skin disease, blinding disorders (such

as age-related macular degeneration), and cancer. More than 10,000 laboratories around the world are involved in angiogenesis research, and more than US\$5 billion has been invested globally in treatment-oriented research and development. This rapidly developing field has witnessed important advances, particularly in the last decade, that have had a major impact on the lives of patients, including those with mCRC.

## Antiangiogenesis Therapies

A paradigm shift in cancer therapy occurred in 2004, when the U.S. Food and Drug Administration (FDA) approved the first antiangiogenesis targeted therapy, bevacizumab (Avastin®), in combination with intravenous 5-fluorouracil (5-FU)-based chemotherapy, for the first-line treatment of patients with mCRC.<sup>11</sup> A monoclonal antibody, bevacizumab targets and inhibits a natural protein called vascular endothelial growth factor A (VEGF-A), which stimulates new blood vessel formation. The FDA has since approved bevacizumab in combination with fluoropyrimidine-based (combined with irinotecan or oxaliplatin) chemotherapy as a second-line treatment for patients with mCRC.<sup>12,13</sup>

Other targeted therapies for mCRC have been approved as well (see Table 2). Two of these drugs, cetuximab (Erbix®) and panitumumab (Vectibix®), are monoclonal antibodies that block epidermal growth factor receptor (EGFR). In 2004 and 2006, the FDA approved cetuximab<sup>14</sup> and panitumumab,<sup>15</sup> respectively, as second-line therapies for patients with EGFR-expressing mCRC. In 2012, cetuximab was also approved for first-line mCRC treatment.<sup>16</sup> Subsequent research found that both of these anti-EGFR drugs did not work in patients whose tumors tested positive for a mutated form of a gene known as KRAS.<sup>17</sup> In 2009, the FDA recommended that patients with mCRC have their tumors tested for KRAS gene mutations and that cetuximab and panitumumab only be given to patients with tumors with non-mutated KRAS genes (a form of the disease known as KRAS wild-type mCRC).

In 2012, the FDA approved two additional antiangiogenic drugs for the treatment of patients with mCRC. One of those drugs is ziv-aflibercept (Zaltrap®), a recombinant

Generic Name	Brand Name	Targets
Bevacizumab	Avastin®	VEGF-A
Cetuximab	Erbix®	EGFR
Panitumumab	Vectibix®	EGFR
Ziv-Aflibercept	Zaltrap®	VEGF-A, VEGF-B, PlGF
Regorafenib	Stivarga®	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, FGFR, TIE-2, KIT, RET, BRAF, RAF-1, BRAF-V600E

**Table 2.** Targeted drugs used for treatment of mCRC



fusion protein that inhibits VEGF-A and two other blood-vessel-stimulating proteins, VEGF-B and placental growth factor (PlGF).<sup>18</sup> It received FDA approval in 2012 for the treatment (in combination with FOLFIRI) of patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following treatment with an oxaliplatin containing regimen. The other drug was regorafenib (Stivarga®), a small molecule kinase inhibitor that also targets multiple proteins that regulate angiogenesis. In 2012, regorafenib received FDA approval as a monotherapy for the treatment of patients with mCRC whose cancer had progressed after treatment with all approved standard therapies. A year later, the drug was approved as a second-line treatment for patients with locally advanced, unresectable, or metastatic gastrointestinal stromal tumor (GIST). Regorafenib has been shown to improve median overall survival.<sup>19,20</sup>

### The Need for Improvement

With these recent advances, the treatment of metastatic colorectal cancer is being transformed into an illness that is increasingly manageable. But progress in prolonging survival has been incremental, and with the new treatment advances comes exposure to acute and long-term toxicities. Much more needs to be done to extend and improve the lives of the hundreds of thousands of people around the world who are diagnosed each year with mCRC.

## Bringing Leading Latin American mCRC Experts Together

Due to the relatively recent development and use of antiangiogenesis therapies, the Angiogenesis Foundation determined by the end of 2012 that it was an opportune time for the mCRC stakeholder community to assess the progress that had been made and the challenges that remain in the prevention, diagnosis, and treatment of the disease. As a scientific nonprofit organization whose mission is to conquer disease through the control of neovascularization, the Angiogenesis Foundation recognized that it is well positioned to play the role of a neutral facilitator of such a review.

As its first major step, the Foundation assembled an interdisciplinary group of U.S. leaders in colorectal cancer treatment and translational science. The U.S. Expert Summit for Metastatic Colorectal Cancer was then convened in Washington, D.C., in March 2013. Building on the success of that meeting, the Foundation convened a second summit, inviting leading experts from around the world. That event, the International Expert Summit for Improving Outcomes in the Treatment and Management of Metastatic Colorectal Cancer, was held in Berlin, Germany, on July 22-23, 2013.



**Figure 1.** A diverse group of experts was convened in Buenos Aires, Argentina by the Angiogenesis Foundation to discuss critical pathways forward for mCRC. Experts included physicians, academics, and patient advocates.

It was clear from the Berlin summit that different regions of the world face their own specific challenges regarding mCRC diagnosis and treatment. One of those regions is Latin America. In partnership with regional leaders, the Angiogenesis Foundation organized a third summit, the International Expert Summit: Improving Outcomes in the Treatment and Management of Metastatic Colorectal Cancer in Latin America, which was convened in Buenos Aires, Argentina, on January 17, 2014. Like the earlier meetings, this third summit was not a traditional scientific conference, but rather an interactive, professionally moderated set of short presentations and roundtable discussions that aimed to establish a dialogue and agreement among its participants.

Before the summit, the Foundation sent a 12-question survey about mCRC and its treatment in Latin America to 32 mCRC experts from eight countries (Argentina, Bolivia, Brazil, Colombia, Costa Rica, Mexico, Peru, and Venezuela). The thoughtful answers they provided helped inform the summit's agenda and its final "calls to action."

The summit itself opened with two experts making short presentations that provided background information on 1) state-of-the-art mCRC treatment and management strategies, 2) disparities in care for mCRC patients in Latin America, and 3) the emergence of mCRC patient-advocacy in the region. Under the direction of a moderator, the assembled experts spent the rest of the summit engaging in a series of provocative and productive discussions. During the morning session, they defined what a successful mCRC care system would look like within the next five years in Latin America, and then outlined the challenges that lie in the path of achieving that state. A graphic recorder captured key points of the discussion, enabling the participants to visually review the content of their conversations as they worked through the tasks at hand. During the afternoon session, the summit participants focused on developing solutions to overcoming the barriers identified earlier. Differences in colorectal cancer awareness and care pathways among the countries were noted and discussed. This was followed by a discussion about gaps in colorectal cancer research, with a specific emphasis on gaps affecting Latin American populations. The meeting ended with the participants outlining a list of key "action steps" needed to enhance the awareness, early detection, diagnosis, and treatment of mCRC in Latin America.

## The Role of the Angiogenesis Foundation

Founded in 1994 and headquartered in Cambridge, Massachusetts, the Angiogenesis Foundation is the world's first 501(c)(3) nonprofit organization dedicated to conquering disease with approaches based on angiogenesis, the growth of new blood vessels in the body. Its global mission is to help people benefit from the full promise of angiogenesis-based medicine, and to make life-, limb-, and vision-saving treatments available to everyone in need.

As a scientific organization, the Angiogenesis Foundation is independent of any individual, institution, or commercial entity, and, as such, it takes a unique approach to achieving its mission to help people lead longer, better, and healthier lives. It has helped propel innovative research involving both angiogenesis inhibitors and stimulators. Although much of this research has been pharmacological, promising studies involving nutrition and biomarkers are also actively pursued. In addition, the Angiogenesis Foundation is constantly looking for ways to innovate new and more effective prevention and care pathways.

Angiogenesis-related research is being conducted across a remarkably wide variety of disease states. In recent years, for example, profound angiogenesis-treatment breakthroughs have been discovered in ophthalmology, wound care, and cardiovascular disease, as well as in oncology. The Angiogenesis Foundation recognizes the challenges of optimizing patient care and outcomes with such paradigm-shifting discoveries as angiogenesis-based treatments for mCRC. It also deeply understands that to meet the goal of improving global health through angiogenesis-based medicine, the complex needs of all the stakeholder groups involved, including patients, caregivers, patient-support organizations, physicians, researchers, scientists, industry leaders, regulators, policymakers, and funders, must be aligned and met. The Angiogenesis Foundation is committed to helping these groups work together to ensure that all people benefit from current and future advances in angiogenesis-based medicine.

# Situation Analysis

The Latin American Expert Summit opened with welcoming remarks from **Dr. William Li**, the president, medical director, and co-founder of the Angiogenesis Foundation. He explained the purpose of the current summit and the history of the two previous ones in Washington, D.C., and Berlin. Dr. Li's remarks were followed by brief presentations by two Latin American mCRC experts. **Dr. Mauricio Lema** of the Clinica de Oncologia Astorga in Colombia reviewed the current, state-of-the-art knowledge about the biology, therapy, and management of mCRC. **Luciana Holtz**, president and CEO of the patient advocacy group Instituto Oncoguia in Brazil, discussed disparities in care for mCRC in Latin America and the emerging role of colorectal cancer advocacy groups in the region.

## State-of-the-Art Knowledge about mCRC Biology, Therapy, and Management

The advent of new drugs for the treatment of mCRC has led to improved survival. Chemotherapy alone has been shown to extend progression-free survival by up to 7 to 8 months and overall survival by up to 20 months.<sup>21-25</sup> The most common conventional chemotherapy drugs used to treat colorectal cancer are the FOLFIRI (5-fluorouracil/leucovorin (5-FU/LV) plus irinotecan) and FOLFOX (5-FU/LV plus oxaliplatin) regimens. Research has shown that the order in which these regimens are given to patients has no impact on the response rate, the progressive-free survival rate, or the overall survival rate.<sup>26</sup> FOLFOX is frequently the preferred first-line treatment, yet it has acute and accumulative neurotoxicities that affect patient quality of life and frequently lead to early discontinuation of the treatment.<sup>27</sup>

A more recent and important advance in the treatment of mCRC is the development of angiogenesis-related drugs. The predominant pro-angiogenic factors in human colorectal cancer are members of the vascular endothelial growth factor (VEGF) family. VEGF expression has been observed very early in the development of colorectal tumors — even before the cells become malignant. The expression then persists at elevated levels throughout the tumors' natural history.<sup>28</sup>

What can be done to mitigate or counteract this effect? Several antiangiogenic approaches have been tried so far, of which two have been shown to have some effectiveness. One successful approach uses monoclonal antibodies that targets circulating VEGF-A and keeps it from binding to its receptors. The first antibody shown to slow tumor growth was bevacizumab, and

its anti-tumor effect has been demonstrated to be even greater when given in combination with chemotherapy. A 2004 randomized clinical trial involving 813 patients with previously untreated metastatic colorectal cancer found that combining bevacizumab with chemotherapy (irinotecan, bolus fluorouracil, and leucovorin [IFL]) for first-line treatment of mCRC extended median progression-free survival by four months.<sup>29</sup> It also extended overall survival by a median duration of slightly more than 4 months, making this discovery one of the most important developments in the treatment of colorectal cancer.

A later clinical trial that investigated the efficacy of bevacizumab when added to an oxaliplatin-based chemotherapy reported a smaller median progression-free survival benefit of 1.4 months.<sup>30</sup> Many of the mCRC patients in this study, however, had treatment withdrawn after six months. The study's results suggest, therefore, that bevacizumab treatment should be continued at least until the time of re-progression of the disease or until treatment-related toxicity becomes unacceptable. Additional research has shown that using bevacizumab plus standard second-line chemotherapy beyond disease progression extends overall survival of mCRC patients.<sup>31,32</sup> Also effective as a second-line treatment (in combination with FOLFIRI) is ziv-aflibercept, a recombinant fusion protein that inhibits several angiogenesis-stimulating proteins. Regorafenib, an oral small-molecule multikinase inhibitor, works as an antiangiogenic drug, and is approved as salvage therapy.

Scientists have also developed therapies that block the epidermal growth factor receptor (EGFR). An overexpression of EGFR can trigger a cascade of molecular events associated with the initiation and progression of colorectal cancer. The monoclonal antibodies cetuximab and panitumumab are used as both first-line (cetuximab) and second-line (cetuximab and panitumumab) therapies for patients with EGFR-expressing mCRC. These drugs are not effective, however, in patients who test negative for certain mutations on KRAS, BRAF, and NRAS genes.

In summary, antiangiogenic agents offer improved outcomes for most patients with mCRC. Special caution must be used, however, when selecting treatments for patients with EGFR-expressing mCRC to ensure that the "right" therapy is chosen for the tumor's mutation status. There is no evidence to support the idea that people living in Latin America will have a different biological response to mCRC treatments than people living elsewhere in the world. Access to high-quality and timely care does, however, result in different outcomes—as it does in all regions of the world. Research suggests



that in Colombia, for example, mCRC patients with a high socioeconomic status live twice as long, on average, compared to those with a low socioeconomic status.<sup>33</sup> That disparity is a direct result of socioeconomic differences in timely access to advanced treatments.

## **Disparities in Care for mCRC Patients in Latin America and the Emergence of Advocacy**

Each year, about 12.7 million new cancer cases are diagnosed worldwide.<sup>34</sup> Unless there are substantial improvements in treatments—and in access to treatments—that number is expected to increase to 21.3 million by 2030, with 13.1 million deaths. The 2030 estimates for Latin America are 1.7 million new cancer diagnoses and 1 million cancer deaths.<sup>34</sup>

In Latin America, colorectal cancer is the fourth most common type of cancer among men and the third most common among women.<sup>8</sup> Based on data from cancer registries, about 11,000 new cases of colorectal cancer are diagnosed annually in Argentina, and about 6,800 people in that country die each year from the disease. In Brazil, about 32,000 new cases are diagnosed each year, with about 14,000 annual deaths. No data are available, however, about the number of Latin Americans diagnosed specifically with advanced disease, or mCRC.

Beyond the numbers, Latin Americans with colorectal cancer often face serious social problems that impede their ability to access early diagnosis and timely treatment. In the best of all possible worlds, each colorectal cancer patient would have access to the latest and most effective treatments, a multidisciplinary team of healthcare professionals, and psychosocial support, including support for the patient's family and friends. All of those things would help ensure the highest possible quality of life for the patient during the treatment of his or her disease. But in today's "real world," access to such benefits does not exist for most Latin Americans. In São Paulo, Brazil, for example, some patients with symptoms of colorectal cancer must wait up to 10 months to undergo a diagnostic colonoscopy and receive an examination by a proctologist.

Many factors impede the early and effective diagnosis and timely treatment of colorectal cancer patients in Latin America. These include a lack of colorectal cancer specialists and an inefficient healthcare infrastructure. The current healthcare infrastructure in many areas of Latin America is often unable to provide screening, chemotherapy, and surgery to all colorectal cancer patients in a timely manner. Even something as basic as getting access to colostomy bags can be extremely difficult for patients in some areas. In addition, innovative chemotherapies for the treatment of the disease are frequently denied or are unavailable to patients who receive their care within the public health system, and the approval of new drugs for public-health patients is often unnecessarily delayed or even denied. Public misinformation and fears about colorectal cancer also keep many Latin Americans from having their colorectal cancer diagnosed early and treated effectively. One recent survey found, for example, that only 27 percent of Brazilians over the age of 50 had been screened for colorectal cancer. (This compares to a rate of about 50 percent in the United States.<sup>7</sup>)

Despite being one of the four most common cancers in Latin America, colorectal cancer has received very little attention from public health officials. Patient advocacy is urgently needed, particularly from organized groups. Advocacy could begin with educating patients about their disease and about their rights as patients so that they could take an active role in all their treatment decisions. A survey undertaken by the Instituto Oncoguia found that many cancer patients do not even understand what the term metastatic means.

The Instituto Oncoguia exemplifies how patient advocacy can be successful. It recently persuaded the Brazilian government to approve 37 more cancer-treatment drugs and to make those drugs available to all patients. It is also working toward ensuring the uniform implementation of any law that is already on the books and would guarantee treatment of cancer within 60 days of diagnosis. Still, much more patient-advocacy work needs to be done, and it is needed throughout Latin America.

# Where We Want to Be

As the summit's opening presentations illustrated, advances in the treatment of mCRC, especially antiangiogenic therapies, are dramatically changing how the disease is treated and managed. Still, as the presentations also made clear, much more needs to be done to develop more effective treatments, to improve the management of the disease, and to ensure that all patients throughout Latin America have access to timely, state-of-the-art medical care.

## What a Successful System of Care Would Look Like

The moderator opened this segment of the summit by asking the meeting's participants to discuss a key question: If they could be completely successful in transforming mCRC screening, diagnosis, and treatment within the next five years in Latin America, what would that system of care look like from the perspectives of various stakeholders?

### From the Perspective of Patients and Caregivers

The participants agreed that in a successful mCRC care system in Latin America, all patients would have timely access to state-of-the-art diagnostic technology and treatment interventions. Each patient would be assigned a multi-disciplinary treatment team that would not only include radiologists, oncologists, surgeons, and other physicians who are colorectal cancer specialists, but

also support personnel, such as psychologists, physical therapists, and nutritionists. Psychosocial support would also be available for each patient's family and/or caregivers.

In addition, awareness about colorectal cancer would be widespread among the public so that people would undergo preventive screening, seek medical care at the first sign of symptoms, and be well informed throughout the treatment process. They would have access to information, presented at a level that would be easy to comprehend, about all their treatment options, including potential side effects and response rates. Armed with this information, the patients would be better able to partner with their clinicians to make an informed decision about which treatment and pathway of care was best for them. Currently, many patients in Latin America who are diagnosed with mCRC do not seek treatment because they mistakenly believe that the diagnosis automatically means death, the summit's participants pointed out. Educating patients about mCRC would help them realize that current treatments make it possible to manage the disease and prolong life. It would also encourage patients to take action to improve their health during treatment. Such lifestyle factors as exercise, diet, and sleep can enhance patients' well-being and, perhaps, their treatment outcomes. In addition, educating patients—and their families—about mCRC would help ensure that close relatives understand that they now have an increased risk profile for the disease.



**Figure 2.** Participants agree that timely access to state-of-the-art diagnostic technology and treatment interventions is the key to better outcomes for patients with mCRC.

## From the Perspective of Healthcare Professionals

be a priority throughout Latin America. They also agreed that medical professionals need more training in how to work efficiently as a member of such a team.

The participants then discussed the need for all healthcare professionals to be better trained and prepared to deal with the complexities of mCRC, from diagnosis through treatment and after-care. Such training would go a long way in ensuring that general practitioners recognize colorectal cancer symptoms early and immediately refer patients for diagnosis. In a successful care system, the participants added, physicians would have the time to educate patients about the disease and its treatments and to explain how urgent it is that the patients receive timely and effective treatment. It was mentioned that ignorance about colorectal cancer causes many Latin Americans who are diagnosed with the disease to turn first to ineffective alternative treatments rather than evidence-based ones.

Any successful mCRC care system developed over the next five years would, of course, include new and more effective targeted drugs for the disease and a clear treatment pathway for the use of those drugs, the summit participants acknowledged. In addition, Latin America's healthcare professionals would have full access to all state-of-the-art treatments and related technologies as they become available. Physicians would also be incentivized to use the treatment pathway that best matches the patient's disease and lifestyle profiles.





### **From the Perspective of Healthcare Institutions and Payers**

Next, the summit participants discussed what a successful mCRC care system would look like from the viewpoint of healthcare institutions and payers, both government and private. In such a system, the participants agreed, there would be an established treatment algorithm, starting with preventive screening and moving through all lines of treatment. The algorithm, which would be used by healthcare institutions throughout Latin America, could then be personalized to match the specific tumor profile and lifestyle needs of individual patients. A successful care system would also offer multidisciplinary teams of mCRC-specializing healthcare professionals, and access to those teams would be spread equitably throughout the region so that all patients could be assured of receiving quality care. In addition, healthcare institutions and systems would ensure that all their healthcare providers—especially primary care providers—were trained to spot early signs of colorectal cancer and to automatically refer patients over the age of 50 or with high-risk profiles to preventive screening.

In a successful mCRC care system, every healthcare-delivery program would provide access to all state-of-the-art technologies and treatments with proven efficacy, the summit participants added. Evidence-based outcomes data and cost-effectiveness models would be made available to help guide payers in approving new drugs and institutions in developing treatment policies. Policies would focus on expanding patient-access to drugs with

well-demonstrated effectiveness, and all stakeholders, including patients, would have input in the development of those policies. Cost-effectiveness models are already being used with some isolated success in Latin America, the summit participants pointed out. Similar studies are needed throughout Latin America. The summit participants stressed that cost-effectiveness studies need to use statistical models that focus on “cost-of-outcomes” rather than “cost-of-therapy.”

### **From the Perspective of Researchers**

The summit participants then moved on to discuss what a successful mCRC care system would look like from the vantage point of the research community. In general, clinical trial designs need to be improved, they said, to find ways of eliciting bigger effects and benefits. In addition, greater funding support is needed for research into genetic strategies for personalized treatments. The summit participants noted that the epidemiology of colorectal cancer in Latin America is different from Europe or the United States; thus, Latin American populations need greater representation in international mCRC trials, and more trials need to be conducted exclusively in Latin America. Greater involvement in international trials would also provide more Latin American patients with access to state-of-the-art treatments and would give their physicians more experience with those treatments. The approval process for new trials needs to be shortened, however; currently, it can take a full year in some Latin American countries to receive government approval to launch a study.

## Existing Barriers and Challenges

With the desired future state of the mCRC care system in Latin America defined, the moderator asked summit participants to discuss the barriers that stand in the way of attaining that goal. The participants identified the following substantive and varied list of barriers:

- Widespread unawareness and misinformation about colorectal cancer among the general public
- A media that is not engaged in or educated about colorectal cancer
- Ineffective and uncoordinated patient advocacy
- Policymakers who lack knowledge about colorectal cancer or about the importance of funding its treatment and research
- General societal negativity about colorectal cancer treatment outcomes
- Scarce financial resources for screening, treatment, and research
- A geographic maldistribution of colorectal cancer resources
- A lack of availability of second- and third-line mCRC drugs, especially a lack of access to biological therapies
- A shortage of physicians trained to screen and treat colorectal cancer
- A fragmented and “silo” approach to medical care
- The cost of colorectal cancer-related technology, such as the genotyping of tumors and imaging
- The cost of mCRC drugs
- A crowded physician schedule that leaves little time for individualized patient care or research
- Lack of knowledge among many physicians about the molecular basis of colorectal cancer and molecular treatments for the disease
- A lack of epidemiological data about colorectal cancer in Latin America
- A lack of cancer registries
- Bureaucratic, financial and other roadblocks that impede the launching of colorectal cancer-related clinical trials in Latin America
- A disconnect between research findings and healthcare policies
- A lack of communication among colorectal cancer stakeholders, especially medical professional societies and advocacy groups

The moderator then asked the summit participants to reflect further on the barriers they had listed. Which ones did they think were most important in terms of making an impact on how the disease is diagnosed and treated? And which ones are most likely to be implemented by colorectal cancer stakeholders within the next few years? The participants concluded that educating the general public, the media, and policymakers about the disease might be the most effective first step in overcoming the barriers. Reaching out to policymakers is particularly important, the participants agreed, because it could lead relatively quickly to the development of more financial resources for researching, diagnosing, and treating the disease.



# Developing Solutions

The summit participants then turned their focus toward developing strategies for overcoming the barriers and challenges that stand in the way of transforming the current system of mCRC care in Latin America into a more successful one.

## Improving Awareness and Early Detection

The discussion opened with participants offering their personal perspectives on their country's overall level of public awareness about colorectal cancer screening, which is the point at which many mCRC patients enter the care system. Early diagnosis and treatment saves lives with colorectal cancer—more so than with almost any other type of cancer. Thus, generating widespread public awareness about the need for screening is essential for better outcomes.

- In **Venezuela**, about 3,000 people are diagnosed with colorectal cancer and about 1,400 die from the disease each year.<sup>35</sup> It's the fourth leading cause of cancer-related deaths for both men and women in the country. Yet, very little is done to raise awareness about the disease and the importance of early detection.
- In **Brazil**, the Ministry of Health has approved screening colonoscopies for all citizens aged 50 and older, but, according to a recent survey, only 27 percent of people in that age group have undergone the screening. The waiting time for a colonoscopy—even when symptoms are present—can be very long for people in the public healthcare system. In Sao Paulo, the wait can be as long as 7 months. To “jump that queue,” many go to a hospital emergency room instead. Dr. Angelita Habr-Gama, a coloproctologist in Sao Paulo, has led efforts to increase Brazil's colorectal cancer screening rates, but public awareness remains low. Government health officials seldom talk about the disease. In addition, primary care physicians often fail to recommend screening to patients in the targeted age group. Yet, even when people are aware of the screening policy for people aged 50 and older, they often are unwilling—or unable—to take time off from work to have the colonoscopy. “We are at the zero point” with colorectal cancer awareness and screening, said one of the summit's Brazilian participants.
- Awareness and knowledge about colorectal cancer is also very low in **Peru**, although it appears to be on the rise. Health officials have launched an official awareness campaign, but the media has thus far provided little coverage, despite the fact that colorectal cancer is the country's fifth leading cause of death. If everybody over the age of 50 were to suddenly ask for a colonoscopy, access would be a problem due to a lack of screening infrastructure. Currently, only about 7 colorectal cancer screening specialists are practicing in Peru; most of the country's gastroenterologists specialize in gastric cancer.
- In **Bolivia**, a general lack of awareness about screening often leads to late-stage presentation of the colorectal cancer. Presently, there's no incentive for public health officials to create greater awareness of the disease.
- A similar situation exists in **Costa Rica**. Colorectal cancer awareness is so low that most patients are diagnosed after the disease has metastasized.
- Awareness of the importance of screening is also low in **Colombia**. Most of the country's colorectal cancer patients, therefore, do not have their disease diagnosed as a result of a routine screening. A Colombia physician participating in the summit noted that of the last 100 colorectal cancer patients referred to him for treatment, only about 5 came directly from a screening colonoscopy.
- **Mexico** has a colorectal cancer awareness campaign that uses an inflatable colon large enough for people to walk through. The educational device helps people visualize what a healthy colon/rectum looks like—and what polyps are. This campaign has not, however, achieved the same level of public awareness for colorectal cancer as have campaigns for breast cancer. Research suggests that the indigenous diet of Mexico, which is high in vegetables and low in meat, lowers the risk of colorectal cancer. That message needs to be promoted throughout the country. Mexican health officials have also noticed that colorectal cancer is being increasingly diagnosed in younger adults. Awareness efforts need to reach Mexicans of all ages.
- In **Argentina**, the National Cancer Institute has launched a colorectal cancer screening awareness program that has met with some success, particularly in urban areas. The program is now being tried in Argentina's rural interior. Health officials are also working to standardize colonoscopy screening across the country.

Although most of their conversation about early diagnosis centered on colonoscopy screening, the summit participants also discussed the value of using the fecal occult blood test (FOBT) and the newer fecal immunochemical test (FIT) in their respective countries. They agreed that these tests are effective in diagnosing the disease early, but they also pointed out that getting older people, particularly those who live in Latin America's more rural areas, to comply annually with the test presents a significant challenge. Mexico, for example, launched an FOBT campaign a couple of years ago that failed to have much impact.

The summit participants then talked about what could be done throughout Latin America to generate more awareness about colorectal cancer in general and mCRC specifically. It was agreed that awareness campaigns should imitate those conducted successfully by other health-advocacy groups, including colorectal cancer advocacy groups in other parts of the world. Belgium's highly effective "Save Brad Pitt" campaign (which publically urged the actor to get a colonoscopy during his 50th birthday year) was cited as an exceptionally successful model.<sup>36</sup>

The summit participants also agreed that overcoming the barriers to a successful mCRC care system in Latin America must be tackled on multiple, yet parallel, fronts. Awareness campaigns will raise demand for screening and treatment. Thus, those campaigns need to be accompanied by efforts to increase (and speed up) access to colorectal cancer-related technology and equipment. In addition, more colorectal cancer specialists will need to be trained.

## Improving Access to Effective Interventions

The moderator next asked the summit's participants to discuss the typical treatment pathway for mCRC patients in Latin America, once they are diagnosed with the disease. The group identified major touch points in that pathway, and described common patient experiences in their countries and throughout the region.

The point at which patients enter the mCRC care pathway depends on several factors, especially insurance coverage and patient knowledge about the disease. Patients who have private insurance and/or who are well

		Folfox	Folfiri	Bevacizumab	Ziv-Aflibercept	Regorafenib
Argentina		●	●	●	●	●
Bolivia		●	●	●	●	●
Brazil	Public	●	●	● except in Sao Paulo	●	●
	Private	●	●	●	●	●
Colombia		●	●	●	●	●
Costa Rica		●	●	●	●	●
Mexico	Public	●	●	●	●	●
	Private	●	●	●	●	●
Peru	Public	●	●	●	●	●
	Private	●	●	●	●	●
Venezuela		●	●	●	●	●

● Available and Covered

● Not Available

● Available and Not Covered

**Figure 4.** This chart indicates which antiangiogenic drugs are approved and/or covered by national health insurance in the countries represented at the summit (updated May 2014).

informed about colorectal cancer tend to be diagnosed at an earlier stage of the disease. Many patients, however—particularly those who have public or no insurance—enter the treatment pathway with a diagnosis of metastatic cancer. In Colombia, for example, about one-third of the patients diagnosed with colorectal cancer have metastatic disease.

The summit participants also discussed how Latin American patients with colorectal cancer—including those diagnosed with mCRC—are often referred after diagnosis to a surgeon for resection surgery to remove the part of the colon or rectum where the cancer is. Although surgery is appropriate in many cases, recent research has shown that a substantial number of patients, especially those with later-stage disease, would benefit from receiving chemo and/or radiation therapy before the surgery or in place of surgery. The summit participants agreed that assigning each patient a multidisciplinary team of experts immediately after diagnosis to evaluate his or her treatment options would help ensure that all patients receive the option that will work best for them. This change in the treatment pathway is already happening among selected populations throughout Latin America.

As part of the discussion on improving access to effective mCRC interventions, the summit participants created a matrix that described the regional similarities in the availability and funding of the five “targeted” therapies available for the treatment of the disease (see Figure 4). They also discussed how important it is to improve access to these therapies—a challenging task given the costs of the drugs. Evidence-based advocacy is needed, the participants agreed, to persuade health ministries and other payers about the cost-effectiveness of the treatments in terms of outcomes. It was also mentioned that governments should negotiate with drug manufacturers for increased access through bulk purchases, as health officials in the United Kingdom have successfully done.

## Developing a Regional Research Agenda

The moderator then led the summit participants in a discussion about developing a colorectal cancer research agenda for Latin America. Many gaps in the current research agenda were identified. More basic research into biomarkers and the progression of mCRC is needed. Scientists now know from translational studies that tumors escape antiangiogenesis treatment by generating different proteins. Understanding the mechanism behind this action would help identify when to stop a particular therapeutic agent—and when to administer another one. Research into next-generation gene sequencing also needs to be accelerated, because in the not-too-distant future, the diagnosis and treatment of colorectal cancer is likely to be based on the molecular profiling of tumors. One participant noted that, hypothetically, even if a drug cures only 1% of cancer patients with tumors that have a very specific and rare gene mutation, the benefits from the drug would be 100% if all patients with that tumor mutation could be identified.

Research is also needed on ethnicity and the metabolism of drugs. Drugs used to treat mCRC may have a higher or lower efficacy among Latin American populations; they may also have different toxicity profiles. Greater efforts should be made to include Latin American populations in international trials, the participants agreed. In addition, governmental regulators should speed up the process for approving regionally-based clinical trials. Latin America also needs more epidemiological studies on colorectal cancer, in part to help determine why the region appears to have an age profile that skews younger than in other areas of the world, as well as more patient registries for the collection of data. In addition, cost-effectiveness studies should be undertaken on all state-of-the-art treatments for mCRC so that policymakers can make timely and well-informed decisions about approving the treatments. Finally, more research is needed on effective palliative interventions for patients with mCRC, particularly for patients living in poor, rural areas.

# Summary of Calls to Action

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Over the course of the summit, the assembled experts discussed the following key actions that need to be taken to create more patient-centered systems of mCRC prevention, diagnosis, treatment, and care in Latin America.

## 1. Improve awareness and early diagnosis

- Develop high-profile colorectal cancer awareness campaigns, including ones that use the Internet and social media; enlist the help of celebrities when possible.
- Enhance the training of primary care physicians to ensure earlier recognition of symptoms and faster referrals to diagnostic screenings.
- Increase resources for screening technology, and make sure the technology is equitably distributed throughout the region.
- Encourage medical schools to train more gastroenterologists.
- Empower patients to demand preventive and diagnostic screenings from their primary care physicians.

## 2. Improve access to timely and effective treatment.

- Put systems in place that ensure patients with symptoms have timely access to diagnostic screenings and state-of-the-art treatments.
- Develop a standardized pathway of care that immediately assigns patients diagnosed with mCRC to a multidisciplinary medical team that will oversee the management of their care; make sure each team has an assigned care coordinator to help the patient understand and navigate the treatment process.
- Provide patients with mCRC with more complete information about all of their treatment options, including information about efficacy and side effects.
- Provide greater access to targeted therapies that have validated clinical benefit for mCRC across different settings (first-line, second-line, third-line, etc.).
- Establish an evidence-based treatment algorithm that starts with preventive screening and moves through all lines of treatment.
- Train more physicians to become colorectal cancer specialists.
- Develop incentives that enable physicians to spend more time caring for their patients with mCRC.
- Educate health policymakers and their advisors about the rapidly evolving progress in effective treatment options for mCRC.
- Encourage governments to negotiate with the pharmaceutical industry to increase access to mCRC drugs.
- Distribute treatment resources equitably throughout the region.
- Support patient advocacy groups in their efforts to improve the quality-of-life and treatment options for mCRC patients.
- Provide patients with supportive care during mCRC treatment, including management of side effects, psychological support of patients, and information about how diet, exercise, and other lifestyle behaviors may improve outcomes.
- Develop programs that offer training and support services for caregivers.



# Summary of Calls to Action

## 3. Expand basic and clinical mCRC research.

- Generate collaborative groups throughout the region to conduct clinical and translational research.
- Invest in epidemiological, genomic, and other research that focuses specifically on Latin American populations; establish cancer registries to support that research.
- Work with government regulators to develop shorter clinical-trial approval processes.
- Initiate cost-effectiveness studies on mCRC drugs and outcomes throughout all of Latin America.
- Conduct research on effective palliative-care interventions for mCRC patients, particularly for patients living in poor, rural areas throughout the region.



**Figure 5.** *The Expert Summit participants gathered around the graphic boards to review their key findings.*



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# Summit Participants

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## Chair:

**William Li, M.D.**  
The Angiogenesis Foundation  
Cambridge, USA

## Co-chair:

**Luciana Holtz de Camargo Barros**  
Instituto Oncoguia  
São Paulo, Brazil

## Co-chair:

**Mauricio Lema Medina, M.D.**  
Clínica de Oncología Astorga  
Medellín, Colombia

**Giovanni M. Bariani, M.D.**  
Instituto do Câncer do Estado de São Paulo  
São Paulo, Brazil

**Marcelo R.S. Cruz, M.D.**  
Hospital São José Beneficência Portuguesa de São Paulo  
São Paulo, Brazil

**Daniel Fernandes Saragiotto, M.D.**  
Hospital Sírio-Libanês  
São Paulo, Brazil

**Helano Freitas, M.D.**  
Hospital AC Camargo Câncer Center  
São Paulo, Brazil

**Carlos Henrique dos Anjos, M.D.**  
Hospital Sírio-Libanês  
São Paulo, Brazil

**Michelle Hutnik, DSc**  
The Angiogenesis Foundation  
Cambridge, USA

**Cintia Solano Castillo**  
Asociación Nacional Segunda  
San José, Costa Rica

**Mayra Y. Galindo Leal**  
Asociación Mexicana de Lucha Contra el Cáncer A.C.  
Mexico City, Mexico

**Erika Betzabe Ruiz Garcia, M.D.**  
Instituto Nacional de Cancerología (INCan)  
Mexico City, Mexico

**Horacio Astudillo de la Vega, M.D., Ph.D.**  
International Medical Support Services (IMSS)  
Mexico City, Mexico

**Jorge Leon Chong, M.D.**  
OncoSalud  
Lima, Perú

**Eva Maria Ruiz de Castilla**  
ESPERANTRA  
Lima, Perú

**Carlos Vallejos Sologuren, M.D.**  
OncoSalud  
Lima, Perú

**Leonardo Sosa Valencia, M.D.**  
Sociedad Venezolana de Gastroenterología  
Caracas, Venezuela

**Gilda Irene Barrera Zuleta, M.D.**  
Oncologa Clínica  
Santa Cruz, Bolivia

**Lucas Angel Damian Gonzales, M.D.**  
Instituto de Efectividad Clínica y Sanitaria (IECS)  
Buenos Aires, Argentina

## Other Contributors

Vincent Li, M.D., M.B.A.  
Robert Mittman  
Susan Perry  
Lisa Arora  
Maria Aufiero  
Katya Margolin  
Diana Saville  
The Angiogenesis Foundation  
Cambridge, MA, USA

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One Broadway, 14th Floor, Cambridge, Massachusetts 02142 USA  
617.401.2779 | [crcreport@angio.org](mailto:crcreport@angio.org) | [www.angio.org](http://www.angio.org)

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