International Expert Summit:

Improving Outcomes in the Treatment and Management of Metastatic Colorectal Cancer

A Report Based on an International Expert Summit Convened in Berlin, July 2013

The Angiogenesis Foundation

Key Points

1. Globally, colorectal cancer is the third most common cancer among men and the second most common among women.

2. Each year, an estimated 1.2 million people are diagnosed with the disease around the world, and more than 600,000 individuals die from it. The incidence and mortality rates are declining in some countries and increasing in others.

3. Most colorectal cancer deaths are preventable with early screening and detection. Yet screening rates for colorectal cancer lag behind those for other cancers.

4. The overwhelming majority of colorectal cancers (95%) are adenocarcinomas, which originate in the inner lining of the colon or rectum. Without treatment, cells from these lesions can spread through blood or lymph vessels to nearby lymph nodes and more distant parts of the body, such as the liver and lung. When the cancer has spread, it is called metastatic colorectal cancer (mCRC).

5. Once colorectal cancer has metastasized, successful treatment becomes much more challenging.

6. New drugs developed during the past decade, particularly targeted anti-angiogenesis therapies, have produced a paradigm shift in the treatment of mCRC, however. Patients with the disease now have treatment options that may extend their lives, with good quality of life, by many months or even years.

7. These treatments have led to a shift in the treatment strategy for patients with mCRC. In many cases, the disease is now treated as a chronic illness rather than as an acute medical condition.

8. Many barriers exist, however, to ensuring that people around the world receive timely and optimal mCRC care. These barriers include:
    - Societal ignorance and negativity about mCRC
    - Inconsistency in the availability of efficacious treatments
    - Uneven distribution and/or shortages of medical professionals with the knowledge to diagnose and treat mCRC
    - Fragmentation in the conduct of mCRC research

9. As a result of these and other barriers, many people around the world do not undergo regular colorectal cancer screening and have difficulty accessing optimal care after diagnosis. In addition, research into new, more effective treatments has progressed at a slower-than-desirable pace.

10. Overcoming the current challenges to the effective treatment of mCRC will require the concerted global efforts of all stakeholders, including patients, caregivers, patient-advocacy groups, physicians, researchers, scientists, industry leaders, regulators, policymakers, funders, the media, and society at large.

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Table of Contents

Introduction

What Is Metastatic Colorectal Cancer?

Colorectal cancer is cancer of the large intestine (colon) or rectum (the end of the colon, nearest the anus). 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 colon. Other types of cancers (lymphoma, sarcomas, melanoma, and carcinoid tumors) can also appear in the colon, 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 colon. 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 and lung. 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.[1] These include age (more than 90% of colorectal cancers are diagnosed in persons aged 50 or older); benign colorectal polyps, especially adenomas; a personal or family history of colorectal cancer and, 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.[2]

Incidence and Mortality

Globally, colorectal cancer is the third most common cancer among men and the second most common among women.[3] 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, intermediate in Latin America, and lowest in South-Central Asia and Africa (except southern Africa). Incidence rates have stabilized or declined in some historically high-risk countries, such as New Zealand, Canada, and the United States.[4] 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.[5] Incidence rates have recently begun to increase, however, in historically low-risk countries, such as Japan, Korea, China, and several Eastern European countries.[4] 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.[6]

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.[7]

Treatment Options

Treatment options for colorectal cancer include surgical resection (with or without colostomy), radiation therapy

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.*

(internal or external), and chemotherapy (systemic or regional). Treatments are recommended based on a variety of factors, including the type 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 colon's tissue environment that contribute to the growth and survival of the cancer. Anti-angiogenesis 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

Anti-angiogenesis-focused research, which began in the early 1970s, made dramatic advances in the late 1990s. Those advances culminated in the identification of specific anti-angiogenic-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.

Anti-Angiogenesis Therapies

A paradigm shift in cancer therapy occurred in 2004, when the U.S. Food and Drug Administration (FDA) approved the first anti-angiogenesis targeted therapy, bevacizumab (Avastin®), in combination with intravenous 5-fluorouracil (5-FU)-based chemotherapy, for the first-line treatment of patients with mCRC.[8] A monoclonal antibody, bevacizumab targets and inhibits a natural protein called vascular endothelial growth factor A (VEGF-A), which stimulates new blood vessel formation.

Most recently, the FDA has since approved bevacizumab in combination with fluoropyrimidine-based (combined with irinotecan or oxaliplatin) chemotherapy as a second-line treatment for patients whose metastatic disease progressed after a first-line bevacizumab-containing regimen.[9,10]

Other targeted therapies for mCRC have followed (see Table 2). Two of these drugs, cetuximab (Erbitux®) and panitumumab (Vectibix®), are monoclonal antibodies that block epidermal growth factor receptor (EGFR). In 2004 and 2006, the FDA approved cetuximab[11] and panitumumab,[12] respectively, as second-line therapies for patients with EGFR-expressing mCRC. In 2012, cetuximab was also approved for first-line mCRC treatment.[13] 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.[14] 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 anti-angiogenic drugs for the treatment of patients with mCRC. One of those drugs is ziv-aflibercept (Zaltrap®), which targets VEGF-A and two other blood-vessel-stimulating proteins, VEGF-B and placental growth factor (PlGF).[15] The anti-angiogenic drug regorafenib (Stivarga®) also received FDA approval in 2012 for the treatment of patients whose mCRC has progressed after treatment with all approved standard therapies. Regorafenib is an oral medication that targets multiple proteins that regulate angiogenesis. It has been shown to improve median overall survival.[16] Ziv-aflibercept and regorafenib received approval in the European Union in 2013.

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-

Generic Name	Brand Name	Targets
Bevacizumab	Avastin®	VEGF-A
Cetuximab	Eribitux®	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*

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 Experts Together

Due to the relatively recent development and use of anti-angiogenesis 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 decided to convene a second summit that would include 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. Like the earlier meeting, this second 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 the participants.

The event opened with three experts making short presentations that provided background information on what the very latest clinical trials and other research have to say about the treatment and management of mCRC. Under the direction of a moderator, the assembled experts spent the rest of the summit's first day engaging in a series of discussions that defined where the field wants to be in terms or preventing, detecting, and treating colorectal cancer, 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 summit's second day, after a brief opening presentation about the issues and challenges regarding mCRC survivorship, the experts focused on mapping current care pathways for the treatment of mCRC, starting with patient awareness and moving through diagnosis, referral, treatment, and follow-up. Differences in care pathways among countries and regions of the world were noted and discussed, as were the general barriers that impede a smooth and effective care-pathway continuum and thus hinder improved treatment outcomes. Summit participants then turned their focus on identifying, mentoring, and training the next generation of mCRC leaders. This was followed by a provocative discussion about where mCRC treatment and research is headed in the coming years. This white paper provides an overview of the group's discussions.

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.

The Angiogenesis Foundation 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 being actively pursued. In addition, the Angiogenesis Foundation is constantly looking for ways to innovate patient-centered 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 those groups work together to make sure that all people benefit from current and future advances in angiogenesis-based medicine.

The Scope of the Problem

The International 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 previous one. Dr. Li's remarks were followed by brief presentations by three experts; each offered an overview of recent developments regarding mCRC research and treatment. **Dr. Dirk Arnold** of the Tumor Biology Centre at the Albert Ludwigs University in Frieburg, Germany, presented highlights from recent clinical trials on the management of mCRC. **Dr. Diether Lambrechts** of the Katholieke Universiteit Leuven in Leuven, Belgium, and **Dr. Annette Byrne** of the Royal College of Surgeons in Dublin, Ireland, reviewed the quest for biomarkers to personalize the treatment of mCRC.

Management of mCRC: New Treatment Paradigms

The idea that angiogenesis plays a role in cancer is not new. More than 70 years ago, a German radiologist, Dr. Gordon Ide, suggested that blood vessel growth might stimulate tumors, and more than 40 years ago,[17] Dr. Judah Folkman, proposed that anti-angiogenic drugs might reverse that process.[18] Today, the therapeutic targeting of angiogenesis is an established field, but it's also a rapidly evolving one, for the process of angiogenesis is highly complex, with multiple mechanisms and pathways.

When looking at the clinical data that supports anti-angiogenesis treatments, the question that must be asked is, "What are the real benefits for the patient?" Improvement of overall survival should be the main goal of clinical trials, but it does not have to be the endpoint of every study. For example, clinical trial results that provide information about the relief and/or prevention of symptoms, whether those symptoms are related to the disease or its treatment, are also valuable.

Clinical trials have demonstrated that overall survival of patients with mCRC has improved in recent years.[19] Two major factors are behind this increased survival: greater patient-access to new drugs and more mCRC patients undergoing secondary resection of tumors that have spread to the liver or lungs. A variety of drug treatments are now available for mCRC, including chemotherapies and targeted anti-angiogenic and anti-EGFR agents. Research has shown that when combined, the benefits of chemotherapy and anti-angiogenesis agents can be additive. More clinical work is needed, however, to determine which combinations may also be synergistic. Clinical research is also needed to determine if and when anti-angiogenic drugs limit the effects of chemotherapy or lead to detrimental effects. Research conducted to date with the first-line anti-angiogenic drug bevacizumab has been encouraging. Clinical trials that combined bevacizumab with either oxaliplatin- or ironotecan-based chemotherapy for the treatment of mCRC have suggested that bevacizumab's effect is additive and perhaps even synergistic, but not negative.[20,21,22] Multiple non-interventional trials conducted in different countries have also shown such benefits.[23,24]

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

Toxicity is an issue that must be considered by clinicians when selecting treatments for a patient. Although the number of patients who suffer from severe toxicity is limited, this feature cannot be ignored. Both chemotherapy and targeted drugs can cause toxicity, yet there is limited evidence regarding which combinations and dosing regimens result in the least amount of unwanted side effects.

New therapies for mCRC have also led clinicians to reconsider the question of how long to treat patients and how to treat patients in specific situations. The ideal outcome measurement is time without symptoms or toxicity (TWiST). With bevacizumab, for example, research has suggested that it may be beneficial to treat until the disease progresses or for a median duration of six months, but recent research suggests that chemotherapy-plus-bevacizumab or single agent bevacizumab maintenance treatments may also be beneficial.[25] Other research has shown that when patients are switched to a second-line chemotherapy, continuing first-line bevacizumab may extend survival.[26] Yet another issue that new therapies raise for clinical practice is how to measure treatment response. A liver lesion, for example, may not shrink as a result of anti-angiogenic therapy, but it may demonstrate histological features and a pathologic response that is associated with better overall survival.[27]

Anti-angiogenic treatments are very complex, and the transmission from pre-clinical research to clinical practice is very difficult. Although these drugs have transformed and improved the treatment of mCRC, many unknowns about their use and effects remain. What are the optimal therapeutic combinations, doses, and duration of therapy? What is the optimal sequence of anti-VEGF agents for treatment beyond disease progression? What biomarkers can predict treatment response? And what are the best strategies for identifying patients who no longer benefit from a specific therapy? Those are just some of the many questions and challenges that still need to be answered.

The Quest for Biomarkers to Personalize mCRC Treatment

The anti-angiogenic drug bevacizumab has been approved for several cancers, including mCRC, advanced non-squamous non-small cell lung cancer (NSCLC), metastatic kidney cancer (mRCC), and glioblastoma (GBM). Clinical trials have shown that bevacizumab prolongs survival in some of these diseases (mCRC and NSCLC) and delays disease progression in others (mRCC and GBM). Yet, although bevacizumab offers benefits, it can also cause serious side effects, including severe hypertension and hemorrhaging. In 2012, the U.S. Food and Drug Administration revoked its approval of bevacizumab for the treatment of first-line metastatic breast cancer after deciding that the risks associated with the drug outweighed the benefits for people with this type of cancer.

Clinical trials have shown that certain patients who receive bevacizumab treatment for metastatic cancer are "outliers." Some of these patients experience a prolonged survival in response to the drug, while others have no response at all. Identifying the outliers at both ends of this spectrum is vital, as it would ensure that the drug would be given only to those who would benefit, thus sparing others from unnecessary exposure to the drug's toxic side effects.

To help determine precisely which patients might most benefit from anti-angiogenic drugs, scientists and clinicians are attempting to identify and validate prognostic biomarkers. The search for such biomarkers has many challenges, however. Angiogenesis is a very complex biological process with numerous pathways. In addition, anti-angiogenic drugs have various mechanisms of action, which may differ between cancer types and between different types of chemotherapy. As a result, no single biomarker is likely to be sufficient to predict a patient's response to the drug.[28]

Scientists have focused their biomarker investigation on many biologic parameters. Research into genetic variants in germline DNA has proven particularly promising. A 2012 clinical trial found, for example, that pancreatic cancer patients with the rs9582036 A allele experienced improved overall survival when treated with bevacizumab; no such improvement was seen in the placebo arm of the trial.[29] The variant appears to increase the expression of the receptor to which VEGF binds (VEGF-R1). Attempts to replicate genetic variants in germline DNA have, however, met with mixed results, an outcome that highlights the complexity of the search for validated biomarkers. In colorectal cancer studies, several different genetic variants have been identified as being predictive of progression-free survival in bevacizumab-treated patients. Variants have also been identified that are predictive of the development of side effects, such as the onset of bevacizumab-related hypertension.[28]

Researchers have also tried to determine if baseline levels of circulating VEGF could serve as a prognostic biomarker. Plasma levels of short isoforms of VEGF have been found to be predictive of bevacizumab response in

several cancer types (breast, pancreatic, and gastric), but not in others (mCRC and mRCC). Additional research is needed to determine if the lack of a predictive response is real or an artifact of sample storage methods. A prospective trial is currently underway to validate short VEGF isoform levels as a prognostic biomarker in breast cancer. Other researchers have been searching for prognostic biomarkers that might occur once treatment begins. One study has found, for example, that patients with high levels of interleukin-8 benefit from anti-angiogenic treatment, whereas those with low levels do not.[30]

The AngioPredict consortium (www.angiopredict.com), which launched in 2012, is an exciting new global research project that is taking a multi-dimensional, integrated strategy to identify and validate novel, predictive biomarkers for anti-angiogenesis therapies in the treatment of mCRC. Consisting of clinicians, small- and medium-sized enterprises, clinical research organizations, and research scientists, the consortium represents a paradigm shift in the field. It will be using a variety of genomic discovery methods to identify and validate predictive biomarker signatures from biological tissue samples collected from a large, prospective study (ANGIOPREDICT). Those samples, as well as retrospective samples being made available by consortium members, are being stored in the ANGIOPREDICT Bioresource, which is based at the University Hospital Mannheim in Germany.

Key to AngioPredict's research efforts is the involvement of mathematicians and bioinfomatic researchers, who will use classical and systems-based tools to incorporate the project's findings. Once biomarkers are identified and validated, the consortium intends to develop diagnostic tests using the biomarkers, which will then enable clinicians to predict patient treatment responses in the future.

The consortium represents a lofty ambition, but it's what the field requires given the complexity of anti-angiogenesis treatments. AngioPredict promises to greatly advance personalized medicine for patients with mCRC.

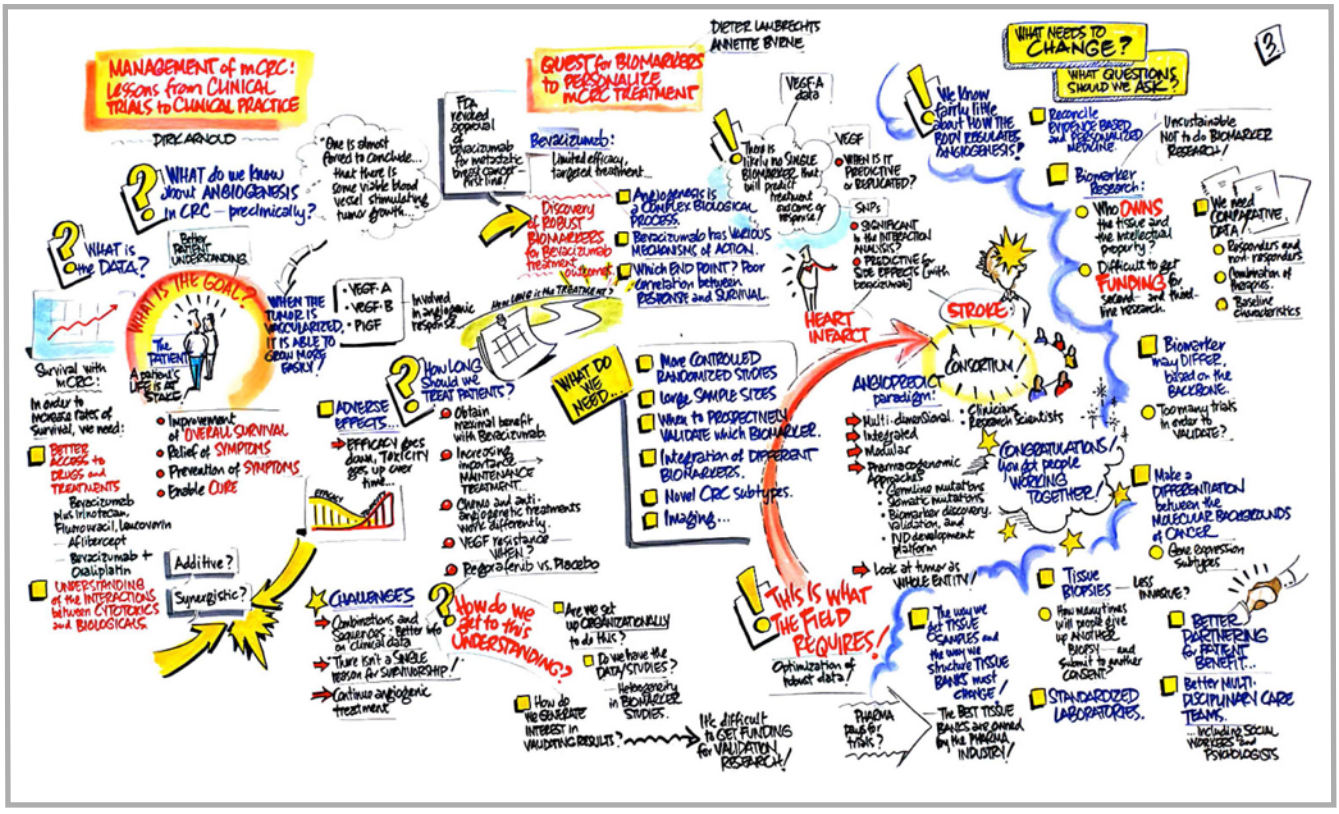

Figure 2. *Graphical representation: Lessons Learned in Management of mCRC and the Quest to Personalize Treatment*

Where We Want to Be

As the summit's opening presentations illustrated, advances in anti-angiogenic therapies are dramatically changing how mCRC is treated and managed. Still, as the presentations also made clear, much more needs to be done to improve the management of the disease, to develop more effective treatments, and to expand basic and clinical research. The moderator opened this segment of the summit by asking the patients, caregivers, physicians, and researchers to discuss a key question: if they could be completely successful in transforming the treatment of mCRC within the next five years, what would that system of care look like from the perspective of various stakeholders?

From the Perspective of Patients and Caregivers

The participants agreed that in a successful patient-centered care system, all mCRC patients would receive current and personalized information about their disease and its treatment. They would be presented with complete information about all their treatment options, including potential side effects and response rates, so they could partner with their clinician in making an informed decision about what treatment and pathway of care was best for them. Yet, clinicians would be careful not to burden their patient with an avalanche of unnecessary information, which might overwhelm the patient, making treatment decisions difficult or causing important elements to be forgotten by the patient during later stages of his or her disease. It was noted that in the United Kingdom, cancer patients receive telephone support throughout the treatment process to help answer their ongoing questions.

The experts also acknowledged that all physicians and other medical clinicians in a successful mCRC care system would have strong communication skills to ensure that their patients understand the information being presented to them. In addition, each mCRC patient would be assigned a care coordinator at the point of diagnosis (or very soon afterwards) to help patients understand and navigate the treatment process. This coordinator could be a qualified nurse or a trained layperson. Patients would ideally also have their caregiver (a family member or friend) at their medical appointments, taking notes and making sure all questions got answered. In addition, patients—and their caregivers—would have access to free or inexpensive support services, including, if requested, a support group. In Peru, for example, cancer patients can join "patient clubs" for their particular disease, where they can talk with others who have been similarly diagnosed. These clubs help lessen patients' fears and serve as useful resources for information about the effects of mCRC and its treatments on everyday life.

Summit participants also discussed how patients in a successful mCRC care system would receive equitable and timely access to treatments, with a minimum of paperwork and other bureaucratic burdens. Patients would also receive supportive care for the management of side effects from their treatment, as well as information about how diet, exercise, and other lifestyle behaviors might enhance their well-being and, perhaps, their treatment outcome. In addition, patients would receive counseling about the financial implications of their care. As summit participants noted, a 2012 U.S. study of patients with stage III colorectal cancer found that 38% had experienced one or more financial hardships (such as accruing debt, refinancing their home, or experiencing a 20% or greater decline in their annual income) as a result of treatment-related burdens.[31] Such hardships were common even among patients who had health insurance. In a successful care system, the summit participants stressed, there would be price transparency, and patients and physicians alike would know what each component of treatment costs.

From the Perspective of Physicians

The summit participants then discussed what a successful mCRC care system would look like from the point of view of physicians. They noted that a societal shift is underway in how malignant metastatic diseases, such as colorectal cancer, are being viewed. Stakeholders—patients, physicians, payers, and policymakers—have begun to recognize that in some cases, colorectal disease can be viewed as a chronic illness that requires ongoing management. To maximize the effectiveness of that management—and, of course, to improve outcomes—oncologists and other physicians will need greater clarity about best practices for the disease, including widespread agreement about optimal treatment pathways.

Any successful mCRC care system developed over the next five years must, of course, include new and more effective targeted treatments for the disease, the summit participants acknowledged. Yet the experts also stressed that physicians need consistently updated information about current drugs and therapies, including detailed information about selecting treatments with reference to co-morbidities. Having access to full and unbiased clinical trial information about mCRC drugs is essential. It would also help, the experts added, if more patients were enrolled in clinical trials and if participating patients were put on a registry and followed after their trial ended.

In an ideal successful care system, physicians would have full access to all mCRC drugs that have been validated and approved by a consensus of countries around the world, the summit participants stressed. Biomarkers would be available to help make treatment decisions and to provide early warnings of a potentially adverse or non-response to a treatment. In addition, physicians would have unlimited access to cutting-edge colorectal cancer diagnostic technologies—although such technologies must minimize the risk of overdiagnosis. Training general practitioners to be more informed about mCRC screening, diagnosis and treatments would help, summit participants said, because it would make it more likely that patients get referred to treatment at an earlier stage of the disease.

From the Perspective of Researchers

The mCRC research community has an immediate need for greater funding for translational research, the summit participants agreed. Better animal models—ones that more closely reflect what happens in humans—are also needed to advance research in the field. Research involving patient-derived xenograph animal models looks particularly promising, the experts pointed out. To ensure tissue and other biospecimens are of consistent high quality and to minimize variation in research results, efforts to collect human samples for research must adhere tightly to standard operation procedures, they added. In addition, researchers should have broader access to clinical trial databases and tissue samples.

Summit participants also discussed the need for better clinical trial designs that focus on how and when to use therapies currently available for the treatment of mCRC. Such studies should address and answer clinically relevant questions. They also need to be larger, so that more meaningful clinical differences among treatments can be identified. In addition, patient-reported outcome measures should be included in trial methodologies and results. Finally, to increase participation in clinical trials, greater efforts should be made to educate patients with mCRC—and their medical providers—on why such studies are important and how to enroll in them. Many people are unaware, for example, that mCRC patients can enroll in clinical trials no matter where they are in their diagnosis.

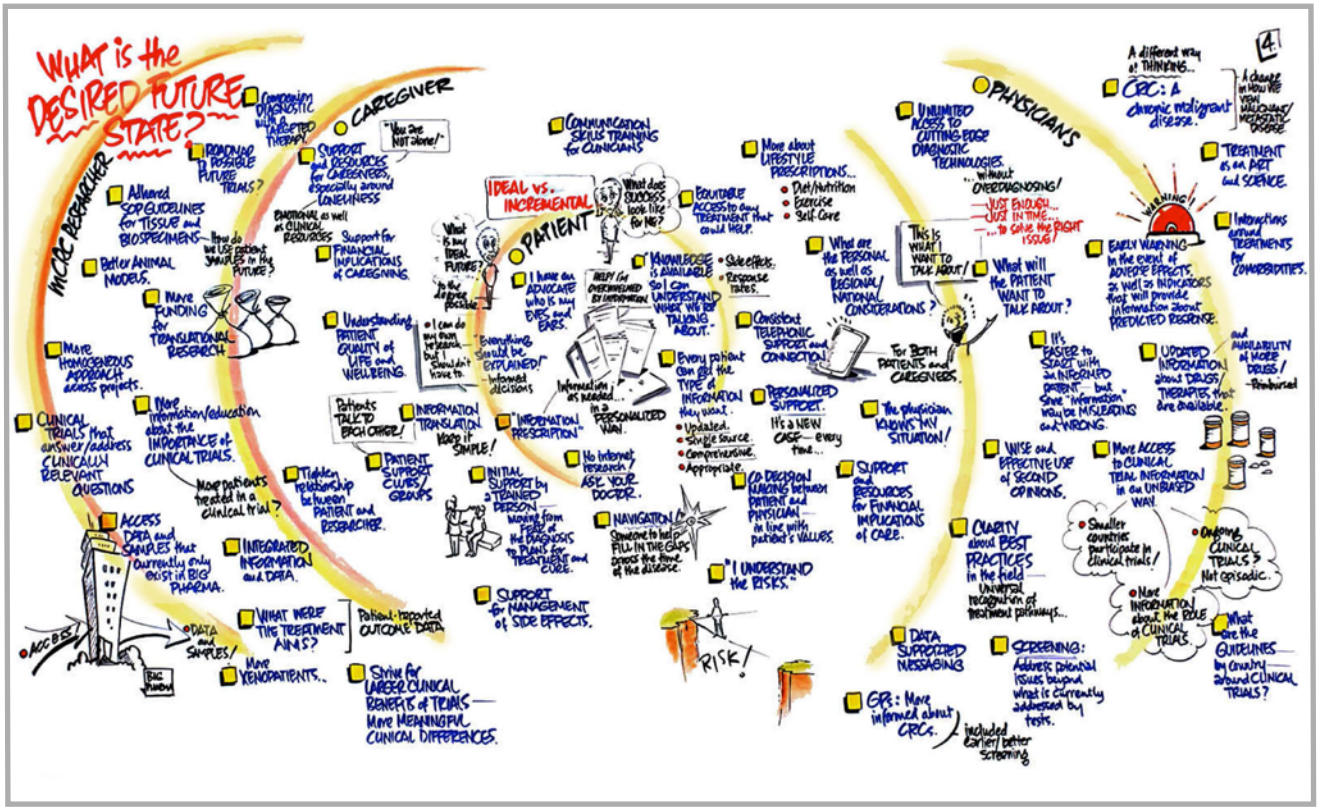

Figure 3. *Graphical representation: the desired future state of care pathways for mCRC*

Existing Barriers and Challenges

With the desired future state of colorectal cancer 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:

In terms of impact, the most important barriers were ranked as follows:

- Societal ignorance and negativity about mCRC
- Knowledge gaps about mCRC screening, diagnosis and treatment among general practitioners
- Too-late diagnosis of the disease
- Fragmentation in the conduct of mCRC research
- Lack of media attention to mCRC
- Inconsistency in the availability of efficacious treatments
- Uneven distribution and/or shortages of medical professionals with the knowledge to diagnose and treat mCRC
- Inappropriate or inadequate tissue collection
- Clinical trial designs that limit the ability of patients and physicians to compare the effectiveness of different treatments
- Scarce financial resources among competing health priorities
- Time pressures on physician office visits that limit the ability for patient and physician to have an adequate exchange of information
- Inappropriate or inadequate animal models for the disease
- The heterogeneity and molecular complexity of mCRC tumors
- Existing patent legislation, which restricts patient access to new drugs and provides a disincentive to develop biomarker tests
- The difficulty of accessing investigational new drugs for investigator-initiated studies
- Research agendas that are not always well aligned between academic groups and the pharmaceutical industry
- Fragmented healthcare delivery systems
- A lack of common language and understanding of fundamental priorities among researchers
- A lack of resources for clinical trials investigating multi-modality treatments
- Short-term academic incentives, which reward the publishing of positive but not negative treatment results
- Current incentives that favor innovation of new drugs rather than increased availability of existing ones
- The cost and complexity of clinical trials
- The emotional difficulty of the diagnosis for patients, and the difficulty of talking about the disease
- Regulatory restrictions on combination therapies
- A risk-averse research landscape

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 mCRC stakeholders within the next few years?

The second day of the summit focused on strategies for overcoming the barriers and challenges that stand in the way of transforming the current system of mCRC care into a more successful one. It began with a brief presentation by Dr. Crystal Denlinger of the Fox Chase Cancer Center in Philadelphia, PA, USA, on the issues and challenges in mCRC survivorship. A summary of that presentation follows.

Issues and Challenges in mCRC Survivorship

Every person diagnosed with cancer becomes a survivor at the time of diagnosis and remains one throughout the balance of his or her life. As the National Cancer Institute (NCI) points out, "family members, friends, and caregivers are also impacted and included in this definition."[32] Researchers have looked at metastatic cancer survivorship and divided it into four "seasons": 1) "acute survivorship" (the high-anxiety and difficult time of diagnosis and treatment); 2) "transitional survivorship" (the transition from active treatment to observation); 3) "extended survivorship" (the period, which may involve remission, when maintenance treatment and/or surveillance is ongoing); and 4) "permanent survivorship" (the period when the patient is cancer-free, but he or she must still deal with the long-term effects of the disease and its treatment).[33] In 2006, the Institute of Medicine (IOM) published a seminal work that defined four elements essential to the care of metastatic cancer survivors: prevention (of recurrent and new cancers, as well as prevention of the late effects of the disease), surveillance (for cancer spread, recurrence, or secondary cancers, as well as for late medical and psychosocial effects), intervention (for long-term effects of the disease and its treatment); and coordination (between specialists and primary care providers).[34]

Survivors of mCRC face many long-term effects from both the cancer and its treatment. Surgery and/or chemotherapy may lead to bowel, urinary, and sexual dysfunction. Up to 60% of patients who undergo colon resection surgery and more than 30% who survive chemoradiotherapy develop ongoing bowel-related symptoms, such as frequent and urgent stools, increased gassiness, liquid stools, or stool incontinence.[35,36,37] In addition, 31% of men and 58% of women develop urinary dysfunction for the first time after rectal cancer surgery,[38] and 76% of men and 62% of women develop some form of sexual dysfunction after surgery and/or chemoradiotherapy for colorectal cancer.[39]

Chemotherapy has other physical effects on the body, including persistent nausea and vomiting, short-term memory loss, and changes in appetite. In one study of mCRC patients being treated with first-line FOLFOX (oxaliplatin, leucovorin and 5-fluorouracil) or FOLFIRI (irinotecan, leucovorin and 5-fluoruracil) with and without bevacizumab, at least half required a dose reduction, a treatment break, a drug discontinuation, or hospitalization due to the treatment-related symptoms.[40] The leading patient complaint associated with chemotherapy is fatigue, which can remain an issue for many years after the chemotherapy has ended. Drug treatments for mCRC can also cause neuropathy (damage to the nerves that results in numbness or weakness), as well as severe, acne-like skin rashes. The rashes, which are triggered by treatment, usually end when treatment ceases; the neuropathy, however, can be both acute and chronic. The side effects of current treatments for mCRC impose, therefore, a significant physical and emotional burden on patients. Not surprisingly, research has found that drug toxicity is the leading reason mCRC patients change therapies.[41] Indeed, treatment toxicity can be as big a burden for patients as the cancer.

Issues other than treatment also affect the quality of life—and survivorship—for patients with mCRC. Good nutrition and physical activity, for example, are associated with improved treatment outcomes and survivorship, yet one study found that more than 80% of colorectal cancer patients with stage III or metastatic disease failed to meet diet and physical activity recommendations.[42] Co-morbidities are also a major issue for patients with mCRC, particularly among patients aged 65 or older. A Dutch study found that 62% of patients newly diagnosed with mCRC had a least one comorbidity, most notably cardiovascular disease or diabetes.[43] Another large study conducted in the United States found that 73% of patients diagnosed with mCRC were taking blood-pressure medications, 29% were taking cholesterol-lowering medications, and 24% were taking medications for the treatment of diabetes.[44]

Patients diagnosed with mCRC often come to view themselves as "living on borrowed time."[45] Many alter the way they think of the future, living in small increments and not planning too far ahead. They also change their daily activities—and priorities—in ways that acknowledge the side effects of their disease and its treatment as well as the vulnerability of their situation. Many caregivers also revise their activities to match those of the patient. Caregivers are "the silent survivor," who provide an average of 3.5 hours per day in patient care, often while continuing outside jobs and/or while

managing their own chronic health problems. Not surprisingly, caregivers have many unmet needs that can lead to psychological distress and a lowered quality of life.[46] They need more support services, including better training to handle the medical needs of the patient. An increasing number of therapies are being delivered to cancer patients in their homes, but caregivers are not receiving sufficient training to deliver or manage those therapies.

Early in 2013, the United States' National Comprehensive Cancer Network (NCCN) published new guidelines for survivorship. These guidelines are targeted, however, at disease-free survivorship. Recognizing that patients with metastatic disease are also survivors is one of the challenges still facing the medical community, as is integrating survivorship care into daily clinical practice.

Current State of Awareness

With that presentation as a backdrop, the moderator then led the summit's experts in a discussion about how to improve the continuum of mCRC-related care, from awareness and diagnosis through treatment and follow-up. The discussion opened with participants offering their personal perspectives on their country's overall level of public awareness about mCRC screening.

Non-European countries:

- **Brazil** has universal government-funded health care, but approximately 30% of Brazilians also pay for private health insurance. Preventive screening for colorectal cancer is not done routinely within the government-funded system. Screening does occur more frequently among people who are privately insured, but there is no national campaign to raise awareness around this issue.
- In **Peru**, most people are not covered by health insurance, although about 20% of Peruvians have military or private health insurance. Government and military insurance do not promote routine colorectal cancer screening. People with private insurance are encouraged to be screened, but the insurance will pay for the screening only if cancer is found.
- **Japan** runs colorectal cancer awareness campaigns to encourage all people aged 40 and older to be screened. The recommended screening is an annual FOBT; patients who receive a positive result are then referred to a gastroenterologist for a colonoscopy. Less than 30% of people in the targeted age group participate in annual screening, however. Both awareness and compliance differ from region to region within Japan. Screening rates tend to be lower in metropolitan areas.
- In the **United States**, awareness about the importance of colorectal cancer screening has risen significantly in recent years, thanks in large part to campaigns sponsored by government and advocacy groups. Colonoscopy is the most common form of preventive screening. Private insurers are now required to reimburse for screening colonoscopies, a factor that has contributed to the rising screening rate. In 2010, the screening rate for colorectal cancer reached 65% among people aged 50 to 75 years.[47]

European countries:

In its guidelines for colorectal cancer screening, the European Commission recommends an annual FOBT for people aged 50 to 75 years, followed by a colonoscopy if the FOBT test returns positive, but the implementation of these recommendations is left to individual countries.

- In the **United Kingdom**, over fifty percent of people in the targeted age group respond to a free FOBT screening invitation each year. In 2012, the U.K. government ran a television ad campaign that was effective in raising awareness about colorectal cancer. Surveys have found that older Britains are reluctant to participant in FOBT colorectal cancer screening for many reasons, some mistakenly believe they are not at risk, while others find screening "too messy" or embarrassing. To address this a new Fecal Immunochemical Test (FIT) test is being rolled out to simplify the process and potentially attract more people to take up the screening invitation.
- In 2012, **Ireland** rolled out a national colorectal cancer screening program for people aged 60 and older. Screening (including a colonoscopy) is free, but there is no widespread awareness of the program yet.
- **Slovenia** has had a colorectal cancer screening program for the past five years. It follows the European Commission's recommendations (annual FOBT with a colonoscopy follow-up, if needed). Awareness of the disease is dramatically better today than it was 15 years ago, when more than 75% of CRC in Slovenians was being diagnosed at stage III and stage IV.
- In **Hungary**, an organized colorectal cancer screening program has yet to be established. Regular FOBT screening is not done. Some private gastroenterology clinics do screening, but colonoscopies are generally performed only on patients with symptoms. This lack of screening is

in marked contrast to the country's very active and two-decade-old breast-cancer screening program.

- In **Poland**, colorectal cancer screening by colonoscopy is funded in full by the country's Ministry of Health, which has instigated a continous quality-control programme of screening to ensure better expediture of limited funds. Despite full access to the screening program, timely diagnostic colonoscopy screening rates among the population remains suboptimal. Poland is currently in the midst of initiating an invitation screening strategy to improve the situation.
- In **Spain**, population based screening program for colorectal cancer is organized on a regional basis using the same target for all of the country (patients aged 50-69 for biennial FOBT). Currently, 8 regions have initiated the implementation of the screening programs, covering about 20% of the Spanish population. Awareness about the disease also varies from region to region.
- Screening programs in **Belgium** are conducted along a north-south divide. In the French-speaking south, a population-based program for colorectal cancer screening involving a mailed invitation and FOBT kit was initiated in 2009. The participation rate was disappointing, reaching only 10% of the population. Health officials are now considering expanding the program to include the even-easier-to-use FIT kit. In Belgium's Dutch-speaking north, a pilot study in 2009 including 20,000 people obtained a 44% participation rate using FIT. On October 1st, 2013, a population based screening program will be rolled out. All fecal blood tests and follow-up colonoscopies are free in Belgium.
- **Germany** has a nationwide colorectal cancer awareness campaign that receives significant funding support from a large private foundation and a screening program that is covered by health insurance companies. Individuals are encouraged to receive a colonoscopy at age 55. In 2013, the program adopted an invitation strategy.

Mapping the Survivorship Continuum

The moderator next asked the summit's participants to map and discuss the various stages of the survivorship continuum. What are the common experiences that patients and clinicians have at each point on the continuum of mCRC care? What issues arise during those experiences for the disease's various stakeholders, especially patients, caregivers, and clinicians? A summary of that discussion follows.

Stage 1: Awareness

Most patients are diagnosed with colorectal cancer because they had symptoms that led to a colonoscopy or they underwent some kind of preventive screening (FOBT, sigmoidoscopy, or colonoscopy) that found the cancer. Less frequently, colorectal cancer is discovered when patients undergo a computed tomography (CT) or other type of imaging scan for an unrelated illness. The scan may reveal lesions, perhaps in the liver or lungs, which, after a biopsy, are traced back to a primary tumor in the colon.

Many patients appear in their general practitioner's office with symptoms (such as a change in bowel habits, weakness or fatigue, or persistent abdominal discomfort) that can lead to a diagnosis. But such symptoms usually do not indicate colorectal cancer, so general practitioners have a tough job deciding which patients who present with such symptoms should be referred for a colonoscopy. Younger adults with colorectal cancer are particularly at risk for not receiving such a referral. General practitioners need better training and more effective algorithms for evaluating symptoms associated with the disease. In addition, colorectal cancer awareness campaigns should target younger as well as older adults.

Stage 2: Diagnosis and Referral

For the patient, a diagnosis of mCRC is an emotional as well as a medical emergency. Information received at diagnosis, including about treatment options, is difficult for many patients to immediately absorb; thus, all information should be personalized and customized to address each patient's specific situation and needs. It's important to have a medical oncologist involved early in the treatment process. A multi-disciplinary approach is also crucial, to ensure that the decision about treatment is not biased by the professional preference of the treating physician. Ideally, all patients with mCRC would be referred to a multi-disciplinary tumor board immediately after diagnosis, and these boards would

meet at least weekly to discuss the patient's treatment options and progress. The percentage of mCRC patients who are currently referred to a tumor board varies widely, from country to country, from region to region within each country, and even from hospital to hospital.

Stage 3: Treatment

With the advent of anti-angiogenic drugs, the landscape of mCRC treatment has changed significantly, and it continues to do so as new single and combination therapies emerge. Indeed, chemotherapy regimens are often out of date by the time the clinical trials on biologic drugs get published. All this change has made treatment decisions highly complex, and although practice guidelines exist, they do not always provide clear direction for clinicians and their patients. They also vary from one country or region of the world to another. The United States' NCCN guidelines, for example, offer many different valid treatment options—a factor that has led some medical experts, particularly those in Europe, to criticize the guidelines for being too broad. Other experts, however, vigorously defend the NCCN guidelines, noting that many oncologists want more leeway to tailor treatment to individual patients.

One of the reasons for the wide range of treatment options is the lack of clinical trials that provide a clear head-to-head comparison of the available drugs and treatment protocols. The lack of this information is one of the reasons health ministries have made different decisions about which of the new anti-angiogenic drugs patients will have access to in their countries. Figure 4 indicates which anti-angiogenic drugs are approved and/or covered by national health insurance in the various countries represented at the summit.

Shaping the Next Generation of mCRC Leaders

After discussing the various continuum-of-care stages and challenges facing mCRC patients and their clinicians, the summit's participants turned to the future to discuss who might lead the way in implementing the needed changes to the pathway that they had just identified. They also talked about the importance of recruiting patient-advocates as well as physicians and researchers for leadership roles. The discussion focused on two questions: 1) What are the key attributes of opinion leaders in this field? 2) How can those individuals be cultivated and encouraged to take on leadership roles?

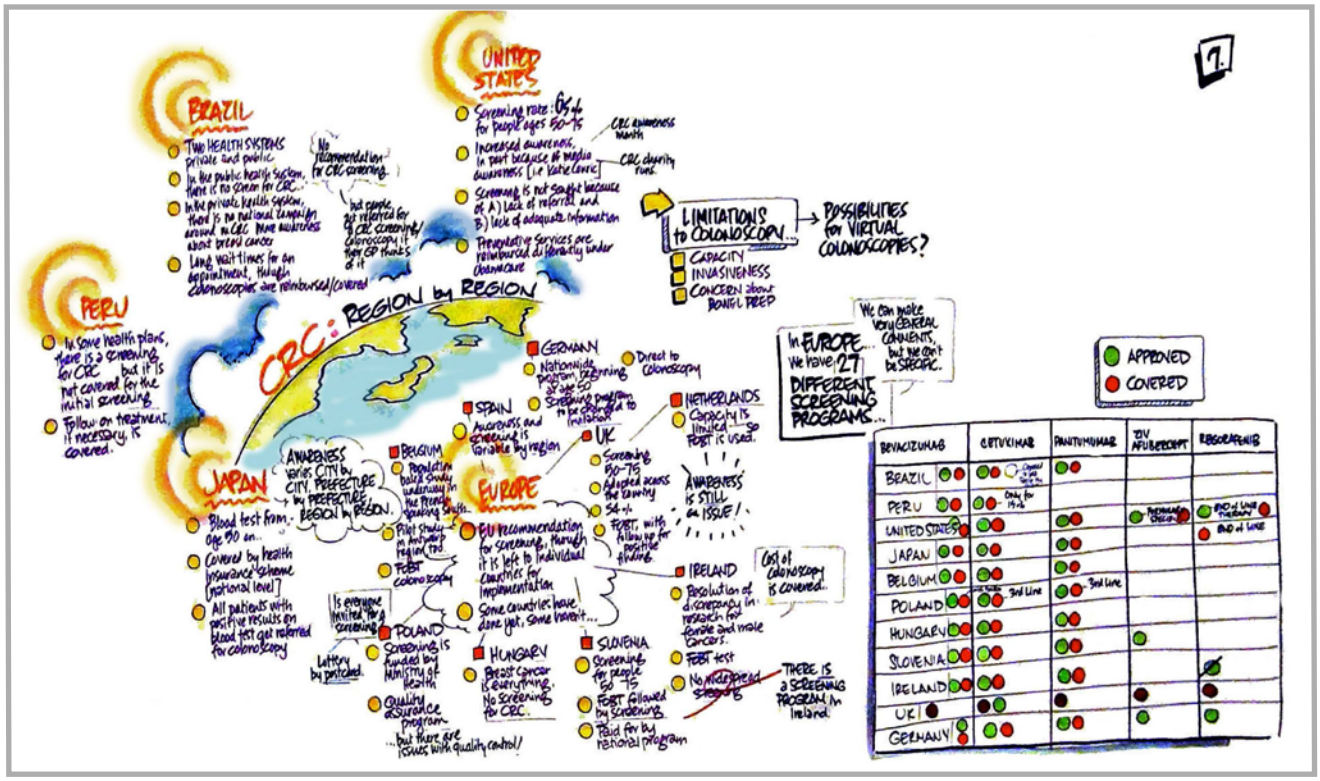

Figure 4. *Graphical representation: This chart indicates which anti-angiogenic drugs are approved and/or covered by national health insurance in the various countries represented at the summit.*

Key Attributes of mCRC Leaders

The summit participants agreed that a variety of personal and professional characteristics are needed by the next generation of mCRC leaders if they are going to successfully move the field forward through advocacy, policymaking, and research. Opinion leaders should have the ability to be independent and unbiased, with full transparency of industrial ties. They should have "a fire in their belly" about their particular area of expertise, but also be willing to put aside professional bias when it conflicts with scientific evidence. Opinion leaders should also be thoughtful about all aspects of mCRC and willing to take a multi-disciplinary approach to solving problems. In addition, they should be knowledgeable in clinical and basic science research—in other words, "real students of the disease." But they must exhibit compassion for patients and not just interest in the disease. That's one reason why it's important to recruit leaders from private practice as well as from academic research laboratories. Being media-savvy and having strong communication skills are also necessary, as is having a solid understanding of the political landscape of health care.

Patient-advocacy leaders need to have attributes similar to those of clinician-leaders, the summit participants agreed. Because they need to be able to represent data and issues related to mCRC accurately, clearly, and without exaggeration, good communication and organization skills are particularly useful. They also need to be good collaborators, as they must work with many different kinds of stakeholders. It's particularly important that they work well with clinicians, who can give their advocacy work the "gravitas" government officials may demand before they consent to making changes in policy.

Developing mCRC Leaders

To develop the next generation of mCRC opinion leaders, the summit participants recommended that current leaders serve as mentors, advising promising clinicians, researchers, patients, and caregivers on how to make presentations, conduct research, organize events, work on teams, interact with the media, and perform other leadership tasks in the field. Programs, both formal and informal, for training future leaders about the workings of healthcare systems, including the politics surrounding the systems, are also needed. Examples for how to go about developing mCRC leaders—and greater public awareness of the disease—can be found in the history of two other health-related activist movements: HIV/AIDS and breast cancer. Early on, both movements nurtured multiple leaders who were not only passionate about their cause, but who also became very knowledgeable about medicine, healthcare systems, media, and politics. Collaboration was also key to their success.

Figure 5. *The Expert Summit discussed the characteristics that are needed by the next generation of mCRC leaders.*

'Tipping Points' and 'Game Changers'

In the final segment of the summit's discussion, the experts focused on identifying and discussing mCRC-related "tipping points" and "game changers." The moderator explained that "tipping points" are things that are occurring in the field of mCRC that are ultimately unsustainable and therefore must eventually come to an end. "Game changers," on the other hand, are things that will be very important to the mCRC field in the future and, therefore, must commence at some point, perhaps soon.

The summit's participants identified the following mCRC-related "tipping points" and "game changers." The asterisked (*****) items are those chosen by the participants as the ones that have (or will have) the biggest impact on the field.

'Tipping Points' (things existing today that will be unsustainable in the future)

- A lack of public awareness about colorectal cancer*****
- Increasing public adoption of unhealthy lifestyles that are associated with an increased incidence of the disease*****
- The current system of funding research, including its rising costs*****
- Duplication and fragmentation of mCRC research*****
- Cost of developing effective diagnostic tests*****
- Clinical trials that don't respect the molecular subtype of the tumor*****
- Shortage of oncologists
- The escalating costs associated with the diagnosis and treatment of mCRC
- Lack of meaningful evidence-based comparative studies about mCRC treatment protocols
- Reliance by clinicians on industry-sponsored funds for clinical research
- Inappropriate pre-clinical research tools (e.g., animal models, cell lines)
- Inequality of access to health care
- Perception by society that mCRC is a terminal condition

'Game Changers" (things not yet occurring that will be very important in the future)

- Global access to all mCRC drugs*****
- Curative molecular therapies for cancer*****
- Therapies that can be used across cancer types*****
- Meaningful comparative effectiveness research on mCRC treatments*****
- Better scientific understanding of how lifestyle factors influence disease and survivorship*****
- Greater public awareness of healthful lifestyles that lower the risk of colorectal cancer*****
- Patients and clinicians, rather than payers, decide on treatment drug*****
- A multi-disciplinary approach to mCRC treatment and survivorship care
- A simplified and streamlined regulatory process
- Use of patient-derived xenograph animal models in clinical trials
- Dramatic increase in media coverage of colorectal cancer
- The development of a vaccine for colorectal cancer
- The development of individualized targeted therapy based on patient's DNA
- Expanded research on the inflammation aspect of colorectal cancer (i.e., the role of gut flora)
- Development of more effective and less-invasive screening and diagnostic tests

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