Advancing Outcomes for the Treatment of Metastatic Colorectal Cancer

A Report Based on a U.S. Expert Summit for
Metastatic Colorectal Cancer Convened
in Washington, D.C., March 28-29, 2013

The Angiogenesis Foundation

Key Points

1. Colorectal cancer is the fourth most frequently diagnosed cancer and the second-leading cause of cancer deaths in the United States.

2. In 2013, more than 140,000 Americans will be diagnosed with colorectal cancer, and some 50,000 Americans will die from the disease.

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

4. Since the mid-1980s, both the incidence and mortality rates of colorectal cancer have decreased in the United States, mostly because of earlier diagnosis through screening, but also because of more sophisticated and effective methods of treatment.

5. New drugs developed during the past decade, particularly targeted anti-angiogenesis 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.

6. 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.

7. Many barriers exist, however, to ensuring that all Americans receive timely and optimal colorectal cancer screening and care. These barriers include:
    - An underfunded, misdirected, and fragmented national colorectal cancer research agenda
    - A national healthcare delivery system that is chaotic and difficult for both patients and medical practitioners to maneuver
    - A public that is often unaware or misinformed about colorectal cancer
    - The growing administrative burden on clinical care and clinical trials
    - Widespread scientific ignorance and illiteracy among the public and policymakers
    - No unified plan among colorectal cancer stakeholders (patients, practitioners, advocacy groups, and researchers) for raising awareness about the need for broader access to screening, state-of-the-art treatments, and greater funding of research

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

9. Overcoming these current challenges to the early diagnosis and effective treatment of colorectal cancer will require the concerted efforts of all U.S. 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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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. 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 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.[2]

Incidence and Mortality

Globally, colorectal cancer is the third most common cancer among men and the second most common among women.[3] It is most prevalent in developed regions of the world, where about 60% of cases are diagnosed. In the United States, colorectal cancer is the fourth most frequently diagnosed cancer, but the second-leading cause of cancer deaths. More than 140,000 Americans will be diagnosed with colorectal cancer in 2013 and some 50,000 will die from the disease, according to National Cancer Institute estimates.[4]

Yet, despite these high numbers, the U.S. incidence of colorectal cancer per 100,000 persons has decreased significantly in recent decades, from a high of 66.3 in 1985 to 40.5 in 2010.[5] Mortality rates have fallen as well. Since 1998, the overall U.S. colorectal cancer death rates have decreased by 2.8% per year in men and by 2.6% per year in women.[6] Those declining rates are largely attributed to earlier diagnosis through screening and more sophisticated and effective methods of treatment. Not all demographic populations have experienced the same benefits from these medical advances, however; this is particularly true for African Americans. In 2010, the colorectal cancer incidence rate was 20% higher and the mortality rate was 30% higher in African Americans than in whites.[5]

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 and stage of the cancer, treatment toxicities, and the patient's overall health.

The U.S. Food and Drug Administration (FDA) has approved nine drugs for the treatment of metastatic colorectal cancer, including five "targeted" therapies

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 FDA approved "targeted" therapies for the treatment of colorectal cancer.*

(see Table 1), which are drugs that target the specific genes, proteins, or other factors in the colon's tissue environment that are contributing 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-angiognesis 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 over 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 FDA approved the first anti-angiogenesis targeted therapy, bevacizumab (Avastin®), for first-line treatment of patients with mCRC.[7] A monoclonal antibody, bevacizumab targets and inhibits a natural protein called vascular endothelial growth factor A (VEGF-A), which stimulates new blood vessel formation. When given in combination with standard fluorouracil (5-FU) based chemotherapy, bevacizumab has been shown to extend patients' lives by about five months.[8] In 2013, the FDA also approved bevacizumab injections in combination with 5-FU based chemotherapy as a second-line treatment for patients whose metastatic disease progressed after a first-line bevacizumab-containing regimen.[9]

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[10] and panitumumab,[11] respectively, as a second-line therapy for patients with EGFR-expressing mCRC. In 2012, cetuximab was also approved for first-line mCRC treatment.[12] 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.[13] 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). In second-line therapy, ziv-aflibercept has been found to significantly, but modestly, improve the median overall survival of mCRC patients (13.5 months for FOLFIRI (5-FU, leucovorin, and irinotecan) and ziv-aflibercept versus 12.1 months for FOLFIRI and placebo).[14] 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 have a modest, yet significant, effect on median overall survival (6.4 months for regorafenib versus 5.0 months for placebo).[15]

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 is reaching a plateau, 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 thousands of Americans diagnosed each year with mCRC.

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*

The U.S. Expert Summit for Metastatic Colorectal Cancer

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 decided to assemble 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. on March 28-29, 2013. Leading mCRC practitioners and researchers, as well as patients, survivors, and patient-advocates identified, discussed, and achieved consensus on the role of early intervention and screening in preventing mCRC; on the need to develop more effective treatments, especially targeted therapies; and on the importance of advocating for greater and more efficient funding of research.

The event opened with two short presentations. One described the current status of mCRC, including what is known about its demographics, risk factors, and treatment options. The second summarized the promise—and challenges—of emerging therapies for mCRC. Under the direction of the moderator, the assembled experts spent the first day of the summit engaging in a series of discussions that defined where the field wants to be in terms of preventing, detecting, and treating colorectal cancer, and outlined the barriers 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, the participants focused on developing solutions to overcoming the barriers identified earlier. These sessions lay the foundation from which a research agenda emerged that could move the field toward the desired future state of mCRC prevention and treatment.

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 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 these groups work together to make sure that all people benefit from current and future advances in angiogenesis-based medicine.

To open the summit, two experts gave 15-minute presentations as background for the subsequent roundtable discussions. **Dr. Al B. Benson** of the Robert H. Lurie Cancer Center of Northwestern University described current knowledge about mCRC, including its demographics, risk factors, and treatment options. **Dr. Herbert Hurwitz** of the Duke University School of Medicine then discussed the promise of emerging therapies for mCRC and the associated challenges currently facing researchers and clinicians.

The Scope of the Problem

Epidemiology

The average person in the United States has a 5% to 6% lifetime risk of developing colorectal cancer.[16] In 2009, an estimated 147,000 cases of colorectal cancer were diagnosed in the United States, and 49,900 individuals died from the disease.[3] African Americans have the highest risk for colorectal cancer, and Asian Americans and Native Americans have the lowest. Globally, colorectal cancer is the third most common cancer, with about 1.2 million cases diagnosed each year. Incidence rates vary by country.[17] The highest incidence rates are found in developed regions of the world, such as Australia, Europe, and North America, while the lowest rates are found in Africa and South-Central Asia. As countries become more developed, the incidence of colorectal cancer rises.

More than 50% of people in the United States present with stage 2 or stage 3 disease, and 20% present with metastatic disease.[18] Even among cured subsets of patients, there is a tremendous variation in five-year survivorship, a factor that needs to be considered in the design of clinical trials.

Risk Factors: Environmental, Genetic, and Epigenetic

Several factors are associated with an increased risk for colorectal cancer: family history, inflammatory bowel disease (IBD), diabetes, obesity, alcohol use, smoking, and a Western-style diet (one high in fat, sugar, refined grains, and red meat). Other factors are associated with a decreased risk: early screening, exercise, the use of aspirin, post-menopausal estrogen, vitamin D, and calcium. Still other factors may help reduce risk, including the use of cholesterol-lowering statins and the consumption of a diet that contains high quantities of fruits, vegetables, and fiber.

While diet and lifestyle are strongly associated with an increased risk of developing colorectal cancer, only a few studies have investigated whether these factors affect disease recurrence, survival, and tolerance to chemotherapy among patients with the disease. Some research has shown that a higher intake of Western diet after treatment for stage 3 colorectal cancer is associated with a greater risk of disease recurrence or death.[19] Other studies have shown that both higher pre-diagnosis plasma levels of vitamin D and regular aspirin use are associated with improved outcomes in patients with advanced colorectal disease.[20,21,22] A high

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

body mass index (BMI) and a lack of physical exercise are also associated with both the development of colorectal cancer and poorer outcomes.[23]

Some 70% to 75% of colorectal cancer can be attributed to sporadic disease in which there is no apparent predisposing cause.[24] About 5% of the disease is associated with highly penetrant inherited gene mutations, such as hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome.[2] The remaining 20% to 30% of inherited colorectal cancer is not well understood. Several pathways have been identified in the adenoma-carcinoma sequence. Most colorectal cancer arises through the chromosomal instability (CIN) pathway, which involves the loss or gain of large portions of chromosomes during cell division.[25] A second pathway for colorectal cancer is microsatellite instability (MSI). It occurs when there is a DNA mismatch in the repair pathway of cells; as a result, the number of repeated sequences of DNA (microsatellites) becomes different than the number that originally occurred when the DNA was inherited.[26] A third pathway involves inflammatory bowel disease (IBD); persons with IBD have a 20-fold increase risk of developing colorectal cancer.[27] More recently, scientists have identified serrated polyps (epithelial polyps with serrated architecture) as a developmental pathway for colorectal cancer. In certain groups of patients, such polyps carry substantial increased risk for the disease.[28] Scientists are studying all these genetic and epigenetic pathways to help determine why some patients respond better to specific treatments and, thus, have better outcomes.

Current Treatment Directions

Many different treatment options, especially anti-angiogenesis therapies, have significantly increased mCRC survival in recent years. Yet, along with the improved median survival rates, the new therapies also present patients with an increased risk of acute and chronic treatment-related toxicities. As a reflection of all these factors, clinicians now use the term continuum of care to describe the delivery of treatment to patients with the disease. The treatment algorithm for the management of mCRC is complex and evolving. It includes, for example, neoadjuvant, adjuvant, and/or "conversion" therapy (chemotherapy administered with the goal of making unresectable or borderline resectable cancer that has metastasized to the liver resectable). It also includes a line of therapies that may differ after each progression of the disease. Advanced colorectal cancer is increasingly being recognized as a disease that requires strategic and individualized care that focuses on quality of life and functional outcomes as well as extension of life.[29,30]

Emerging Therapies and New Research Directions

No one-size-fits-all therapy exists for the treatment of mCRC. Nor do researchers and clinicians agree about which endpoints matter most or to which patients. The findings from several recent studies, summarized below, are helping scientists unravel the complexities of mCRC and are leading to a better understanding of how to use current therapies more effectively and where to direct future research efforts. These findings also illustrate, however, the need to develop more individualized targeted treatments:

- The results of the multi-center phase III TRIBE clinical trial were reported early in 2013.[31] For the study, 508 Italian patients with unresectable metastatic colorectal cancer were randomized into two treatment groups. One group received bevacizumab plus FOLFIRI; the other received bevacizumab plus FOLFOXIRI (FOLFIRI plus oxaliplatin). Median progression-free survival at follow-up of 26.6 months was 12.2 months in the FOLFOXIRI plus bevacizumab arm of the study compared with 9.7 months in the FOLFIRI plus bevacizumab arm. The FOLFOXIRI-plus-bevacizumab combination also increased the response rate from 53% to 64%. Despite this significant increase in response, the increased toxicity of the FOLFOXIRI-plus-bevacizumab treatment (higher incidence of diarrhea, mouth sores, and infections), limits its use for only certain patients.

- The results of the randomized phase III AVEX clinical trial were also reported early in 2013.[32] This study compared bevacizumab plus capecitabine with capecitabine alone as a first-line treatment for elderly mCRC patients (median age: 76). This was the first phase III study to assess the effectiveness of a targeted therapy in an older population with mCRC. Patients in this age group are typically underrepresented in clinical trials, despite the fact that nine out of 10 patients with mCRC are at least 50 years old. Some 280 patients from 10 countries participated in the AVEX trial. Median progression-free survival was 9.1 months in the combination arm of the study compared to 5.1 months in the monotherapy arm. Median overall survival also tended to be higher in the combination arm (20.7 months versus 16.8 months), but that longer survival was not considered statistically significant. The combination arm of the study reported a higher incidence of adverse effects (59% versus 44.1%).

A comparison of the TRIBE and AVEX study results indicate that adding more chemotherapy does not equate to longer survival.

- In January 2013, the FDA approved bevacizumab in combination with chemotherapy (fluoropyrimidine-based irinotecan or oxaliplatin chemotherapy) for the second-line treatment of mCRC. This approval was based on data from the recent multi-center phase III study known as ML 18147.[33] In this study, 820 patients with unresectable mCRC that had progressed after initial treatment were randomized to second-line treatment of bevacizumab plus chemotherapy or chemotherapy alone. Which chemotherapy (fluropyrimidine-irinotecan or fluoripyrimidine-oxaliplatin) a patient in the combination arm received depended on his or her first-line treatment. Median overall survival was 11.2 months for bevacizumab plus chemotherapy compared to 9.8 months for chemotherapy alone. Median progression-free survival was 5.7 months in the bevacizumab arm compared with 4.1 months in patients receiving chemotherapy alone. No significant difference was found in the response rate. Adverse effects, including bleeding, gastrointestinal perforation, and blood clots, were more common among patients in the combination arm of the study.

- In August 2012, the FDA approved ziv-aflibercept in combination with FOLFIRI for the second-line treatment of patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing treatment regimen, with or without bevacizumab. This approval was based on the results of the multi-center, phase III VELOUR clinical trial.[14] For this study, 1,226 patients were randomly assigned to be treated with either ziv-aflibercept plus FOLFIRI or FOLFIRI alone. Patients in the combination arm of the study lived for one month longer than those given FOLFIRI plus placebo (13.5 months versus 12 months). Median progression-free survival was 6.9 months in the ziv-aflibercept arm and 4.7 months in the placebo arm. Adverse side effects, including fatigue, infection, diarrhea, high blood pressure, and blood clots, were more common in the ziv-aflibercept arm of the study and led to a higher discontinuation rate (26.6% of patients compared to 12.1% in the placebo group).

- In September 2012, the FDA approved regorafenib for mCRC patients who have progressed after previous treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and if KRAS wild type, with an anti-EGFR therapy. The agency based its approval on the CORRECT clinical trial, a study that involved 760 patients from 16 countries who were previously treated for mCRC.[15] The patients were randomized to receive either regorafenib or placebo in addition to best supportive care (treatments to help manage the disease's side effects and symptoms). Treatment continued until the patients' cancer progressed or side effects became unacceptable. Median overall survival was 6.4 months in the regorafenib group compared with 5.0 months in the placebo group. In addition, progression-free survival was modest but significantly improved in the regorafenib group (1.9 months versus 1.7 months). Adverse side effects in the regorafenib arm included fatigue, loss of appetite, hand-foot syndrome, diarrhea, mouth sores, infection, and high blood pressure. Rare but severe liver toxicity was also observed in the regorafenib arm of the study.

Many additional treatments for mCRC, including ones that target tumor angiogenesis, are on the horizon. Much more research is needed, however, to develop drugs that are more effective and less toxic to patients. Of particular urgency is the development of validated biomarkers that would identify which patients are most likely to have a positive response to these treatments.

Improvements in screening technologies and advances in anti-angiogenic therapies have made a remarkable difference in the lives of people with colorectal cancer. Still, as participants in the U.S. Expert Summit for Metastatic Colorectal Cancer acknowledged, much more needs to be done to increase screening access, develop effective treatments, and expand basic and clinical research.

The Desired Future State of mCRC

The moderator opened this segment of the summit by asking participants to discuss a key question: As leading mCRC practitioners, researchers, and patient-advocates, what would a patient-centered system of mCRC treatment and care look like in the United States if that system could become completely successful?

From the Perspective of the Patient

The participants agreed that patients want strong support that begins at the moment of diagnosis and continues through treatment and follow-up care. From the onset, they want a multidisciplinary team of medical professionals to help them develop a clear and individualized treatment plan, one that is effective but has the minimum level of toxicity and side effects. The plan should "work for me;" in other words, it should target not only the specific patient's disease, but also reflect the patient's values and desired treatment goals. In addition, patients want someone, preferably other than their oncologist, to spend the necessary time to help them "navigate" in an unhurried way through their treatment's complicated pathway of care.

The summit participants also stressed that easy-to-understand, reliable, and timely information about mCRC is crucial for patients. They want to be told about all their available treatment options, including the side effects they should anticipate and the steps they can take to help minimize those adverse effects. They also want to know what they can do themselves in terms of diet and other lifestyle changes to enhance their treatment and to prevent recurrence or secondary cancers. In addition, patients want "full access" to all aspects of care that they may need, including social/psychological, rehabilitative, and dietary support; such care should be culturally appropriate as well. Finally, patients want to have open and non-judgmental communication with their medical practitioners.

From the Perspective of Caregivers

Caregivers, who may be spouses, close family members, or friends, are being increasingly expected to provide medical care in home settings, including complex care, such as the handling and monitoring of portable infusion pumps. Summit participants agreed that caregivers want training and support for these medical tasks; such support is particularly needed in minority and other underserved communities. Many caregivers also need psychological support—a trained psychologist or social worker to help them deal with the stress and isolation of caring for their loved one. Other forms of social/community support would help as well, such as paid time-off, assistance with health insurance issues, and a general societal recognition of the burden of caring for someone with a life-threatening illness.

From the Perspective of Medical Practitioners

Summit participants then discussed what a successful mCRC care system would look like from the point of view of physicians, nurses, and other medical practitioners. They agreed that a successful system would reimburse practitioners not just for the volume of patients they treat, but also for the quality of the care they provide to those patients. In addition, all patients would have equitable access to that quality care. Summit participants also agreed that better cross-communication among oncologists and other physicians treating patients with metastatic colorectal cancer is needed. Evidence-based treatment algorithms tailored to different "real-world" clinical scenarios would greatly improve this communication; the multi-disciplinary team could then customize those algorithms for individual patients, based on each patient's treatment preferences. Also needed is the development of more predictive tools for personalized medicine, especially biomarkers.

From the Perspective of Researchers

To better understand the pathogenesis of colorectal cancer and to create more effective and less toxic treatments, researchers need better animal and other pre-clinical models for metastatic disease, as well as standardized procedures for collecting and analyzing human tissue, summit participants pointed out. Clinical trial designs also need to be improved. Those improvements should include greater participation in the studies by underrepresented demographic groups, such as African Americans; more effective and less expensive tools for recording and analyzing patient-reported outcomes; a wider choice of targeted agents; and recruitment incentives for both patients and community oncologists. One participant noted that in the United Kingdom, mCRC patients are automatically screened for

participation in clinical trials; as a result, cancer patient enrollment in U.K. trials is much higher. In 2006, 14 percent of Britain's 32,000 cancer patients participated in clinical trials.[34] By contrast, a 2013 study found that 4.8 percent of U.S. patients with newly diagnosed colorectal cancer enroll in clinical trials.[35]

There is also an urgent need for more research of biomarkers for colorectal cancer risk assessment, early detection, and treatment prognosis. Of particular interest are molecular and biomarker studies of drug trial "outliers"—individual patients whose response to a specific drug is either strongly positive or strongly negative. Such research could lead researchers to the development of more effective treatments. There also needs to be more sharing of "hidden data." Researchers can often learn as much from negative data as they do from positive data, yet negative data are rarely published. It was pointed out that the European Medicines Agency (EMA), the drug regulator for the European Union, is expected to require the public release of all clinical trial data submitted by drug companies starting January 1, 2014.

Existing Barriers

With the desired future state of colorectal cancer in the United States 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:

- An underfunded, misdirected, and fragmented national mCRC research agenda
- A national healthcare delivery system that is chaotic and difficult for both patients and medical practitioners to maneuver
- A lack of public awareness about colorectal cancer
- The growing administrative burden on clinical care and clinical trials
- Widespread scientific ignorance and illiteracy among the public and policymakers
- No unified plan among colorectal cancer stakeholders (patients, practitioners, advocacy groups, and researchers) for raising awareness about the need for greater research and funding
- Limitations imposed by payers on mCRC treatments
- Payer reimbursement policies that discourage patients from seeking initial and/or follow-up screening colonoscopies
- Large and growing economic disparities among patients
- "Fractionalized" patient access to treatment, with little cross-communication or coordination among medical providers
- Unwillingness of the U.S. healthcare delivery system and society-at-large to prioritize the social and psychological support of patients and caregivers
- Lack of a clear and timely "pathway of care" for the patient
- Media-disseminated medical misinformation, including premature conclusions about clinical trial results
- The high cost of conducting pragmatic clinical trials
- The reliance on industry funding for clinical trials
- The politics of cancer research, including "identity" politics within the cancer-advocacy community
- A lack of clear communication between patients and their oncologists that results in misunderstanding about the patient's desired treatment outcomes
- The projected shortage of oncologists, including the lack of incentives for medical students to study oncology

With key barriers defined, the summit participants engaged in a discussion about how these barriers might be overcome. The discussion had three main focuses: 1) raising colorectal cancer awareness, 2) improving care pathways, and 3) expanding research efforts.

Raising Colorectal Cancer Awareness

Summit participants agreed that despite being a leading cause of cancer deaths, colorectal cancer has not grabbed the American public's attention as much as other life-threatening chronic diseases, such as diabetes, heart disease, and breast cancer. To improve the detection, diagnosis, and treatment of colorectal cancer, the summit participants focused on how to increase preventive screening rates and how to raise awareness of mCRC and its treatment.

Improving Colorectal Cancer Screening Rates

Although colorectal cancer can be almost always prevented with screening and is highly curable when detected early, the screening rates for CRC lag behind those for other cancers. In 2010, the U.S. screening rate for colorectal cancer was 58.6%, compared to 72.4% for breast cancer and 83.0% for cervical cancer.[36] Summit participants stressed the need for directed, targeted screening-awareness initiatives aimed at the public and policymakers. Such initiatives should focus on the benefits of screening rather than on its discomforts; it should also present the public with full information about all CRC-screening options (FOBT/FIT, flexible sigmoidoscopy, double-contrast barium enemas, colonoscopy, computer tomography colonography, and fecal DNA), so that individuals can choose the method or combination of methods that fits their needs and that ensures they will undergo screening.

It was noted that the CRC screening rates are considerably higher among individuals with private and government-sponsored (Medicare) health insurance, as most insurance plans help pay for colorectal cancer screening among persons aged 50 and older. Deductibles and co-pays for screening tests can be significant, however; that factor can deter even those individuals with insurance from having them done. Another major screening deterrent is the way in which some insurance companies reimburse for colonoscopies. A company may cover the cost of the procedure, but only if the results are negative. If cancer is found, the screening is then considered therapeutic, and the patient is expected to pay all or part of the cost of the screening. In addition, once a person is diagnosed with colorectal cancer, a company may consider all future colonoscopy screenings therapeutic, and thus deductibles and co-pays are charged to the patient. Such policies discourage patient adherence to screening schedules. It was noted that under a provision in the Affordable Care Act (ACA), which is scheduled to go into effect in 2014, all new

Figure 2. *Graphical representation of the panelists' discussion on solutions to improving disease state awareness*

health insurance plans must cover colorectal screening without charging a deductible or co-pay, although only those procedures that have received a high rating by the United States Preventive Services Task Force (FOBT, flexible sigmoidoscopy, and colonoscopy) are included in that coverage.

The summit participants stressed that efforts must be undertaken to lower out-of-pocket screening costs for patients if colorectal cancer screening rates are to be improved. In addition, greater funding is needed to develop less invasive, less expensive, and less time-consuming screening technologies. Including preparation, a colonoscopy is at least a two-day event, and it often requires taking time off from work—for both the patient and the family member or friend who must drive the patient to and from the procedure.

Initiatives to better educate payers and policymakers about the economic benefits of colorectal cancer screening should also be undertaken, according to the summit participants. Although it requires a significant net investment by governments and insurance companies, colorectal cancer screening is cost effective, particularly given the rising costs of chemotherapy.[37] A 2002 meta-analysis, for example, found that the cost-effectiveness of common single or multiple screening strategies (FOBT, flexible sigmoidoscopy, or colonoscopy) was between $10,000 and $25,000 per life-year when compared with no screening.[38] The economic benefit of virtual colonoscopy (computer tomography colonography) is less clear; summit participants agreed that research on the cost-effectiveness of that technology is needed.

Colorectal screening also needs to be built automatically into patient scheduling systems once a patient reaches age 50, the summit participants stressed. Primary care physicians can currently order a mammography screening for their patients, but they can't order a colonoscopy. Instead, the patient must set up a consultation with a gastroenterologist who then, in turn, schedules the colonoscopy. Summit participants agreed that this system should be less complicated. In addition, the system should provide primary care physicians with incentives that encourage spending more time during well-patient visits to discuss colorectal cancer prevention and screening with their patients. The summit participants also discussed the need for medical schools to train more gastroenterologists to handle the future demand for screening, especially given the rapid aging of the U.S. population.

Increasing Awareness About mCRC

In addition to increasing awareness about colorectal cancer screening, public awareness campaigns should provide accurate, sharpened messages about metastatic disease, including its diagnosis, pathology, and treatments, according to the summit participants. Individuals tend to care about a disease only when they or someone they know has it, so mCRC messaging should be primarily aimed at patients and their families, friends, and caregivers. Misinterpretations of clinical trial data and inaccurate commentary about treatments in the media need to be quickly counteracted. In addition, efforts should be made to educate the media about the scientific process so that clinical trial results are presented without excessive hype or negativity.

Summit participants also conversed about the need to enroll more mCRC patients in clinical trials. Initiatives to raise awareness about the importance of clinical trials should focus not only on patients, they said, but also on community oncologists. To increase patient enrollment, both patients and practitioners need easier access to information about current trials; the access must also be timely, as any initiated treatment may result in a patient being denied acceptance into a particular trial. In addition, stage 4 colorectal cancer patients should be informed about the benefits of seeking multi-disciplinary team care from an academic cancer center.
Summit participants stressed that for both general and specific (i.e. mCRC) colorectal cancer awareness campaigns to be effective, all CRC stakeholders need to be well-organized and willing to work together.

Future Action Steps

Based on their discussion, summit participants concluded that the following actions could be undertaken to improve colorectal cancer awareness and screening rates:

- Develop directed, targeted, and coordinated initiatives that raise public awareness about CRC screening and the diagnosis and treatment of mCRC.
- Encourage programs and policies that lower out-of-pocket CRC screening costs for patients.
- Require insurers to fully cover screening costs regardless of diagnostic outcome.
- Provide greater funding for the development of less-invasive and less-expensive screening technologies.
- Educate payers and policymakers about the cost-effectiveness of CRC screening.
- Build automatic CRC screening into patient scheduling systems.
- Encourage medical schools to train more gastroenterologists.
- Develop initiatives to help raise the scientific literacy of the public, the media, and policymakers.
- Create programs and systems that encourage greater participation in mCRC-related clinical trials.

Improving Care Pathways

Over the past decade, new treatment strategies and regimens involving anti-angiogenesis agents have significantly improved outcomes for mCRC patients. Yet many patients do not have full and timely access to those and other treatment advances. In this segment of the summit, the experts discussed what interventions are needed to close those gaps and improve patient access to effective, evidence-based mCRC care.

Reducing Administrative Burdens

Administrative inefficiency and waste need to be overcome to improve patient care, summit participants agreed. In the current multi-payer healthcare system, the referral and reimbursement processes are long, complicated, and widely variable. A 2012 study by the Institute of Medicine found, for example, that $190 billion is wasted annually in the United States on unnecessary healthcare-related administrative costs.[39] The current complex and inefficient multi-payer system imposes more than an economic burden on the delivery of medical care in the U.S., however. The system can also result in less than optimal care for patients, either through delay or denial of treatment. This problem is a particular issue for patients with mCRC, partly due to the high cost associated with recent treatment advances. What is needed, summit participants agreed, is a healthcare system that minimizes administrative paperwork and delays while still ensuring that evidence-based treatments and procedures are followed.

Expanding Practice Guidelines

A discussion then ensued about the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for mCRC. It was agreed that the guidelines provide the best-available evidence-based standards of care, and are continually being updated to reflect new research findings. They are thus a useful starting point for treatment. The guidelines also offer patients a highly reliable, detailed, and easy-to-understand source of information; thus, efforts to distribute them more widely to patients and community oncologists should be encouraged. Summit participants noted, however, that the guidelines focus heavily on drug therapies, and, as a result, insurers often deny coverage for psychological, rehabilitative, nutritional, and other support therapies that offer patients a fully effective continuum of care. The experts agreed that expanding the practice guidelines to include supportive care would be beneficial to patients and caregivers.

Directing the Care Pathway

In addition to clearer and more accurate information about their disease, mCRC patients also need better guidance about "where to go" after their disease is diagnosed, summit participants agreed. Typically, patients are seen first by their primary care physician, who, based on their symptoms, refers them to a gastroenterologist for diagnosis. After diagnosis, patients are then sent to a surgeon for resection of the tumor and then to an oncologist for chemotherapy. The summit participants agreed that this pathway of care is not optimal. Patients should see the medical

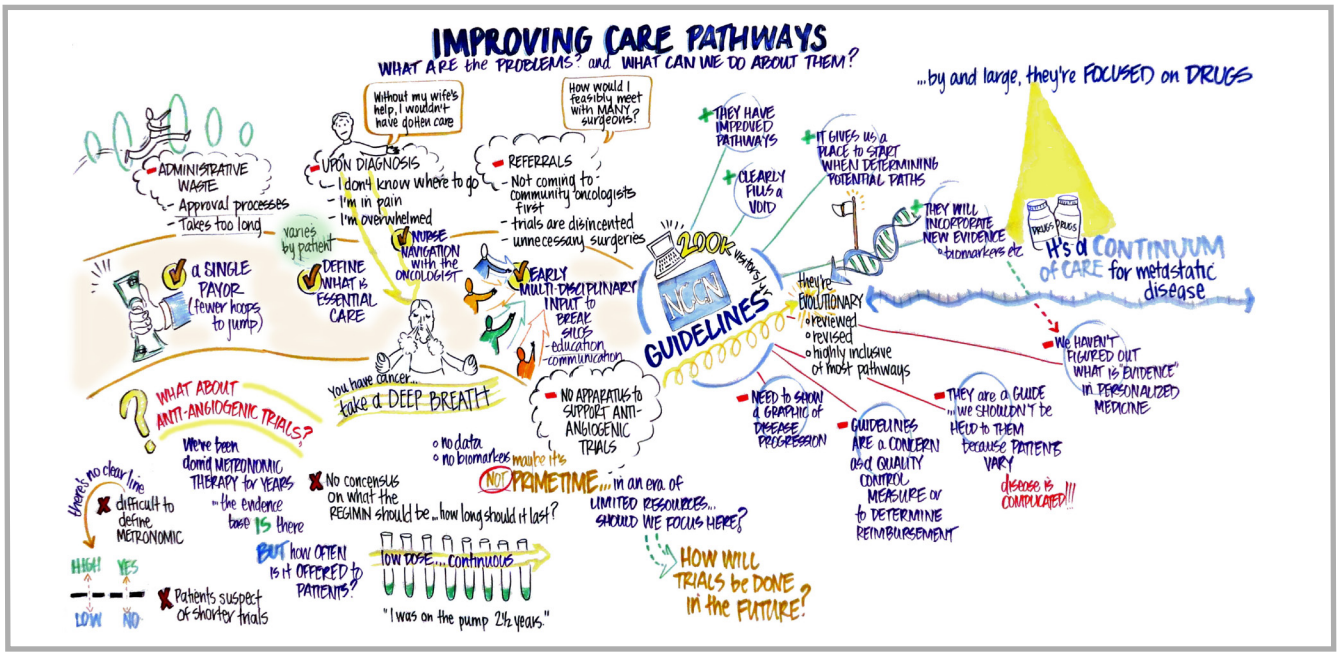

Figure 3. *Graphical representation of necessary improvements to care pathways defined by the Expert Summit*

oncologist before the surgeon, in part because not all mCRC patients need immediate surgery and because the initiation of any treatment may preclude the patient being accepted later into an appropriate clinical trial. In addition, each mCRC patient should be assigned the support of a full multidisciplinary medical team, and that team should be in place as quickly as possible after diagnosis. In most cases, the oncologist is best positioned to oversee and manage a patient's treatment plan, with input, of course, from all others on the patient's medical team. That treatment plan may or may not include enrollment in an appropriate clinical trial, but such trials should be discussed with the patient. Each patient should also be assigned a separate "navigator"—perhaps a trained nurse—who would work closely with the patient and the oncologist to ensure that the care received matches the values and desired treatment goals of the patient.

Future Action Steps

The summit discussion led to the following list of actions that could be taken to improve care pathways for patients diagnosed with mCRC.

- Develop new healthcare-system processes that reduce administrative inefficiency and waste.
- Expand insurer reimbursement policies to support individualized patient-treatment plans and appropriate support therapies (e.g., psychological, rehabilitative, nutritional).
- Create initiatives that ensure that all newly diagnosed mCRC patients are made aware of and have access to the NCCN clinical practice guidelines.
- Develop a standardized pathway of care that immediately assigns patients diagnosed with mCRC to a multidisciplinary medical team, including a medical oncologist who will oversee the management of their care.
- Promote treatment practices that assign each patient a specially trained "navigator" to help them understand and negotiate the treatment process.
- Create initiatives to encourage community oncologists to develop a multidisciplinary medical team approach to treating mCRC and to ensure they are aware of and have access to the NCCN clinical practice guidelines.

Expanding Research Efforts

Targeted drug therapies and other recent treatment advances are extending the lives of many individuals with colorectal cancer. Yet these therapies have significant limitations and toxicities, and do not help all patients with mCRC. The experts at the summit focused part of their conversation on the interventions that are needed to help the research community move forward more efficiently with the development of better treatments for the disease.

Increasing Funding

Summit participants agreed that mCRC research is currently underfunded. The federal government, in particular, needs to invest more heavily in both basic and clinical mCRC research, but persuading policymakers of that need in the current political climate is challenging. As a result, other funding sources, such as pharmaceutical companies and nonprofit private foundations, will need to take up the funding slack. Whether those sources are able or willing to do so, however, is unclear. It was pointed out that the pharmaceutical industry may be particularly unlikely to fund comparative-effectiveness or other types of studies that are not aimed specifically at bringing a new drug to market.

Increasing Patient Enrollment in Clinical Trials

Clinical trials not only perform a crucial role in the discovery of new cancer treatments, they also offer state-of-the-art treatment and care to the patients who participate in them. Yet, the number of mCRC patients who enroll in clinical trials is low, causing many studies to be cancelled before they begin. Summit participants discussed ways of increasing enrollment in clinical trials, including making sure patients are told of their clinical trial options before they commence other treatments and offering greater incentives to community oncologists to enroll patients into appropriate trials. The experts also discussed the strong need to increase the clinical trial enrollment of patients from demographic groups with high mCRC incidence and mortality rates, such as African Americans. Diversity in clinical trials is also important because some research suggests that different populations may have different responses to angiogenesis-related therapies.

Making More Effective Use of Current Knowledge

Summit participants reiterated the need for greater sharing of clinical trial data, including negative data. Researchers could then use that data to determine, for example, why some patients respond well to treatments and why others fail to respond at all. In addition, the experts talked about the urgent need for expanded research into how existing therapies could be used more effectively. The therapeutic potential of metronomic dosing schedules (low, long-term doses rather than periodic, "maximally tolerated" doses) was also discussed.

Future Action Steps

During the summit discussion, the experts identified several actions that would help expand both basic and clinical mCRC research efforts.

- Increase government and private funding for mCRC research.
- Design and promote initiatives that encourage patients, including those in high-risk demographic groups, to enroll in clinical trials.
- Create incentives for community oncologists to refer patients to clinical trials.
- Encourage the sharing of clinical trial data.
- Expand research that investigates how to optimize the use of existing therapies.

Value Analysis: Defining Successful Outcomes

After discussing possible solutions for increasing colorectal cancer awareness, improving care pathways, and expanding research, the summit's participants turned their attention to how they would define success regarding the outcomes of such efforts. The central concern of this discussion was how to determine the value of mCRC treatment. What balance of factors, such as extension of life, quality of life, and toxicity, should go into making that assessment?

Improving Outcome Measurements

Summit participants agreed that value in reference to cancer treatment is patient-dependent and, thus, has many dimensions. The value of a mCRC treatment can be measured by outcomes beyond extension of life, including functionality, qualify of life, mental health, and cost. For certain patients, the effects of a treatment on the patient's caregiver(s) may also be a factor in determining its value. Which outcomes hold more value does, of course, vary widely among patients. For example, some patients may define an acceptable quality-of-life outcome as being able to return to work, while others may define it much more narrowly.
The summit participants agreed that better patient-centered outcome measurement tools are needed. The

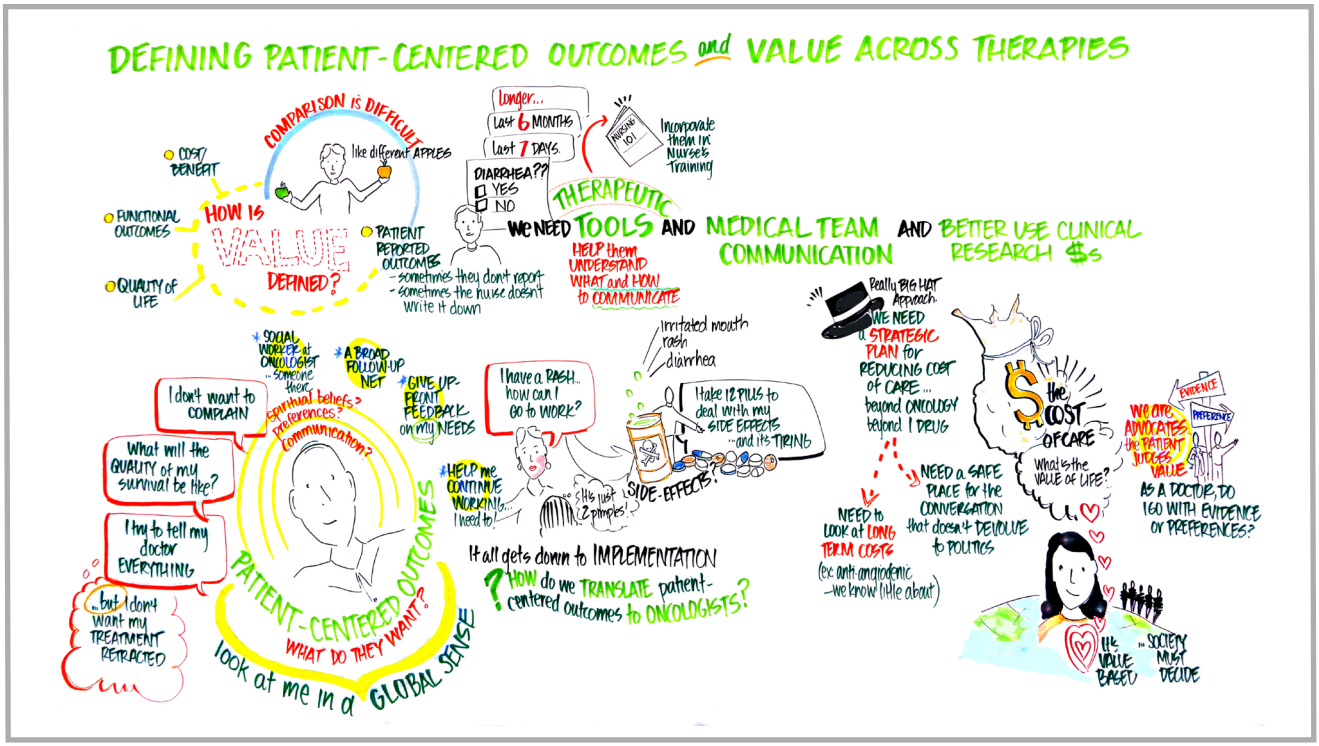

Figure 4. *Graphical representation of the panelists' discussion of how to determine the value of mCRC treatment*

current ones are often too blunt or too difficult to interpret, they said. Functional quality-of-life tools, for example, need to include social-psychological factors, such as the effects of treatment on the patient's mental health and family life. It was noted that the European Organization for Research and Treatment of Cancer has developed a 30-item, cancer-specific questionnaire (EORTC 30-QOL) for assessing quality of life in cancer patients; it has been shown to be effective in helping physicians assess quality-of-life changes in patients being treated for advanced disease.[40]

Improving Patient-Physician Communication

Summit participants also discussed the need for better communication between oncologists and their mCRC patients. When determining the value of a particular treatment, oncologists tend to focus primarily on life extension. Patients, however, may place equal or more value on other outcomes, such as how the treatment's side effects will affect their functionality, mental health, and quality of life. Out-of-pocket treatment costs, as well as lost wages, are also often a concern for patients. It was noted that a 2011 study involving almost 232,000 adult cancer patients found that cancer patients in the United States face significant financial stress due to treatment-related costs. Indeed, the study found that five years after diagnosis, cancer patients were four times more likely to declare bankruptcy than the general population. Colorectal cancer was ranked fifth among the cancers most likely to lead to bankruptcy, behind lung, thyroid, leukemia/lymphoma, and uterine cancers.[41] Summit participants agreed that oncologists should avoid imposing their own values on patients during the treatment-decision process. Instead, they should present each patient with full information about all of treatment options and let the patient determine the relative value of those options.

Improved patient-physician communication is also needed in regard to treatment side effects, the summit participants stressed. Time constraints during office visits can make it difficult for oncologists to fully capture the details or extent of a patient's adverse reactions to treatment; in addition, patients do not always report those reactions to physicians even when asked. The patients may not realize that an adverse reaction is the result of their treatment or they may worry that if they complain, they will be taken off treatment. Processes that improve patient-physician communication are needed, summit participants agreed. In addition, physicians need more effective tools for capturing and measuring treatment toxicities, particularly for the newer targeted therapies, whose long-term side effects are less understood.

Figure 5. *The Expert Summit discussed patient characteristics and values, emphasizing individual and categorical differences.*

Developing a Strong Research Agenda

One of the themes voiced throughout the summit was the need for more research. As a final item of business, the summit participants discussed colorectal cancer knowledge gaps and research priorities.

- **Basic research:** An enhanced understanding of the pathogenesis of colorectal cancer and how it metastasizes is urgently needed. Better animal models and other pre-clinical models for metastatic disease would help in this effort, as would a greater research focus on tumor stroma and on the microenvironment of the surrounding healthy tissue; the effect of anti-angiogenesis drugs occurs mostly in the capillary-rich stroma. Using the tools of DNA sequencing and genomic profiling, scientists have made progress in identifying whether or not certain treatments may be effective for particular patients, but much more research is needed in this area. The identification and validation of colorectal cancer biomarkers is also essential to making progress against this disease. Such biomarkers could then be used not only to determine a patient's risk profile, but also to identify which therapies might be most effective for that particular patient.

- **Prevention and diagnostic research:** A greater understanding of colorectal cancer risk factors, such as diet, exercise, body weight, and supplements, including nonsteroidal anti-inflammatory drugs (NSAIDs), on colorectal cancer risk and prevention, is needed. So is the development of more advanced computer-aided imaging techniques and screening technologies that are less invasive and less costly.

- **Treatment-effectiveness research:** More research is needed on angiogenesis inhibitors, including studies on combining the inhibitors with other treatments that target blood vessels. In addition, endogenous anti-angiogenesis agents need to be explored and translated into clinical use. The emphasis should not be only on developing new drugs, however; research investments should also be made on optimizing already approved drugs. What are the most advantageous dosing, scheduling, and sequencing of currently available treatments? And how can those optimal regimens be personalized? Also, what kind of inter-disciplinary medical team works most effectively with patients in terms of both overall survival and quality-of-life outcomes? Researchers also need to embark on fuller investigations of the effects of diet and lifestyle on patients following a CRC diagnosis, including the potential effects for therapeutic synergy or antagonism.

- **Disparities research:** Both the incidence and mortality rates for colorectal cancer in the United States are disproportionately high among African Americans[42] and persons with low socioeconomic status.[43] The reasons for these disparities need to be fully explored so that more effective prevention and treatment interventions for African Americans and other underserved populations can be implemented.

Research Gaps Requiring Action

From the discussion came the following summary list of knowledge/research issues that need to be addressed to achieve the desired patient-centered outcomes for colorectal cancer:

- A greater investment in basic CRC research is needed.
- More research into biomarkers, both to help develop risk profiles and tailor treatments to individual patients.
- Better animal models and other pre-clinical models for metastatic disease need to be developed.
- Endogenous anti-angiogenesis agents need to be researched.
- Current therapies need to be better understood, including their most effective potential for combination and sequential treatments.
- The effects of diet and other lifestyle factors on prevention and on treatment outcomes need to be studied.
- CRC incidence and mortality disparities among different racial and income populations need to be more fully understood.
- Outcome data must include quality-of-life as well as overall survival outcomes.
- Develop biomarker studies of patient "outliers."

The summit participants agreed that resolving these and other CRC-related knowledge gaps would require a unified effort of all interested stakeholders.

Summary of Future Action Steps

Over the course of the two-day summit, the assembled experts agreed that certain key actions should be taken to create a more patient-centered system of mCRC prevention, diagnosis, treatment, and care.

1. Improve awareness and early detection.

- Develop directed, targeted, and coordinated initiatives that raise public awareness about colorectal cancer screening, diagnosis, and treatment.
- Encourage programs and policies that lower out-of-pocket CRC screening costs for patients.
- Require insurers to fully cover screening costs regardless of diagnostic outcome.
- Provide greater funding for the development of less-invasive and less-expensive screening technologies.
- Educate payers and policymakers about the cost-effectiveness of CRC screening.
- Build automatic CRC screening into patient scheduling systems.
- Encourage medical schools to train more gastroenterologists.
- Develop initiatives to help raise the scientific literacy of the public, the media, and policymakers.

2. Improve access to effective treatment.

- Expand research that investigates how to optimize the use of existing therapies.
- Develop new healthcare-system processes that reduce administrative inefficiency and waste.
- Expand insurer reimbursement policies to support individualized patient-treatment plans and appropriate supportive therapies (e.g., psychological, rehabilitative, nutritional).
- Create initiatives that ensure that all newly diagnosed mCRC patients are made aware of and have access to the NCCN clinical practice guidelines.
- Develop a standardized pathway of care that immediately assigns patients diagnosed with mCRC to a multidisciplinary medical team, including a medical oncologist who will oversee the management of their care.
- Advocate for the development of better tools for capturing and measuring treatment toxicities.
- Advocate for initiatives that break down racial and socioeconomic treatment disparities.

Summary of Future Action Steps

3. Improve outcome value for stakeholders.

- Advocate for reimbursement systems that reward practitioners not just for the volume of patients they treat, but also for the quality of the care they provide to those patients.
- Advocate for training and practice processes that improve communication between oncologists and mCRC patients.
- Promote treatment practices that assign each patient a specially trained "navigator" to help them understand and negotiate the treatment process.
- Improve patient access to evidence-based lifestyle and behavioral adjuvant interventions.
- Advocate for the development of more efficient tools for measuring patient-valued outcomes.
- Improve the education of patients, families, and caregivers about possible adverse effects from treatment to help patients better manage their disease.

4. Improve basic and clinical research.

- Advocate for a greater private and public investment in basic mCRC research.
- Promote research into biomarkers and the development of animal and other pre-clinical models for metastatic disease.
- Promote research into the effects of diet and other lifestyle factors on the prevention and treatment of the disease.
- Promote research into the effects of psychological, rehabilitative, and other supportive therapies on treatment outcomes.
- Create programs and systems that encourage greater participation in mCRC-related clinical trials.
- Increase government and private funding for mCRC research.
- Design and promote initiatives that encourage patients, including those in high-risk demographic groups, to enroll in clinical trials.
- Create incentives for community oncologists to refer patients to clinical trials.
- Advocate for transparency in the sharing of clinical trial data.

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