FIGHT COLORECTAL CANCER®

PATH TO A CURE REPORT

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FIGHTING IN MEMORY OF

Dr. Tom Marsilje

Diagnosed at 40 | Stage IV CRC

P A T H

FIGHTING IN MEMORY OF

Victor Menoscal

Diagnosed with Stage IV CRC

FIGHTING IN MEMORY OF

Rose Hausmann

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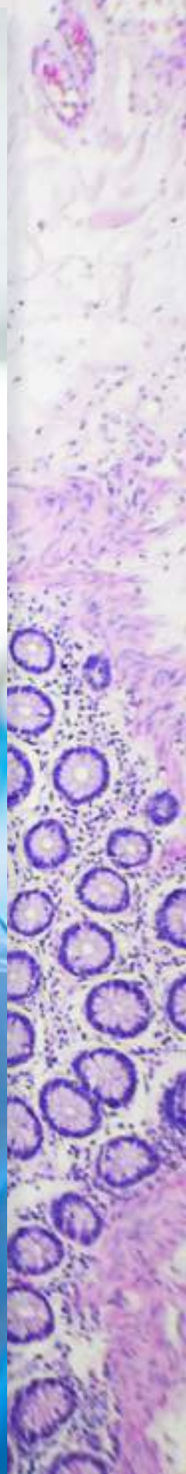
Betty Lewis

Diagnosed with CRC

FIGHTING IN MEMORY OF

John MacLeod

Diagnosed at 45 | Stage IV CRC



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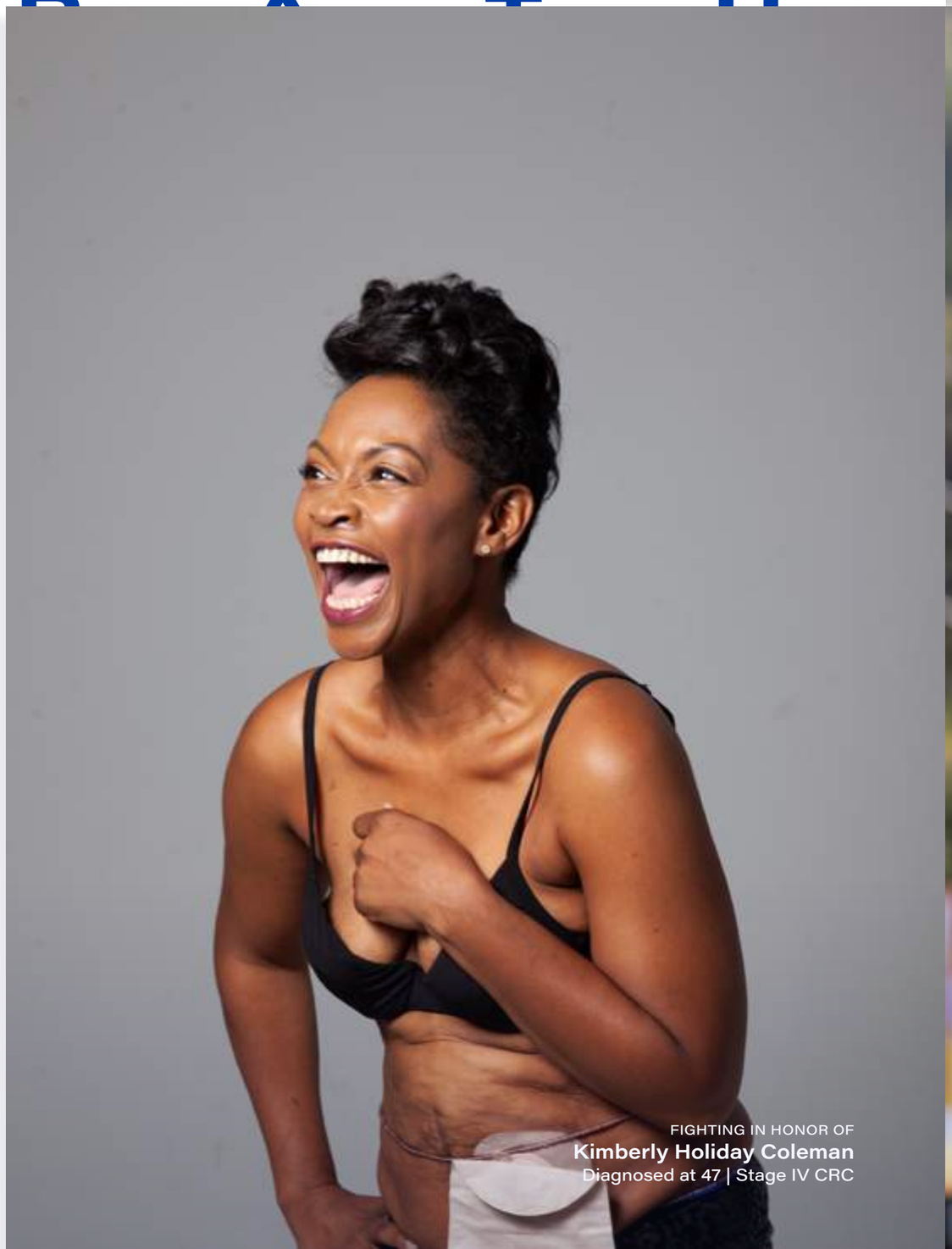

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Former US Congressman | CRC Survivor

P A T H

FIGHTING IN HONOR OF

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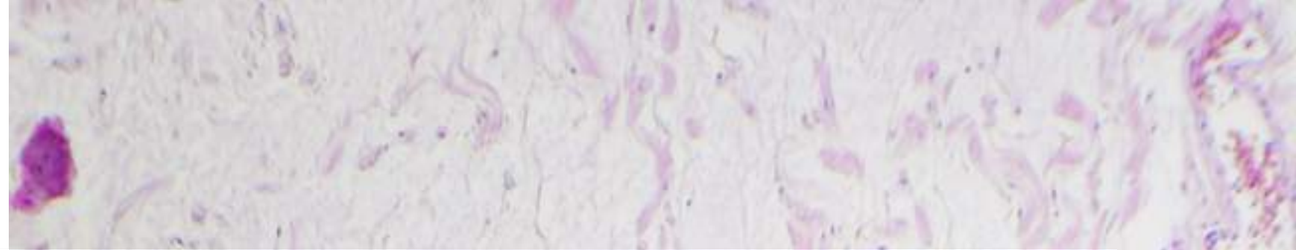


P A T H

We intentionally left this page devoid of faces because we cannot possibly include everyone impacted by colorectal cancer.

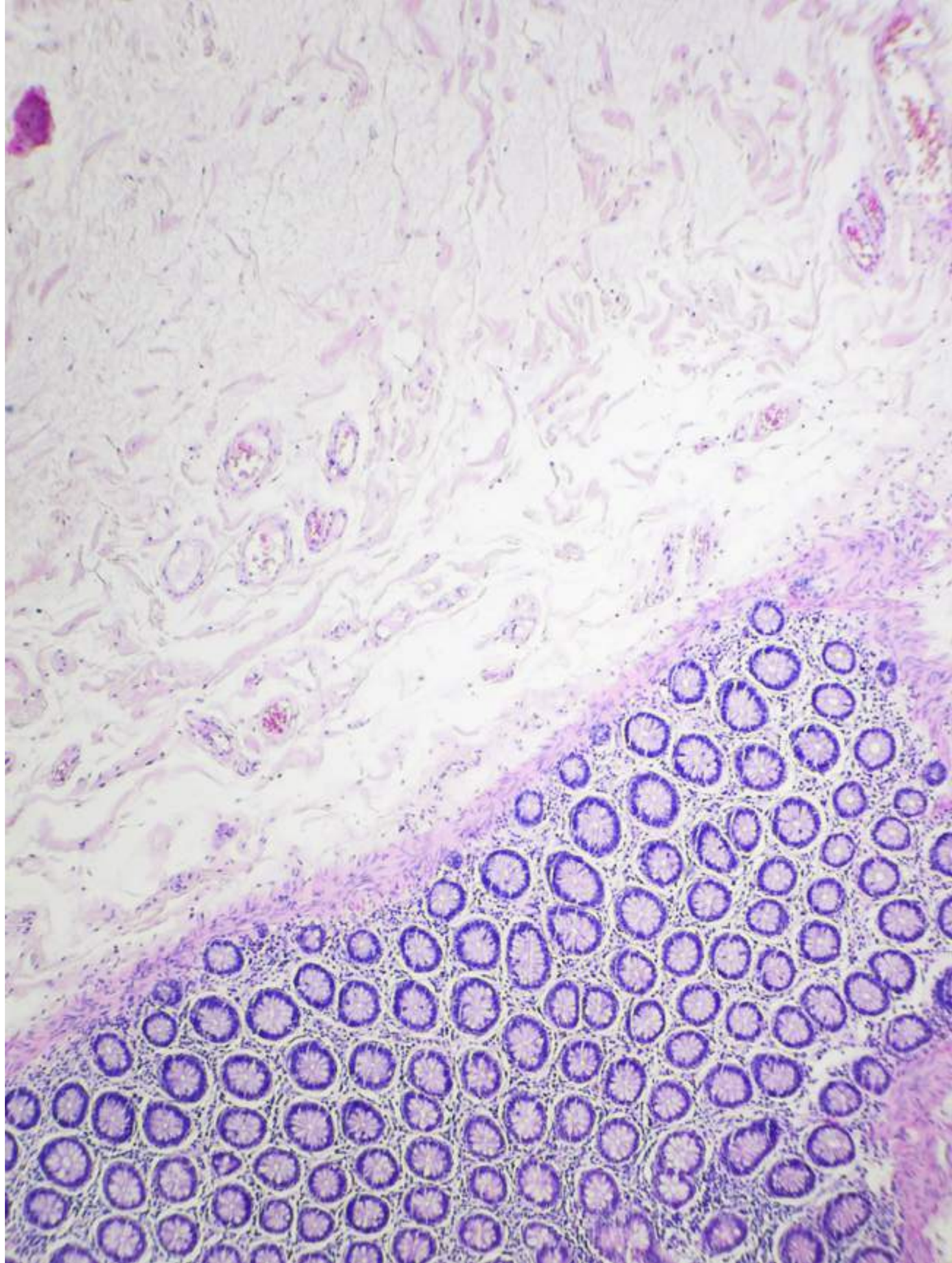
If you are the one fighting colorectal cancer, picture yourself on this page. This Path to a Cure report is for you. We hope it provides you with hope and the knowledge that we are fighting with you, researching, advocating, and pushing forward on a path to a cure every day.

For family, friends, and caregivers: Picture the face of your loved one, and copy it from your mind and heart onto this page. Close your eyes and imagine that person's smile, dimples, or maybe silly grim-lipped smile. Think of the way their eyes crinkle with happiness. This Path to a Cure report is dedicated in their honor or memory. This report is for them.

Colorectal cancer can't be wished away. But it can be fought—with science, wisdom, and support. That is the crux of this report: Taking actionable steps, locking arms, and forging ahead on a path to a cure together.

We dedicate this report to those who fight colorectal cancer every day of their lives. We dedicate this report to those who have lost their fight against colorectal cancer. We dedicate this report to those who don't even know that they may one day be impacted by colorectal cancer.

We dedicate this page and this report to funding and finding a path for a cure for colorectal cancer in our lifetime.



RELENTLESS CHAMPIONS *OF* HOPE *IN THE* FIGHT AGAINST *COLORECTAL CANCER*

Acknowledgments

Fight Colorectal Cancer (Fight CRC) expresses our deepest appreciation to all those who provided time, effort, and expertise to complete this report.

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All medically-reviewed content was written by Fight CRC. This report was made possible thanks to the support from a legacy gift given by board member Steve Depp. His legacy is never forgotten.

Dedication

This report is dedicated to every person impacted by colorectal cancer and in honor of all our dear friends lost to this disease. This effort is a commitment to saving lives and our pursuit for a cure.

In special dedication to:

* Dr. Dennis Ahnen
* Ron Doornink
* Kathy Dwyer-Keefe
* Julienne Gede-Edwards
* Rose Hausmann
* Andrea Kramer
* John MacLeod
* Dr. Tom Marsilje
* Joe Maschke
* Kate Murphy
* Nancy Roach

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FIGHTING IN HONOR OF

Kenny Toye
Diagnosed at 25 | Stage III CRC

STRATEGY & FRAMEWORK

OUR MISSION

INTRODUCTION AND BACKGROUND

STRATEGY & FRAMEWORK

We fight to cure colorectal cancer and serve as relentless champions of hope for all affected by this disease through informed patient support, impactful policy change, and breakthrough research endeavors.

It takes passionate, informed people to advocate. We believe this advocacy will lead to more research. We trust this research to lead to a cure.

Fight CRC is the leading patient advocacy group in colorectal cancer. We're known for our extremely loud (some will say, "feisty"), authoritative, enthusiastic, and fervent voices.

We have no plans of slowing down or stopping until we reach our goal: a cure.

FIGHTCRC.ORG

LET'S GET STARTED. OUR PATH TO A CURE.

INTRODUCTION AND BACKGROUND

Setting Priorities And Investing Wisely

Colorectal cancer is the second-leading cause of cancer death. By 2030, it's expected to become the first-leading cause of cancer death for those under 49. Yet, it's the cancer no one wants to talk about.

Fight CRC works to support and inform patients while driving policy change and breakthrough research. Together, with our community of patients, families, and caregivers, Fight CRC works relentlessly to bring attention to colorectal cancer and all the issues surrounding it.

Driven by this increased sense of urgency, Fight CRC is propelling science forward by ensuring patients' real needs are at the core of conversations.

The overall survival rate for people with colorectal cancer has not budged, and the treatment pipeline has stagnated. We need to re-evaluate how we look at overall survival and begin to look beyond only "stage of colorectal cancer." We need to adjust narrow goals of targeted therapies for specific demographics: We need to push the science.

We must be willing to meet emerging challenges in care and explore new ways to partner with and support the scientific and patient communities. It's time to innovate and implement more fearless approaches to fighting this disease. It's time to take risks on new ideas.

It's time to be a catalyst for change.

STRATEGY & FRAMEWORK

INTRODUCTION AND BACKGROUND

INTRODUCTION AND BACKGROUND

FIGHT COLORECTAL CANCER™

Path to a Cure

The Path to a Cure report is a professional, multidisciplinary publication, which seeks to summarize and communicate a plan for our community to rally around: pushing forward critical areas of research; care for patients; and policy, from early detection and prevention to survivorship.

The use of technical jargon and associated acronyms is avoided as much as possible. This report is not exhaustive and will be updated as our community takes critical steps forward.

The Path to a Cure report is broken down into four sections. Each section provides progress indicators, key messages, opportunities and challenges, and the voice of survivors.

Each indicator has a plan of action to ensure that all our partners, collaborators, and champions know how they can play a role in contributing to a path to a cure by:

* Creating awareness by helping identify preventable and unpreventable causes of colorectal cancer;
* Promoting the importance of screening so colorectal cancer is found early when it is most treatable with less invasive methods, while also advising people to be screened if showing signs and symptoms;
* Supporting ongoing research and advancements in innovative treatment options; and
* Addressing quality of life beyond diagnosis, treatment, and surgery.

1

BIOLOGY AND ETIOLOGY

PROGRESS INDICATOR

Applying What We Know from Biology and Hereditary Risk to Reduce Late-Stage Colorectal Cancer

2

PREVENTION AND EARLY DETECTION

PROGRESS INDICATOR

Advancing colorectal cancer prevention and early detection.

3

TREATMENT

PROGRESS INDICATOR

Expanding Treatment Strategies for Colorectal Cancer Patients, which have not progressed quickly enough over time.

4

SURVIVORSHIP AND RECURRENCE

PROGRESS INDICATOR

Address quality of life issues and preventive steps to avoid recurrence.

Together, we can provide cancer care for all.

Everyone has a role to play.

Set priorities

WHAT

Priorities established by Fight CRC Medical Advisory Board, key subject matter experts, and research advocates

WHO

All stakeholders

Host an Annual Dialogue

WHAT

Convene action planning with subject matter experts, agencies, and survivors

WHO

Curated list of stakeholders

Establish Criteria for Progress Indicators and Measure Each

WHAT

Identify resources, data collection, and clear baselines

WHO

Technical experts in the field

Update Stakeholders and Provide Outcome Reporting

WHAT

Collaborate with stakeholders to monitor impact

WHO

All stakeholders

Select Policy-Level Interventions

WHAT

Finalize and garner support for prioritized interventions

WHO

Policymakers and/or legislative and public health organizations

Put Pressure on Implementation

WHAT

Expedite implementation of progress indicators

WHO

Federal and state agencies, industry, funders, and advocacy organizations

INTRODUCTION AND BACKGROUND

Path to a Cure

GOAL:
Decrease late-stage disease, increase overall survival, decrease incidence of EAO

GOAL:
Decrease late-stage disease, increase overall survival, decrease incidence of EAO

BIOLOGY AND ETIOLOGY

OBJECTIVE 1
Further research the nature, biology, and implications of CRC throughout the continuum of age

OBJECTIVE 2
Research the role and impact of health disparities in those developing colorectal cancer

OBJECTIVE 3
Improve dissemination and implementation of evidence-based and population-based strategies for genetic and hereditary cancer

OBJECTIVE 4
Progress research and exploratory science to advance our knowledge of Lynch syndrome

PREVENTION AND EARLY DETECTION

OBJECTIVE 1
Improve dissemination and implementation of evidence-based CRC screening interventions for the average-risk population

OBJECTIVE 2
Improve dissemination and implementation of evidence-based CRC screening for the increased, high-risk, and symptomatic patients

OBJECTIVE 3
Further research of CRC screening uptake for those younger than 50 to reduce EAO CRC

OBJECTIVE 4
Research in minimally invasive strategies for preventive cancer

TREATMENT

OBJECTIVE 1
Increase clinical trial enrollment, particularly for late-stage disease, MSS, and EAO patients

OBJECTIVE 2
Increase biomarker and molecular testing (localized vs. metastatic)

OBJECTIVE 3
Design trials that are individualized-sequence therapies

OBJECTIVE 4
Strengthen infrastructure design and development to advance treatment and clinical care

OBJECTIVE 5
Increase federal funding for CRC research to achieve above

SURVIVORSHIP AND RECURRENCE

OBJECTIVE 1
Develop/research survivorship care delivery intervention and approaches which take into account the whole person

OBJECTIVE 2
Increase the capacity of health care delivery systems, primary care, public health, and health workforce to bridge needs of CRC patients post treatment

OBJECTIVE 3
Expand research efforts to improve and advance development of emerging and new technologies for early detection, screening and prevention of recurrence

THE IMPACT:
Equitable approaches, collective buy in, provider/patient education, informed policy efforts, more research dollars

THE IMPACT:
Equitable approaches, collective buy in, provider/patient education, informed policy efforts, more research dollars

1 BIOLOGY AND ETIOLOGY

PROGRESS INDICATOR

Applying what we know from biology and hereditary risk to reduce late-stage colorectal cancer

WHAT DO WE NEED TO FIGURE OUT?

- ETIOLOGY THROUGH AGE CONTINUUM (20s, 30s, 40s, 50s)
- HEALTH DISPARITIES AND HOT SPOTS

WHAT'S THE PLAN?

- Determine clinical symptomatology → Patient-level data extraction
- Establish common data research instruments, including environment → Review evidence-based tools and metrics
- Analyze tumor/biology/demographics, PROs through research registry → Create a centralized location

→ Collective buy in from the medical, research, advocacy, and policy communities

→ Increase research funding and advocate for stronger policy

→ Promising practices/evidence-based interventions and recommendations

→ Decrease incidence of CRC

The Tricky Stuff

The boxes in orange are complicated issues. We use short phrases but don't let this give you the impression this is easy. Keep reading!

2 PREVENTION AND EARLY DETECTION

PROGRESS INDICATOR

Advancing colorectal cancer prevention and early detection

WHAT DO WE NEED TO FIGURE OUT?

- INTEGRATED, WHOLE-PERSON CARE
- INCREASE SCREENING FOR HIGH-RISK AND THOSE WITH SYMPTOMS
- DO WE NEED TO SCREEN BEFORE 45?

WHAT'S THE PLAN?

- Determine preferred screening methods for 45-50
- Determine quality metrics
- Understand drivers to increase screening in primary care
- Examine increased incidence within subpopulations

→ Collective buy in from the medical, research, advocacy, and policy communities

→ Increase research funding and advocate for stronger policy

→ Promising practices/evidence-based interventions and recommendations

→ Decrease incidence of CRC

The Tricky Stuff

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INTRODUCTION AND BACKGROUND

3 TREATMENT

PROGRESS INDICATOR

Expanding treatment strategies for colorectal cancer patients, which have not progressed quickly enough over time

WHAT DO WE NEED TO FIGURE OUT?

- **INCREASE CLINICAL TRIAL ENROLLMENT**
  FOCUSING ON LATE-STAGE DISEASE, MICROSATELLITE STABLE, AND EAO CRC
- **INCREASE BIOMARKER TESTING**
  LOCALIZED VS. METASTATIC
- **DESIGN TRIALS THAT ARE INDIVIDUALIZED SEQUENCE THERAPIES**

WHAT'S THE PLAN?

- Patent and provider education and inclusion of social determinants of health, research advocates, and incentivization of patient recruitment into open trials
- Patent and provider education and stronger alignment with quality and accreditation measures through NCCN and CoC
- Integrate multidisciplinary teams, increase knowledge of ctDNA and tumor microenvironment, subgrouping by molecular phenotype, optimize treatment strategies (IO/microbiome)

Building infrastructure and inclusion of equitable approaches

Collective buy in from the medical, research, advocacy, and policy communities → Establish overall survival goal

Increase research funding and advocate for stronger policy

Increase overall survival

The Tricky Stuff

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4 SURVIVORSHIP AND RECURRENCE

PROGRESS INDICATOR

Address quality of life issues and preventive steps to avoid recurrence

WHAT DO WE NEED TO FIGURE OUT?

- **DEVELOP COLORECTAL CANCER SPECIFIC SURVIVORSHIP**
- **INCREASE CAPACITY FOR HEALTH CARE TEAMS AND SYSTEMS**
- **ADVANCE AND IMPROVE TECHNOLOGY TO PREVENT RECURRENCE**

WHAT'S THE PLAN?

- CoC consensus recommendations for screening
- Models of care
- Include research advocates
- Quality measures
- Methods of care delivery for telehealth model vs. in-person
- Educate PCPs
- Advocate with CDC for community-based services
- Understand utility of ctDNA tests to guide treatment decisions and monitor for recurrence
- Gather stronger data from patients to monitor recurrence and Identify high-risk patients with remaining microscopic disease to inform treatment

Policy expertise to create sustainable patient navigation services

Collective buy in from the medical, research, advocacy, and policy communities

Increase research funding and advocate for stronger policy

Improve patient clinical outcomes

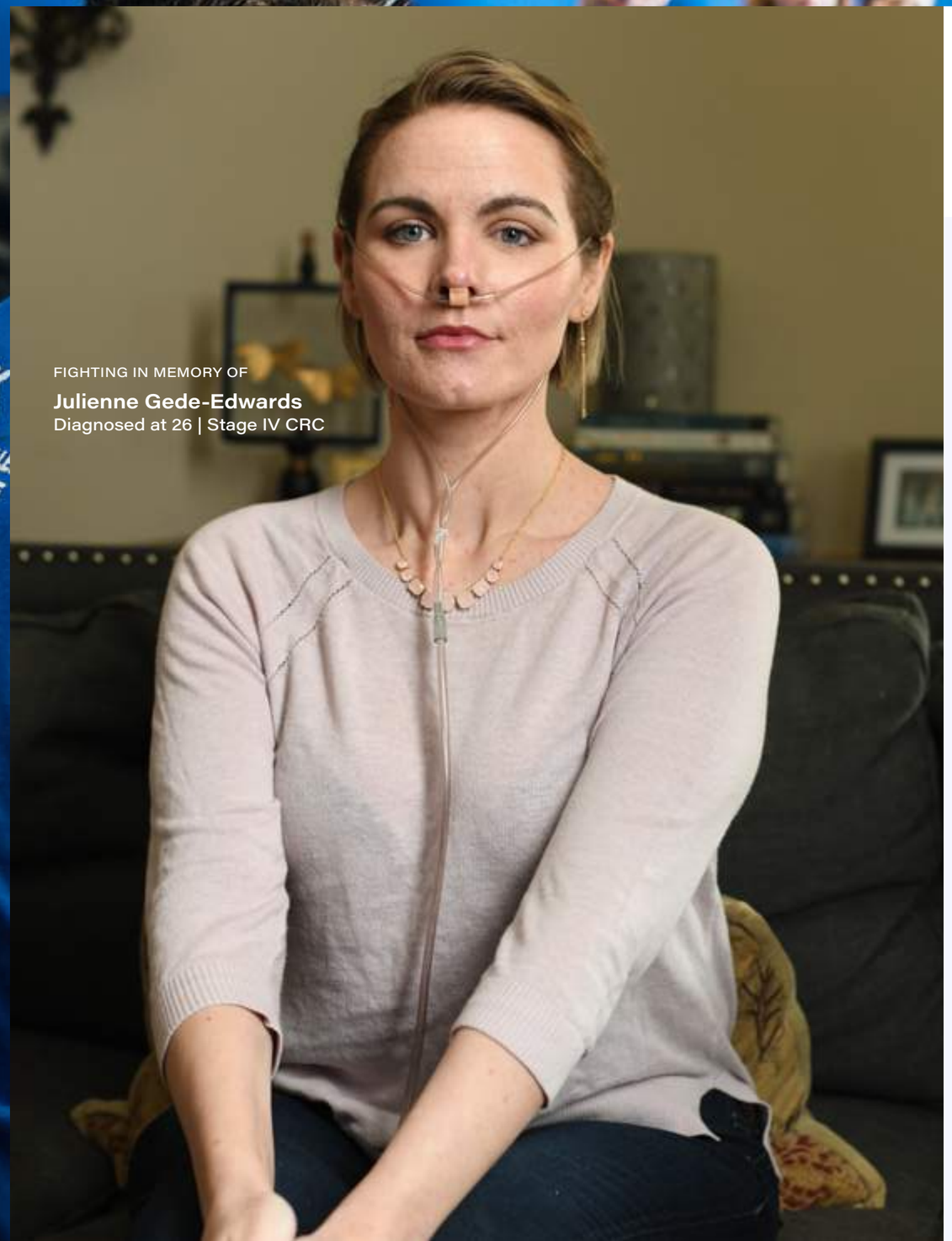
Better reimbursement of survivorship care

The Tricky Stuff

The boxes in orange are complicated issues. We use short phrases but don't let this give you the impression this is easy. Keep reading!

INTRODUCTION AND BACKGROUND

INTRODUCTION AND BACKGROUND



FIGHTING IN MEMORY OF

Julienne Gede-Edwards

Diagnosed at 26 | Stage IV CRC

Prevention Is The Biggest Opportunity

CRASH COURSE ON COLON AND RECTAL CANCERS

Colorectal cancer is one of the only preventable forms of cancer with a variety of screening options. Early removal of polyps during regular colonoscopy screenings can help prevent colorectal cancer

medical condition, likelihood of getting the test, resources available for testing, and follow-up.

New screening modalities are emerging, such as blood-based screening and the
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This trend lasted for
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* Patients on Medicare were more likely than patients on private insurance to report having difficulties affording food and basic supplies during this period of time.

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Prevention Is The Biggest Opportunity

Colorectal cancer refers to cancer that originates from either the colon or rectum. Colorectal cancer is the second deadliest cancer in the U.S. and worldwide, when women and men are combined. [1, 2] The American Cancer Society (ACS) estimates that in 2021, there will be over 149,000 newly diagnosed cases of colorectal cancer in the United States with 1.5 million survivors.

The World Health Organization (WHO) estimates 1.93 million cases of colorectal cancer were diagnosed worldwide in 2020, with 935,000 people dying from the disease. By 2030, it has been estimated that early-age onset colorectal cancer will be the leading cause of cancer-related deaths in people ages 20-49 years old. [3]

Colorectal cancer is thought to be caused by mutations, which are either inherited or acquired, in several different genes. For many patients, colorectal cancer starts as a polyp (an abnormal growth on the mucous membrane of the colon or rectum). The polyp may remain benign (or noncancerous) or become malignant (cancerous).

Several risk factors contribute to the development of colorectal cancer including age, race, personal disease history, family disease history, and lifestyle.

Colorectal cancer is one of the only preventable forms of cancer with a variety of screening options. Early removal of polyps during regular colonoscopy screenings can help prevent colorectal cancer

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WHAT WE'RE UP AGAINST

Prevention Is The Biggest Opportunity To Curb Colorectal Cancer

Colorectal cancer is one of the only preventable forms of cancer with a variety of screening options. Early removal of polyps during regular colonoscopy screenings can help prevent colorectal cancer.

However, there are a variety of recommended and approved stool-based testing options such as FIT/FOBT and stool DNA, as well as colonoscopy, virtual colonoscopy, and flexible sigmoidoscopy. [4]

There is no single "best test" for any person. Which test to use depends on preference, medical condition, likelihood of getting the test, resources available for testing, and follow-up.

New screening modalities are emerging, such as blood-based screening and the science that allows great opportunity but possible complexity for patients.

Primary prevention is also a big part of the equation, as well as knowing one's family history and monitoring of genetic and hereditary colorectal cancer.

COVID-19 Pandemic Complicates Screening

Before COVID-19, conveying the importance of getting screened for colorectal cancer was difficult enough.

However, COVID-19 compounded the issue as it became more difficult for in-person doctor visits, and overall patient concerns and anxiety about visiting their healthcare providers.

In addition, we faced a national crisis that required and forced hospital systems across the country to stop all preventive and elective services.

The pandemic has played an extreme role in creating further disparities related to colorectal cancer screening. In 2020, during the height of the COVID-19 pandemic, it is estimated that colorectal cancer screening declined by over 90% in March 2020 versus the same time period in 2019. This trend lasted for nearly four to six months. [5]

- Nearly 40% of colorectal cancer patients and caregivers reported disruptions in care, especially as it related to in-person visits and imaging. Of these, 25% said they did not know when their care would be rescheduled.
- Approximately 78% of colorectal cancer patients felt nervous, anxious, or on edge about being screened during the pandemic, and 57% reported they were concerned about contracting COVID-19 through the screening process.
- People living in rural areas were more likely to experience treatment disruptions compared to those who live in suburban or urban areas.
- Patients on Medicare were more likely than patients on private insurance to report having difficulties affording food and basic supplies during this period of time.

Based on Fight CRC research within the colorectal cancer community.

The combined impact of these factors pose dire implications and undo decades of progress. Over the next ten years, it is projected that there will be almost 10,000 more deaths from breast cancer and colorectal cancer. These deaths are the result from delayed screenings due to the COVID-19 pandemic. The number of excess deaths are most likely to peak in the next year or two. This analysis is conservative as it doesn't take into account the delays in treatment and access to care issues patients faced during the pandemic.

INTRODUCTION AND BACKGROUND

Current Treatment Options

The evolution of the genomic landscape through novel sequencing techniques has uncovered major clues about the key mechanisms behind the development of colorectal cancer. More importantly, this knowledge was used to develop and tailor state-of-the-art therapies in accordance with specific genetic key markers.

However, despite these discoveries, survival for patients suffering from metastatic colorectal cancer (mCRC) has remained quite grim, with some biomarkers, such as the RAS mutation, playing a major role in limiting the potential of therapeutic options.

Other treatment options, such as immunotherapy or anti-BRAF agents have proven effective only for a very small percentage of patients, having a very limited or even a non-existent contribution for the vast majority of patients. (6)

Constant refinement of advancement of treatment and the discovery of new ones are required to better understand the molecular intricacies behind the evolution of colorectal cancer.

However, a change in the mentality is beginning to prevail, with more professionals embracing the idea that individual biomarkers are as important to the diagnosis and treatment as the localization and histological aspect of the tumor. (7)

Colorectal Cancer Doesn't Discriminate

Health disparities are defined as health outcomes that are greater or less between populations defined by age, race/ethnicity, sex, and geographic region among others.

A number of health determinants (personal, social, economic, and environmental factors that influence health status) are thought to contribute to health disparities and fall into five broad categories including biology/genetics, individual behavior, health services, social factors, and policies.

These disparities are illustrated in Figure 0.13, which depicts incidence and mortality in several ethnic groups. Interventions aimed at remedying these disparities are ongoing and need to be expanded. (8)

(Table 1.1 and Table 1.2 show some of the specific areas related to what we know about differences by race/ethnicity for environment, health conditions, and tumor characteristics.)

Figure 0.1

Colorectal Cancer Treatment Approaches Based on Stage and Procedure Type

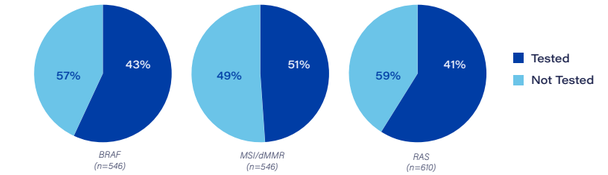
Colorectal Cancer Treatment Approaches Based on Stage and Procedure Type

STAGE	SURGERY	CHEMOTHERAPY/ BIOLOGICS	RADIATION
Stage 0	Endoscopic Resection	No	No
Stage I	Yes	No	No
Stage II	Yes	Yes, for rectal and high-risk colon cancers. FOLFOX or CapeOx	Yes, for rectal cancer. Given in tandem with 5-FU or Xeloda
Stage III	Yes	FOLFOX, CapeOx	Yes, for rectal cancer. Given in tandem with 5-FU or Xeloda
Stage IV	Yes, if the tumor is obstructive or blocking the bowel. Some patients become surgical candidates for liver, lung, or peritoneal surgery. Usually not, if the tumor is not blocking the bowel.	FOLFOX, FOLFOXIRI, or FOLFIRI plus Avastin or Erbitux or Vectibix or Zaltrap, Stivarga, Lonsurf Pembrolizumab for MSI-H, Encorafenib/Cetuximab for BRAF V600E, and Trastuzumab/ Lapatinib—Trastuzumab/ Pertuzumab—or Trastuzumab Deruxtecan for HER2.	Yes, for rectal cancer and in certain other cases. Interventional radiology for liver and lung metastases.

Adapted from Colorectal Cancer Alliance https://www.ccalliance.org/

Figure 0.2

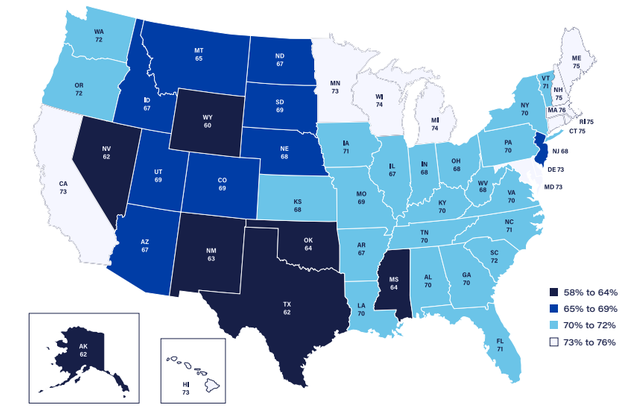
Patients With Metastatic Colon Cancer Who Received Guideline-Aligned Testing by Actionable Mutation



Narozniak, R. (2020, January 16). Molecular testing for colon cancer falls far short of the guidelines. OncLive. Retrieved November 4, 2021, from https://www.onclive.com/view/molecular-testing-for-colon-cancer-falls-far-short-of-the-guidelines.

Figure 0.3

Colorectal Cancer Screening Test Use* (%), Adults 50 and Older by State, 2018



*Blood stool test, sigmoidoscopy, or colonoscopy in the past one, five, and 10 years, respectively.
Note: Estimates are age-adjusted to the 2000 U.S. standard population and do not distinguish between examinations for screening and diagnosis.
Source: American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Atlanta: American Cancer Society, 2020.

Patients Are Getting Younger

By 2030, it has been estimated that early-age onset colorectal cancer will be the leading cause of cancer-related deaths in people ages 20-49 years old. [3]

Fortunately, the overall incidence and death rate from colorectal cancer has been dropping since the mid-1980s for those over the age of 50. Alarmingly, however, among those under age 50, both incidence and death rates have been rising since the mid-90s. [9]

People who develop early-age onset colorectal cancer are more likely to present with colorectal cancer in the distal colon or rectum, and to be diagnosed at advanced stages.

However, survival rates are similar between early-age onset colorectal cancer patients and patients that develop colorectal cancer over age 50. [10]

For all colorectal cancer patients combined, the five-year survival rate is approximately 90% for localized colorectal cancer, which accounts for about 38% of all patients. Survival rates drop to approximately 72% if the cancer has spread to surrounding areas including organs, tissues, and regional lymph nodes; and if the cancer has metastasized, the survival rate is approximately 14%. [11]

In May 2021, the United States Preventive Services Task Force (USPSTF) expanded their screening recommendations to begin screening at age 45 for average-risk individuals, a drop from the original recommended age of 50. [12]

If the recommended USPSTF screening guidelines are followed, estimates suggest that between 42 to 61 colorectal cancer cases per 1,000 adults screened would be prevented; and between 24 to 28 colorectal cancer deaths among 1,000 adults screened would be prevented. [12]

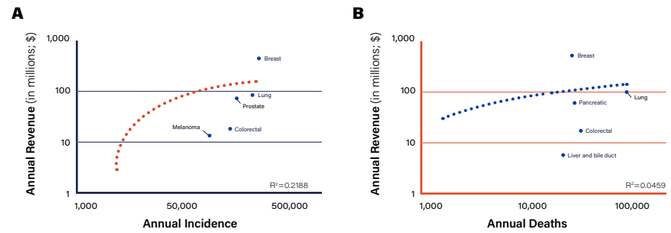
Money And Advocacy Matters

Compared to other cancers, including breast, leukemia, and lymphoma, colorectal cancer is generally underfunded relative to its incidence and mortality.

Prior research shows that little correlation exists between nonprofit funding and disease burden, and that funding levels for various cancer types are not equal. Increased non-governmental organization (NGO) spending on research and patient education aligns with higher annual revenue, whereas NGO spending on professional education and policy education has a low correlation with annual NGO revenue. [13]

Figure 0.4

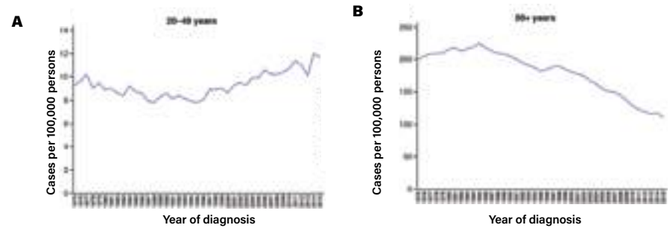
Scatter plots using logarithmic scales for annual revenue versus annual incidence and mortality for top 5 most common cancers (A) and top 5 most deadly cancers (B)



Adapted from: Kamath, S. D., Kircher, S. M., & Benson, A. B. (2019). Comparison of cancer burden and nonprofit organization funding reveals disparities in funding across cancer types. Journal of the National Comprehensive Cancer Network, 17(7), 849–854. https://doi.org/10.6004/jnccn.2018.7280

Figure 0.5

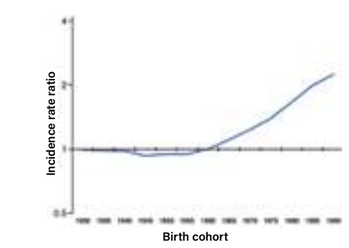
Incidence rates increased by 50% (from 1995-2015) in those ages 20-49 years and decreased by 50% from (1985-2015) in those ages ≥50.



Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database. Incidence - SEER 9 Regs Research Data with Delay-Adjustment, Malignant Only, Nov 2017 Sub (1975-2015) <Katrina/Rita population adjustment> - linked to county attributes - total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018.

Figure 0.6

Incidence rate ratios by birth cohort (1930-1990)

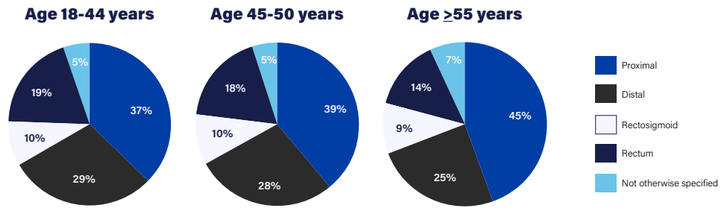


Murphy C.C., Singal A.G., Baron J.A., et al.
Decrease in incidence of young-onset colorectal cancer before recent increase.
Gastroenterology. 2018; 155: 1716-1719

Figure 0.7

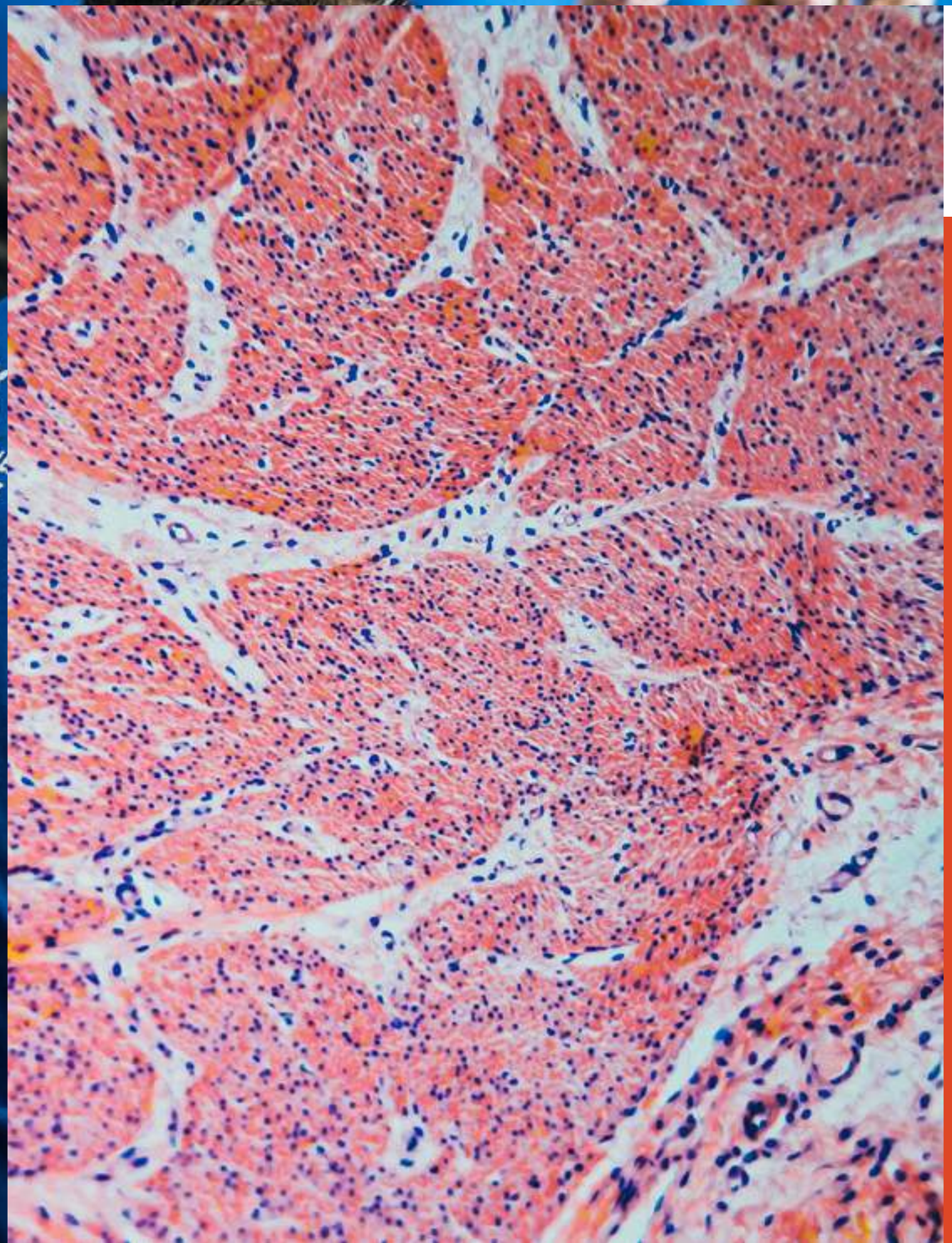
Trend in Colorectal Tumor Primary Location by Age —

Younger patients tend to have more distal colon and rectal primary cancers than older patients.



Adapted from: Weinberg, B. A., Marshall, J. L., & Salem, M. E. (2017, May 15). The growing challenge of young adults with colorectal cancer. Cancer Network. Retrieved November 4, 2021, from https://www.cancernetwork.com/view/growing-challenge-young-adults-colorectal-cancer.

INTRODUCTION AND BACKGROUND



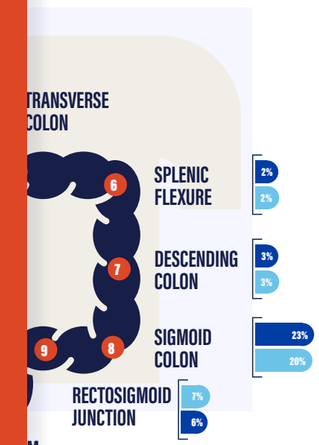
Colon *vs.* Rectal

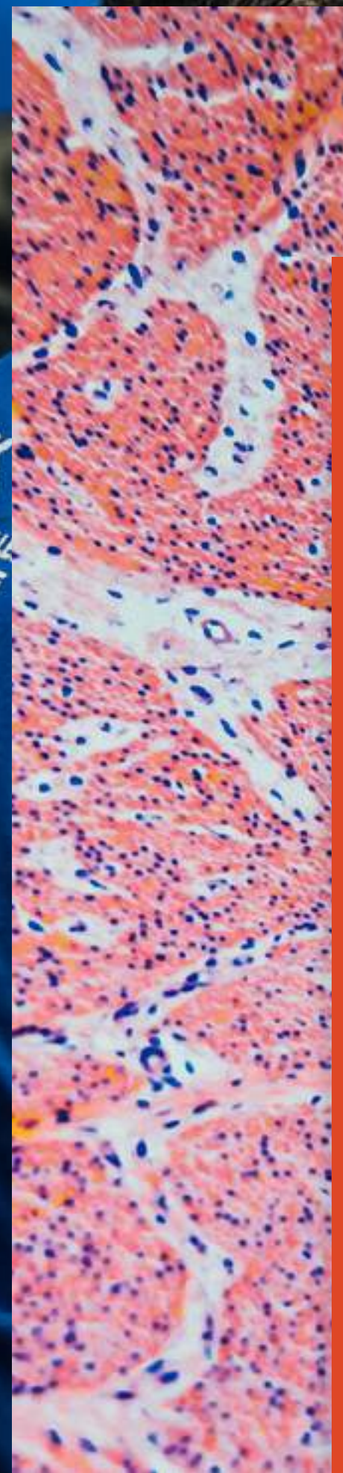
The colon is the largest part of the large intestine, extending from the cecum to the rectum. It is 5 feet long, and its function is to reabsorb

Although colorectal cancer is often portrayed as one cancer, colon cancer and rectal cancer treatment options may be ely different.

atient with colon ht undergo surgery hemotherapy; a n rectal cancer might emotherapy, then efore ever having t even more unique n cancer on the right colon may have mifications than colon the left side of the therapy responses mpletely different.

THIS IS WHERE IT GETS TRICKY.





COLORECTAL CANCER IS MORE THAN ONE SINGLE DISEASE.

Colorectal cancer refers to the colon or the rectum. There is a lot of distinction even among the types of cancers that develop through the anatomy of colon and rectum.

Essentially colorectal cancer is a unique and individual experience, and it's necessary to think beyond generic approaches or "bucketing" to expand and accelerate the prevention and treatment of colorectal cancer.

Colon *vs.* Rectal

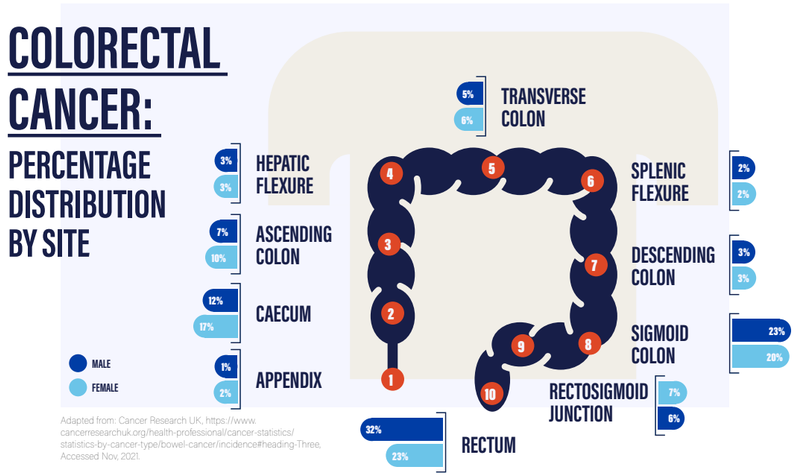
The colon is the largest part of the large intestine, extending from the cecum to the rectum. It is 5 feet long, and its function is to reabsorb water from digested food and concentrate solid waste material, known as stool. The colon is made of several sections. The ascending colon travels up the right side of the abdomen; the transverse colon goes across the abdomen; and the descending colon drops down on the left side of the abdomen. [14]

The rectum is a part of the lower gastrointestinal (GI) tract. The rectum is a continuation of the sigmoid colon and connects to the anus. The rectum follows the shape of the sacrum and ends in an expanded section called the rectal ampulla, where stool is stored before its release via the anal canal.

Although colorectal cancer is often portrayed as one cancer, colon cancer and rectal cancer treatment options may be completely different.

Where a patient with colon cancer might undergo surgery first, then chemotherapy; a person with rectal cancer might undergo chemotherapy, then radiation before ever having surgery. But even more unique is that colon cancer on the right side of the colon may have different ramifications than colon cancer on the left side of the colon, and therapy responses may be completely different.

Figure 0.8



Adapted from: Cancer Research UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-Three, Accessed Nov, 2021.

Left Side *vs.* Right Side Colorectal Cancer

The right-side colorectal cancer (RCRC) tumors arise from the ascending colon and proximal two-thirds of the transverse colon. The left-side colorectal cancer (LCRC) tumors arise from the descending and sigmoid colon and distal one-third of the transverse colon.

Besides the difference in their origins, these tumors exhibit different histology.

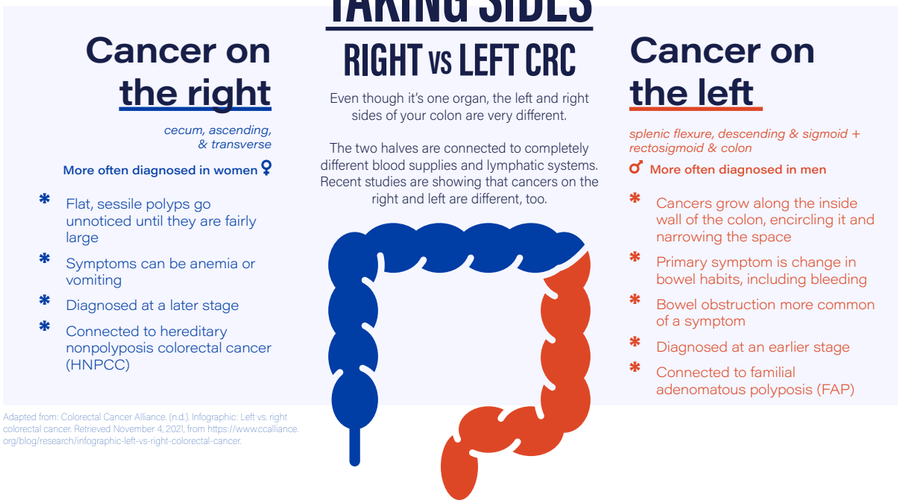
Colorectal cancer is not a single type of tumor. The manner in which it develops depends on the anatomical location of the tumor.

Tumors in the proximal colon (right side) and distal colon (left side) exhibit different molecular characteristics and histology. [15]

In right-sided tumors, mutations in the DNA mismatch repair (MMR) pathway are commonly observed, and these tumors generally have a flat histology. In left-sided tumors, chromosomal instability pathway-related mutations, such as KRAS, APC, PIK3CA, and p53 mutations are observed. These tumors demonstrate polypoid-like morphology. [15]

Therapy responses are different between left-side and right-side tumors. [15]

Figure 0.9



Adapted from: Colorectal Cancer Alliance. (n.d.). Infographic: Left vs. right colorectal cancer. Retrieved November 4, 2021, from https://www.ccalliance.org/blog/research/infographic-left-vs-right-colorectal-cancer.

Younger *vs.* Older

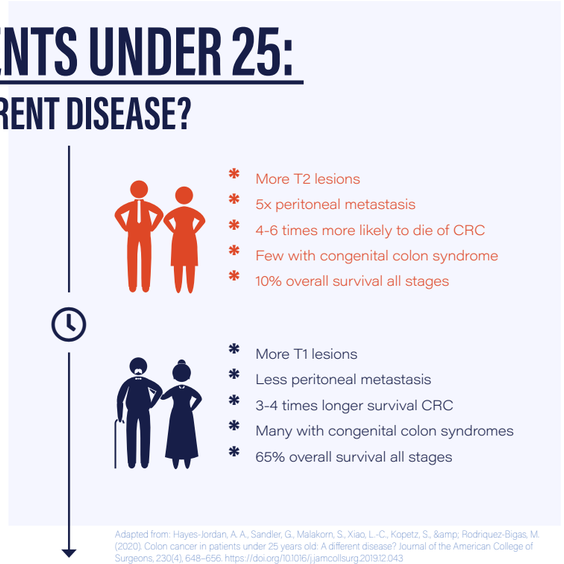
The research is still emerging, but it is believed that younger colorectal cancer patients (less than 50 years old) without relevant predisposing risk factors have more advanced stages of disease, more aggressive histopathologic characteristics, and poorer prognosis when compared with older patients (over age 50). [16]

Data suggests that differences may exist among age spans possibly due to differences in biology.

For example, colorectal cancer presents differently between adolescents and people in their 20s, and it also presents differently between people in their 20s and people in their 40s. [17]

There are differences in the type of cancer occurring, and because early-age onset colorectal cancer is a more recent (though alarming) trend, data is still emerging.

Figure 0.11



Adapted from: Hayes-Jordan, A. A., Sandler, G., Malakorn, S., Xiao, L.-C., Kopetz, S., & Rodriquez-Bigas, M. (2020). Colon cancer in patients under 25 years old: A different disease? Journal of the American College of Surgeons, 230(4), 648–656. https://doi.org/10.1016/j.jamcollsurg.2019.12.043

Biomarker Testing

AKA:

"Tumor Testing"

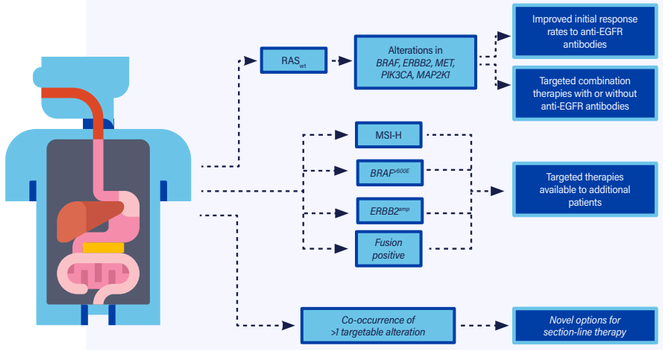
Biomarker is short for biological marker. Biomarker testing is sometimes called "tumor testing," "molecular testing," and "genomic testing."

Cancer biomarkers are biological, chemical, or biophysical entities that are present in tumor tissues or body fluids, and they can give valuable information about the characteristics of a tumor.

They can also give information about the tumor's future behavior (how it may grow or react to treatment), as well as give an idea as to whether cancer is still present or not in a person after treatment. [18]

Figure 0.12

Clinical implications of biomarker interactions in colorectal cancer



Adapted from: Sveen, A., Kopetz, S. & Lothe, R.A. Biomarker-guided therapy for colorectal cancer: strength in complexity. Nat Rev Clin Oncol 17, 11–32 (2020). https://doi.org/10.1038/s41571-019-0241-1

Men *vs.* Women

Researchers have discovered differences between women and men related to colorectal cancer. For example, colorectal cancer cells on the right side generate metabolites that enable more aggressive growth in women than in men.

Researchers also determined that the colons of men produce different metabolites than women. Emerging data shows that survival rates for women with late-stage colorectal cancer are higher than for men. [19]

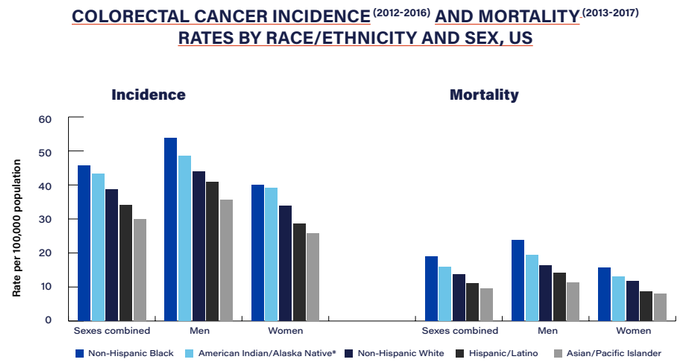
THIS IS CRAP!

This needs to change:

* Between 25%-30% of colorectal cancer patients have a family history of colorectal cancer. [1]
* One in 23 men and one in 25 women will be diagnosed with colorectal cancer. [2]
* Less than 50% of Asian Americans are up-to-date with colorectal cancer screening, with variability across Asian subgroups. [3]
* Ashkenazi Jewish people have one of the highest colorectal cancer risks of any ethnic group in the world. [4]
* Black Americans are about 20% more likely to get colorectal cancer and about 40% more likely to die from it than most other groups. [5]
* Indigenous communities have higher rates of colorectal cancer than their white counterparts. [5]

1. Patel SG, Ahnen DJ. Familial colon cancer syndromes: an update of a rapidly evolving field. Curr Gastroenterol Rep. 2012;14(5):428-438.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2020. CA Cancer J Clin. 2020;70(1):7-34.
3. Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Data. 2019; cdc.gov/brfss/. Accessed 09/04/2019.
4. Locker, GY., Lynch, H.T. Genetic factors and colorectal cancer in Ashkenazi Jews. Familial Cancer 3, 215–221 (2004). https://doi.org/10.1007/s10689-004-9547-x
5. American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Atlanta: American Cancer Society; 2020.

Figure 0.13



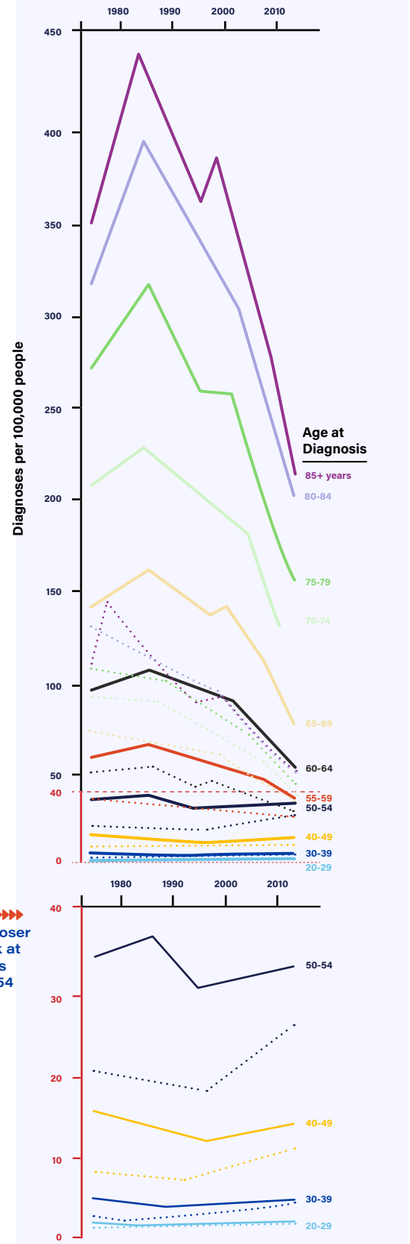
AI: American Indian, excluding Alaska; AN: Alaska Native. Rates are age adjusted to the 2000 US standard population. *Statistics based on data from Purchased/Referred Care Delivery Area (PRCDA) counties. AI/AN incidence rates exclude data from Kansas and Minnesota. Incidence rates for Alaska Native men and women are not statistically significantly different.
Adapted from: Source: Incidence – NAACCR, 2019. Mortality – NCHS, 2019.

LET'S GET TO WORK

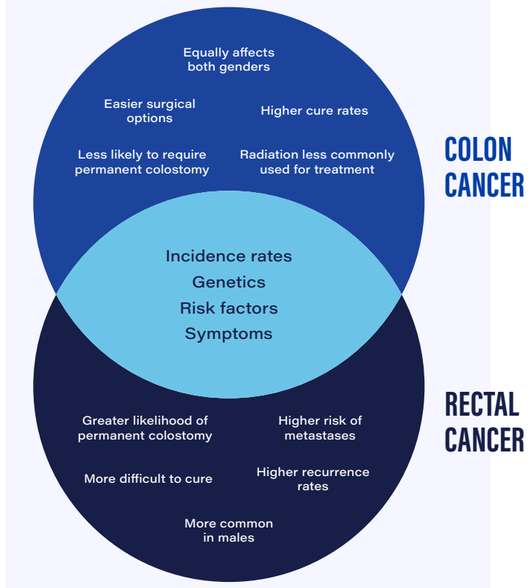
WHAT'S TRENDING?

Colorectal cancer is often touted as a success story in the war on cancer. Rates have dropped abruptly over the past two decades. But when you zoom in, it becomes clear that the decline is driven by older adults.

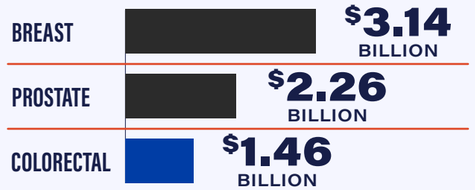
Both colon cancer and rectal cancer are rising in the younger age groups, and researchers don't yet understand why.



Credit: Jen Christiansen; Source: "Colorectal Cancer Incidence Patterns in the United States, 1974–2013," by Rebecca L. Siegel et al., in Journal of the National Cancer Institute, Vol. 109; August 2017 (data)



CANCERS WITH THE HIGHEST OUT-OF-POCKET COSTS*



*Data from 2019
Data from Yabroff KR, et al. J Natl Cancer Inst. 2021;doi:101093/jnci/djab192.

BIOLOGY AND ETIOLOGY

SECTION ONE: BIOLOGY AND ETIOLOGY

CHALLENGES & OPPORTUNITIES

1

PROGRESS INDICATOR:

APPLYING WHAT WE KNOW FROM BIOLOGY AND HEREDITARY RISK TO REDUCE LATE-STAGE COLORECTAL CANCER

CHALLENGES & OPPORTUNITIES

WENDY
CHAMPION HIGHLIGHT

Wendy Lewis is a stage III rectal cancer survivor who was diagnosed at age 42. She carries the Lynch syndrome gene from her late father, and Wendy has been a fierce advocate since her diagnosis.

Wendy joined the Fight CRC Research Advocacy Training and Support (RATS) program in 2015 and since then has served on review panels, and attended RATS academies to actively learn more about immunotherapy and hereditary colorectal cancer risk.

More recently, Wendy has been involved as a research advocate with the College of American Pathologists (CAP) helping develop clinical practice guidelines for MSI-H testing.

KEY MESSAGES

SECTION ONE: BIOLOGY AND ETIOLOGY

PATH TO A CURE

KEY MESSAGES BIOLOGY AND ETIOLOGY

- Technical developments in cell and molecular biology, biochemistry, genetics, imaging, statistics, and bioinformatics have propelled colorectal cancer research forward, with recent findings and developments opening up new opportunities to further reduce the toll of this disease.
- It is now well-known that colorectal cancer emerges from mutations that accumulate within the genomes of normal cells that line the colon and rectum, eventually "hitting" critical genes that change their levels of expression and/or the structure of their encoded products. [20]
- A very large number of genes contributing to colorectal cancer development have been identified over the years and remain a major focus of current research efforts. In many cases, we understand the role of these genes and how they regulate colorectal cancer. Every tumor is genetically unique.
- Genetic mutations (those that change the DNA sequence) and epigenetic mutations (those that do not change the DNA sequence) can lead to the development and progression of colorectal cancer. This can happen somatically, within the cells, or be inherited from family members. Lynch syndrome is the most common inherited condition.
- In the U.S., the burden of early-age onset colorectal cancer falls disproportionately on minorities and individuals in specific geographic regions, mirroring colorectal cancer disparities observed in older adults [20].

CHALLENGES & OPPORTUNITIES

SECTION ONE: BIOLOGY AND ETIOLOGY

CHALLENGES &

BASIC BIOLOGY

It has been observed that over the past few decades, colorectal cancer incidence and mortality have risen in younger adults (those under age 50). This is in contrast to adults over 50, for whom colorectal cancer rates are decreasing.

Data from ACS (see Figure 0.5) shows that those younger than age 50 have experienced a steady increase in incidence and mortality since the mid-90s, while those older than age 65 have experienced a decline.

In people ages 50-64, declines have also been observed, though they appear to have leveled off more recently, due in all likelihood to younger adults moving into their 50s and 60s.[2]

CHALLENGES

* We don't know what is causing this increase in colorectal cancer in people under age 50. While there is emerging data and independent research, there is still not a cohesive understanding of why this is happening at such an alarming rate.
* With the discussion about early-age onset colorectal cancer in people under 50, data is starting to emerge that there may be differences among patients with colorectal cancer based on their ages. For example, colorectal cancer may not be presenting the same among adolescents as compared with people in their 40s or even people in their 20s.[17]

OPPORTUNITIES

* As the data show an increased incidence of cancers in young people, the National Cancer Institute (NCI) and National Institutes of Health (NIH) in 2020 devoted resources for provocative research questions in understanding etiology and addressing the unexplained rising incidence in certain early-age onset disease, including colorectal cancer.[18]
* The Department of Defense (DOD) and a number of advocacy and private foundations have begun to dedicate funding to further study etiology, particularly in those who are under 50 years old.[19]

HEALTH DISPARITIES

Health equity means everyone has access to quality health care and can live a healthy life, regardless of race, ethnicity, sexual orientation, gender identity, disability, religion, and socioeconomic status. Colorectal cancer incidence and mortality rates are not uniform across race and ethnicity.

CHALLENGES

* Family colorectal cancer history is an established risk factor with an approximately two-fold increased risk among first-degree relatives with recommendations to begin screening at age 40.[20]
* One in four early-age onset colorectal cancer patients who could have undergone earlier screening based on family history guidelines was not screened. Despite these observations about genetic contributions to early-age onset colorectal cancer patients, the fact that genetic risk factors do not change for a population over time suggests that the greater focus should be on generational differences in diet, lifestyle, or environmental risk factors.[20]
* The relationship between health determinants is hard to unpack and addressing health disparities requires a multilevel approach.

OPPORTUNITIES

* To date, disparities by race/ethnicity and, to a lesser extent, geographic location in outcomes of early-age onset colorectal cancer suggest that biology/genetics, individual health behaviors, and access to and utilization of health services likely all have a role.
* Other social factors such as systemic racism, chronic stress, and neighborhood deprivation also deserve more rigorous investigation. Improving resources and coordinating efforts in communities where people of low socioeconomic status live and work would increase access to evidence-based interventions.
* Scientists have called out that we need to better understand the role diet, intestinal microbiome, and/or inflammation contribute to differences in colorectal carcinogenesis. Studies of large cohorts with diverse populations are needed to identify epidemiologic and molecular factors that contribute to colorectal cancer development in different populations.[21]

OPPORTUNITIES

SECTION ONE: BIOLOGY AND ETIOLOGY

CHALLENGES &

HEREDITARY

The mutations that drive the appearance and progression of colorectal cancer can be genetic (i.e., involve DNA sequence changes) or epigenetic (i.e., do not involve changes in DNA sequence). Most occur somatically within specific cells of the intestinal lining; others may be inherited and passed on within families.

Among the most common is Lynch syndrome, due to inherited changes (mutations) in genes that affect DNA mismatch repair, a process that fixes mistakes made when DNA is copied. These genes* normally protect you from getting certain cancers, but some mutations in these genes prevent them from working properly.

It is also noted that nearly one in five individuals diagnosed with colorectal cancer under age 50 was found to carry a pathogenic variant in a cancer-related gene. [20]

*MLHL, MSH2, MSH6, PMS2, and EPCAM

CHALLENGES

* When looking at population-based testing, it is estimated that 95% of individuals with Lynch syndrome are not aware of their diagnosis. Current studies indicate that 16% (one out of every six) of colorectal cancer patients diagnosed under age 50 carried an inherited susceptibility. [22]
* The inherited colorectal cancer syndromes are a series of diseases that have specific mutations that predispose a person to colorectal cancer. These are more aggressive and have a worse prognosis since they correlated with other tumors and some do not respond to chemotherapy. Early diagnosis is a challenge for physicians due to the absence of pathognomonic clinical findings. [23]

STARTED BUT NOT FINISHED!

* The Obama administration founded the Cancer Moonshot℠ Blue Ribbon Panel. They recommended calling for a nationwide effort to do universal tumor screening for Lynch syndrome amongst all colorectal cancer patients. While there have been several Cancer Genetics grants and Moonshot grants awarded, to date, there hasn't been a fully dedicated approach for researching Lynch syndrome.

OPPORTUNITIES

* A number of professional organizations have recommended universal tumor screening for all newly diagnosed colorectal cancer patients at the time of diagnosis.
* There is strong support for universal tumor screening for Lynch syndrome among colorectal cancer patients, including: Evaluation of Genetic Applications in Practice and Prevention (CD), Healthy People 2020, National Comprehensive Cancer Network, European Society of Medical Oncology, U.S. Multi-Society Task Force on Colorectal Cancer, American College of Gastroenterology, American Society of Clinical Oncology, and National Institute for Health and Care Excellence (UK).
* As a result of these findings, researchers have concluded that due to this high percentage, genetic counseling and multigene panel testing should be considered for ALL patients with early-age onset colorectal cancer, which is currently not widely implemented. There is a lot of opportunity to inform the metrics, accreditation, and policy for the genetic and hereditary landscape.

POLICY SHOUT OUT

The Affordable Care Act ensures coverage of any Grade B or higher USPSTF recommendation, which includes some genetic referral guidelines, cancer screening with no co-pays or co-insurance, and allows parents to keep their children on their plans until age 26 if they are still in school. [12]

The Genetic Information Non-Discriminatory Act prevents health insurance and employment discrimination based on genetic test results or family history, but does not include protections for life insurance, disability insurance, or long-term care insurance.

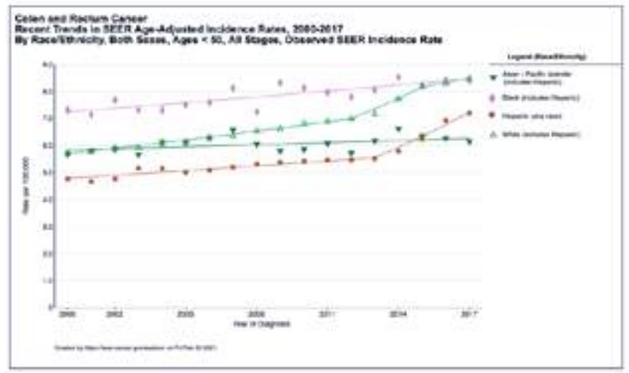
A focus for USPSTF to make guidelines for referral of patients for Lynch syndrome genetic testing routine could be explored. [12]

OPPORTUNITIES

CHALLENGES &

Figure 1.1

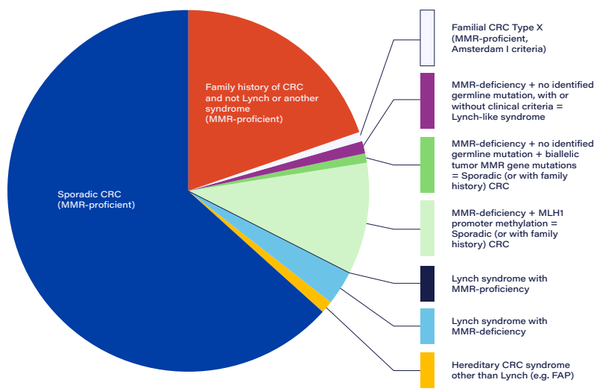
Colon and Rectum Cancer: Recent Trends in SEER Age-Adjusted Incidence Rates, 2000-2027 by Race/Ethnicity, Both Sexes, Ages < 50, Observed SEER Incidence RATES



National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Available online: https://seercancergov/explorer/ (accessed on 4 Nov 2021)

Figure 1.2

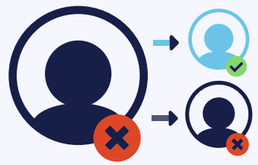
Categories of colorectal cancer (CRC) with a focus on concepts and terminology related to Lynch syndrome.



Adapted from: Ladabaum, U. (2020). What Is Lynch-Like Syndrome And How Should We Manage It? Clinical Gastroenterology and Hepatology, 18(2), 294–296. https://doi.org/10.1016/j.cgh.2019.08.009

Figure 1.3

LYNCH SYNDROME: GET THE FACTS



* Individuals with Lynch syndrome have a 50% risk of passing the mutation on to their children.

* Individuals with Lynch syndrome have a greater than 90% risk of developing some type of cancer.

* Individuals with Lynch syndrome have a 82% risk for colorectal cancer by age 70.

Adapted from: Cleveland Clinic

OPPORTUNITIES

TIME TO GET SHiT DONE

BIOLOGY AND ETIOLOGY

PROGRESS INDICATOR:

APPLYING WHAT WE KNOW FROM BIOLOGY AND HEREDITARY RISK TO REDUCE LATE-STAGE COLORECTAL CANCER

OBJECTIVE 1

Further research the nature, biology, and implications of colorectal cancer, throughout the continuum of age (while also considering younger adults versus older adults). Understanding parameters, including stage, location, histopathology, and underlying genetic and molecular "drivers."

Strategies:

1. Explore further themes of etiology of early-age onset colorectal cancer; looking beyond the known risk factors and applying the most recent research developments.
2. Consider biology, risk exposure, and socioeconomic status in development.
3. Create an index of common research and reporting metrics.
4. Share common data and registry information.
5. Support research to develop a stronger understanding of symptomatology and clinical presentation of patients.

OBJECTIVE 2

Research the role and impact of health disparities in those developing colorectal cancer, exploring factors such as biology and socioeconomic status; research to inform evidence-based interventions in areas of biology and healthcare policy.

Strategies:

1. Analyze existing and emerging "hot spots" for colorectal cancer incidence, particularly in younger groups to examine factors for increased incidence.
2. Specifically analyze colorectal cancer tumor characteristics, such as anatomic location, somatic mutations, microsatellite instability, and epigenetics.
3. Further understand the potential environmental risk factors for early-age onset colorectal cancer and how these could contribute to disparities by race/ethnicity.
4. Explore possible policy and research strategies to inform evidence-based interventions in areas of biology and healthcare policy.

SECTION ONE: BIOLOGY AND ETIOLOGY

OBJECTIVE 3

Improve dissemination and implementation (D&I) (spreading the information and putting into practice) of evidence-based and population-based strategies for genetic and hereditary colorectal cancer, specifically Lynch syndrome.

Strategies:

1. Advocate for Commission on Cancer (CoC) to include multigene panel testing/universal testing measure for Lynch syndrome.
2. Advance the Access to Genetic Counseling Services Act Center for Medicare and Medicaid services coverage for genetic counseling and testing, and possible alignment with the Cure 2.0 legislation.
3. Collaborate with the President's National Advisory Board to further engage initiatives promoted through the NCI Moonshot for further Blue Ribbon Panel recommendations.
4. Further integrate screening for Lynch syndrome as a measure for the College of American Pathologists (CAP)/American Gastroenterological and The Merit-based Incentive Payment System (MIPS).

OBJECTIVE 4

Progress research and exploratory science to advance our knowledge of Lynch syndrome.

Strategies:

1. Prioritize vaccine research for Lynch syndrome.
2. Further chemoprevention research for Lynch syndrome and other hereditary colorectal cancer syndromes.

Table 1.1

Potential environmental risk factors for early-age onset colorectal cancer and their contributions to disparities by race/ethnicity.

Factor	Potential Impact of Disparities
Obesity	Increased prevalence of childhood obesity and extreme obesity in Black people and Hispanic people
Type 2 diabetes	Increased prevalence in Black people and Hispanic people Increased prevalence of metabolic syndrome in Hispanic people
Western diet	Poorer quality diet in Black people
Sedentary lifestyle	Increased rates of television viewing and decreased physical activity among minority children

Table 1.2

Colorectal cancer tumor characteristics in African American patients vs. white patients. In most cases, these characteristics have not been studied specifically in the context of early-onset colorectal cancer unless otherwise noted.

Characteristic	Details for African American Patients
Anatomic location	Overall more proximal tumors versus distal tumors. Younger Black people have higher prevalence of distal tumors versus older Black people
Somatic mutations	Unique mutations in *EPHA6*, *FLCN*, and *CDH5APC*-negative tumors more frequently in younger Black people
Microsatellite instability	20% lower rate of microsatellite instability. Higher rate of EMAST in rectal tumors
Epigenetics	Unique pattern of epigenetic signature in proximal colon
EMAST — elevated microsatellite alterations at selected tetranucleotide repeats	

SECTION ONE: BIOLOGY AND ETIOLOGY

PREVENTION AND EARLY DETECTION

CHALLENGES & OPPORTUNITIES

2

PROGRESS INDICATOR:

ADVANCING COLORECTAL CANCER PREVENTION AND EARLY DETECTION

SECTION TWO: PREVENTION AND EARLY DETECTION

CHALLENGES & OPPORTUNITIES

WENORA
CHAMPION HIGHLIGHT

Wenora Johnson is a three-time cancer survivor, a Navy veteran, and a Fight CRC research advocate. She advises on panels for the Department of Defense, Patient Centered Outcomes Research Institute (PCORI), and the College of American Pathologists (CAP) to name a few.

Wenora has served as a research advocate reviewing protocol and patient-facing materials for an industry partner investigating the most impactful educational methods for increasing screening rates, particularly in the African American community.

Wenora's expertise has helped researchers understand study feasibility and implementation challenges. Including patient perspectives early in trial design improves the likelihood that the trial is designed with patients in mind, and that any challenges that the patient community may face are lessened. It also ensures that trial sites are geographically and racially diverse and are inclusive of all colorectal cancer patients.

KEY MESSAGES

SECTION TWO: PREVENTION AND EARLY DETECTION

CHALLENGES & OPPORTUNITIES

PATH TO A CURE

KEY MESSAGES

PREVENTION AND EARLY DETECTION

* A number of factors have been shown to contribute to the risk of colorectal cancer. Factors that cannot be changed are older age, a personal or family history of colorectal cancer or colorectal polyps, a history of inflammatory bowel disease (IBD), inherited genes (e.g., Lynch syndrome), and racial/ethnic background. Factors that can be changed include lifestyle choices such as being overweight or obese, lack of physical activity, smoking, alcohol use, high dietary intake of red meats and sugars, and low intake of fruits and vegetables.[23]
* Symptoms of colorectal cancer include a change in bowel habits (diarrhea, constipation), chronic rectal bleeding, cramping/abdominal pain, weakness and fatigue, and unintended weight loss.[8]
* Screening is essential for early detection. Options for screening now include visual methods (colonoscopy, sigmoidoscopy, CT colonography) and stool-based (fecal occult blood test, fecal immunochemical tests, multi-targeted DNA test).[8]
* It is still widely acknowledged that our greatest opportunity to prevent late-stage colorectal cancer is through preventive screening. Colorectal cancer is one of the only truly preventable forms of cancer.[8]
* Colorectal cancer incidence and mortality rates also vary substantially by race and ethnicity. Among the five major racial/ethnic groups, rates are highest in non-Hispanic Blacks (hereinafter "Blacks"), followed closely by American Indians/Alaskan Natives, and lowest in Asian Americans/Pacific Islanders. Fewer than one-half of individuals who receive care at federally qualified health centers are up-to-date for screening.[2]

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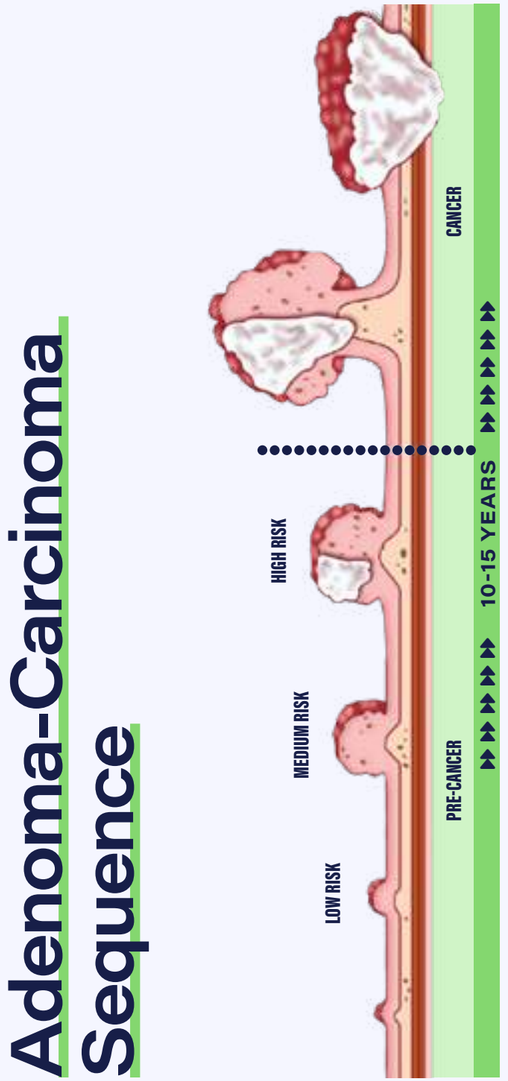

SECTION TWO: PREVENTION AND EARLY DETECTION

CHALLENGES & OPPORTUNITIES

Screening is essential to early detection.

Colorectal cancer progresses from early, localized stages characterized by the presence of small polyps and adenomas that generally have a favorable prognosis to more advanced stages defined by larger polyps and eventually cancer. [4]

SECTION TWO: PREVENTION AND EARLY DETECTION

CHALLENGES &

INCREASE IN SCREENING OF AVERAGE-RISK POPULATION

Dissemination of guidelines for the average-risk population for screening by organizations, such as the American Cancer Society, resulted in increased engagement of the population in preventive screening and led to marked reduction in disease incidence and mortality in older adults (i.e., those over age 50). [12]

In May 2021, the U.S. Preventive Services Task Force (USPSTF) officially lowered the recommended age of screening from 50 to 45, following extensive review of research, as well as recognition of the increasing incidence of colorectal cancer among young adults. [12]

More than 40 million people in the U.S. are eligible for colorectal cancer screening.

CHALLENGES

* The national screening rate based on 2018 Behavioral Risk Factor Surveillance System (BRFSS) data is 67%-68%. This accounts for those ages 50 and over. [25]

  In 2021 when the USPSTF reduced the screening age from 50 to 45, the eligible population increased by an estimated 60%, expanding the population of people who need to be screened from 27 million to 44 million.

  Compounding this challenge is the rapidly growing aging population. The diagnosed incident cases of colorectal cancer are expected to increase by an annual growth rate of 1.9% from 2018-2028. [12]

* The multitude of modalities and options for screening differ with regard to advantages and disadvantages. While there is great opportunity in choice of options, the challenge is to keep the public and medical providers fully up-to-date, so as to foster their ability to make informed decisions as to which option is best for them.

  Which test to recommend continues to be controversial within the healthcare community. Debates continue to complicate public health efforts over colorectal cancer screening methods, age to start and to stop screening, and post-colonoscopy/polypectomy surveillance guidelines. [3]

It's a win/win!

Implementation science leads to increased colorectal cancer screening in communities across the country.

Here's what the CDC determined:

"The findings presented in this study can assist CRCCP grantees, other colorectal cancer screening programs, and policymakers to understand programmatic cost, screening promotion cost distribution, and projected cost per person screened to guide future program planning and implementation.

Research should be undertaken to understand the optimal mix of screening promotion activities, as a complementary set of approaches may prove to be the most cost-effective combination to increase colorectal cancer screening rates.

Although the CRCCP was largely successful in fostering the use of evidence-based interventions, future implementation should use targeted approaches that specify interventions rather than broad-based recommendations to ensure grantees use strategies recommended by the Community Guide to deliver high-impact programs." [29]

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OPPORT ES

CHALLENGES &

INCREASE IN SCREENING OF AVERAGE-RISK POPULATION

Investments in Cancer Research

Part of the funding for colorectal cancer research, funded by the NCI, is targeted to colorectal cancer screening. There is a variety of industry and foundation support for program implementation and research-based opportunities for advancing the science in development of emerging minimally invasive strategies for preventive cancer screening.

Stand Up to Cancer and PCORI invested $8 million and $32 million in 2021, respectively with strong commitment to prevention research. [30]

Charities That Support Cancer Research:

American Cancer Society · Colon Cancer Coalition · colorectal cancer alliance · FIGHT Colorectal Cancer · Friends of Cancer Research · LIVESTRONG · prevent cancer · Stand Up To Cancer

OPPORTUNITIES

* National and local efforts to bring awareness of the benefits of colonoscopy screenings have paid off: When people are screened, colorectal cancer is prevented or caught early. Screening saves lives.

  In December 2020, the Removing Barriers to Colorectal Cancer Screening Act of 2020, which waives co-insurance charges for average-risk colorectal cancer screening of Medicare beneficiaries, regardless of whether tissue is removed during the test, was passed. This Act will be phased in during an eight-year period beginning in 2022. [26]

* Related to quality measures and incentives for providers to keep cancer prevention as a topic priority, two very important measures are in effect. The first is the Healthcare Effectiveness Data and Information Set (HEDIS), a tool used by more than 90% of America's health plans and is a comprehensive set of standardized performance measures. The measure consists of members ages 50-75 who receive the appropriate screening for colorectal cancer. [27]

  The second is within Medicare: Colorectal cancer screening is also now a National Quality Strategy Domain: Effective Clinical Care. This measure is to be submitted once per performance period for patients seen during that period. This measure may be submitted by Merit-based Incentive Payment System eligible clinicians. [27]

  Integrating quality measures and incentives with key indicators and benchmarks for success have been proven to help ensure providers meet designated metrics. As a result, providers are more likely to recommend colorectal cancer screenings to their patients. [27]

* The Centers for Disease Control and Prevention (CDC) currently funds the Colorectal Cancer Control Program (CRCCP) and is focused on increasing colorectal cancer screening rates in 35 states within the safety net and primary care clinics in reaching those patients who have the lowest screening rates.

  This is one of the largest investments in screening the medically underserved, and understanding and disseminating best practices. The Centers for Disease Control also has a variety of mechanisms in their funding portfolio to research implementation of colorectal cancer screening, as well as data repositories. [28]

OPPORTUNITIES

CHALLENGES &

SCREENING IN INCREASED-RISK, HIGH-RISK, AND SYMPTOMATIC PATIENTS

Family History and Increased Risk

Guidelines for those who are at increased and high-risk are well-established for colorectal cancer screening. The most common guidelines include U.S. Multi-Society Screening Guidelines, American College of Gastroenterology, and the American Gastroenterology Society.[31, 32]

We have identified genetic and hereditary syndromes and risk factors that we know increase the likelihood of colorectal cancer. The lifetime risk of colorectal cancer in average-risk individuals is approximately 4.5% and approximately double in individuals with a positive family history.[11]

Familial colorectal cancer may have some component that is genetic in origin or may be an effect of shared environmental exposures. It is estimated that approximately 10% of the general population ages 30-70 years old have a first-degree family history affected by colorectal cancer and up to 30% will have a first-degree family member or second-degree relative with colorectal cancer.[33]

It is also well-established that Inflammatory Bowel Disease (IBD), including either ulcerative colitis or Crohn's disease, also increases risk of colorectal cancer.[9]

CHALLENGES

* Despite being at increased risk for colorectal cancer due to positive family history, first-degree relatives (FDR) are not always screened according to guidelines.

  One study found that 40% of individuals with a family history of colorectal cancer were screened appropriately according to the American Gastroenterological Association guidelines.[34]

  Other research suggests that 47% of individuals at increased risk for colorectal cancer (defined as a FDR diagnosed before age 55, or two relatives diagnosed with colorectal cancer) adhered to colorectal cancer screening guidelines.[34]

  Results of these studies indicate an opportunity to increase screening adherence among first-degree family members of colorectal cancer patients.

  This does not take into account advanced adenomas within families and the need for colonoscopy screening, which is another area of attention that could be addressed for the biggest potential in colorectal cancer prevention.[33]

OPPORTUNITIES

* The Affordable Care Act ensures coverage of any Grade B or higher USPSTF recommendation, which includes some genetic referral guidelines, cancer screening with no co-pays or co-insurance, and allows parents to keep their children on their plans until age 26 if the children are still in school.[12]

  Additionally, the Genetic Information Non-Discriminatory Act prevents health insurance and employment discrimination based on genetic test results or family history.[12]

* As colorectal cancer screening evolves and we continue to push forward, it will be critical that we find mutually beneficial partnerships that can produce groundbreaking research and innovation that solves complex problems, drives economic growth, and creates a more skilled workforce.

OPPORTUNITIES

TIME TO GET SH!T DONE

PREVENTION AND EARLY DETECTION

PROGRESS INDICATOR:
ADVANCING COLORECTAL CANCER PREVENTION AND EARLY DETECTION

OBJECTIVE 1

Improve dissemination and implementation (spreading the information and putting into practice) of the evidence-based colorectal cancer screening interventions for the average-risk population.

Strategies:

1. Advocate for stronger integration of preventive screening for comprehensive care for the average-risk population as a "default." No longer recommending only colorectal, breast, cervical, lung, and other screening recommendations in isolation, by body parts, but rather recommending screening guidelines as a whole.
2. Provide a dedicated approach to target-specific screening interventions and campaigns to reach communities with the lowest colorectal screening rates.
3. Continue state and federal level policy work to remove out-of-pocket costs for colonoscopy following a positive noninvasive screening test.
4. Advocate for a HEDIS measure that will ensure completion of follow-up colonoscopy for positive noninvasive tests and abnormal screening, denoting that preventive screening is not complete until a follow-up colonoscopy is completed.
5. Create consumer-driven awareness by advocates with payers and policymakers.

SECTION TWO: PREVENTION AND EARLY DETECTION

OBJECTIVE 2

Improve dissemination and implementation of the evidence-based colorectal cancer screening for the increased, high-risk and symptomatic patients.

Strategies:

1. Increase the number of patients who have completed family history and referral for genetic and hereditary colorectal cancers, including family history of advanced adenomas, colorectal cancer, and other genetically linked cancers.
2. Increase screening rates for those who have first-degree family members with hereditary and genetic adenomas, colorectal cancer, and other genetically linked cancers.
3. Reduce stigma for patients who have signs and symptoms of colorectal cancer for more timely follow-up for colonoscopy.

OBJECTIVE 3

Further research and examination of colorectal cancer screening uptake for those younger than age 50 to reduce early-age onset colorectal cancer.

Strategies:

1. Research to help define common signs and symptoms to create a clinical screening tool to assess for potential colorectal cancer in those younger than age 50.
2. Engage primary care associations and providers for greater awareness of issues related to work-up of signs and symptoms of colorectal cancer.
3. Create awareness campaigns and strategies for consumers about the increase of colorectal cancer in people younger than age 50 and addressing stigma.
4. Examine patient preference in specific screening modalities for the 45-50-year-old-age group in the average-risk population.

OBJECTIVE 4

Research minimally invasive strategies for preventive cancer screening, including analysis of blood, urine, and saliva (i.e., "liquid biopsies"); and examination of the oral and intestinal microbiome.

Strategies:

1. Define sensitivity and specificity based on patient needs and preferences.
2. Determine common quality and clinical thresholds and standards for emerging technologies.
3. Further engagement in ensuring patient accessibility.

TREATMENT

CHALLENGES & OPPORTUNITIES

3

PROGRESS INDICATOR:

EXPAND TREATMENT STRATEGIES FOR COLORECTAL CANCER PATIENTS

SECTION THREE: TREATMENT

CHALLENGES & OPPORTUNITIES

LEE
CHAMPION HIGHLIGHT

Lee Jones, a 17-year stage IV colon cancer survivor and longtime member of the RATS program, currently serves as one of 10 colorectal cancer research advocates on a team of researchers from five countries that are investigating the relationship between the human microbiome and colorectal cancer to understand how a patient may respond to treatment.

This research, known as OPTIMISTICC, is funded by a five-year grant from Cancer Research UK as part of their Cancer Grand Challenges program (now in partnership with the U.S. National Cancer Institute).

Advocates play a crucial role translating lab findings to the real world to provide more value to patients, including their feedback on the collection of dietary information and tumor, blood, and stool samples at several points during participating patients' chemotherapy or immunotherapy treatments.

So far, this research has demonstrated strong associations between several microbes and colorectal cancer, and aims to better understand the role the microbiome may play in early-age onset colorectal cancer.

KEY MESSAGES

SECTION THREE: TREATMENT

CHALLENGES & OPPORTUNITIES

PATH TO A CURE

KEY MESSAGES TREATMENT

- Approximately 85% of patients diagnosed with colorectal cancer have tumors that are microsatellite stable (MSS), which are predominantly treated with fluorouracil-based chemotherapy such as 5-FU, FOLFOX, FOLFIRI, or similar drugs. The most promising response rates vary a bit but range from approximately 38%-45%. (35)
- The remaining 15% of patients diagnosed with colorectal cancer have tumors that are Microsatellite Instable (MSI-H). One of the most notable treatments is Pembrolizumab (humanized monoclonal antibody against PD-1 receptor), which in 2017 was approved for all MSI-H cancers, based on results from five clinical trials for different cancers.

  It was the U.S. Food and Drug Administration's (FDA's) first tissue/site-agnostic approval. (36)
- Overall survival rates for late-stage colorectal cancer have not seen much improvement in the past decade, and stronger treatments and clinical trial improvement are imperative for progress. (35)
- A 2020 study noted a strong association between geographic residence and early-age onset colorectal cancer stage and survival, finding rural residences and those living long distances from the treating hospital were associated with later stage diagnoses and lower survival. (37)

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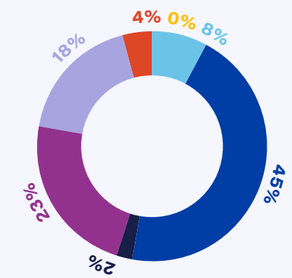


GlobalData Colorectal Cancer Development Pipeline, by Phase

- Discovery
- Preclinical
- IND/CTA Filed
- Phase I
- Phase II
- Phase III
- Pre-Registration

Adapted from: Colorectal cancer pipeline insight. Clinical trials arena. (2018, April 26). Retrieved November 4, 2021, from https://www.clinicaltrialsarena.com/comment/colorectal-cancer-pipeline-insight/.

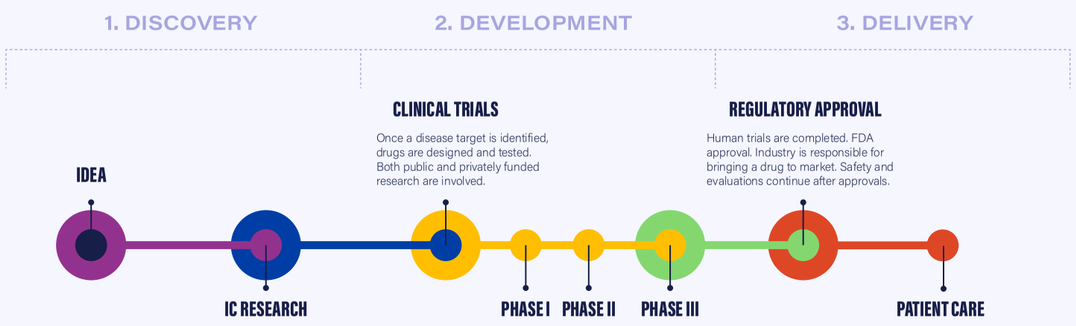
At the heart of the issue is the fact that despite being the second-leading cause of cancer deaths for men and women in the U.S., and the startling increase in diagnoses among young people, federal funding for colorectal cancer research has not kept pace.

While there have been consistent increases in overall funding for the NCI over the past several years, funding for colorectal cancer research did not see a commensurate increase, and in fact, mostly decreased from FY14-FY17. Of the top five cancer killers, colorectal cancer is the only cancer that does not have its own research program within the Department of Defense Congressionally Directed Medical Research Program (DoD CDMRP). (19)

The National Cancer Institute reported medical expenditures were projected to reach $16.5 billion for breast cancer, $14 billion for colorectal cancer, $12 billion for lymphoma, $12 billion for lung cancer, and $12 billion for prostate cancer in 2020. (19)

SECTION THREE: TREATMENT

Getting Treatment to Patients is a Process



Adapted from: Warren, J. (2017, December). Achievements and Next Steps to Tackle Cancer Grand Sciences. McGill Integrated Cancer Program Institute for Applied Cancer Science . https://slideplayer.com/slide/13852896/. https://slideplayer.com/slide/13852896/.

CHALLENGES & OPPORTUNITIES

CHALLENGES &

ACCELERATING TREATMENT STRATEGIES

CHALLENGES

* Drugs like Pembrolizumab have been a breakthrough, with improved response and survival patterns compared to chemotherapy for patients with advanced mismatch repair-deficient/Microsatellite instable (dMMR/MSI-H) colorectal cancer, but have shown disappointing results in mismatch repair-proficient/Microsatellite stable (pMMR/MSS) colorectal cancer.[38]

  While there is considerable support and discussion about focusing on utilization of circulating tumor DNA (ctDNA) and novel therapies in the adjuvant setting, biomarker-selected studies for mCRC and treatment of oligometastatic disease (limited metastatic disease), there is a sense of frustration about the lack of advancement of immunotherapy in MSS mCRC patients. Making progress in immunotherapy for MSS patients is specifically noted as an unmet need.

* But perhaps the most perplexing issue is that colorectal cancer is actually a very individualized disease and "bucketing"' into colon, rectal, MSS/MSI, etc. is not specific enough to truly provide the types of treatments and therapies that will overall improve colorectal cancer survival.

  We must confront the reality that treatment for colorectal cancer has only seen incremental improvements. A paradigm shift in thinking about treatment is needed. The real challenge and issue is that despite the advancements in treatment, not enough gains have been made to create any real change in overall survival for late-stage disease in several decades.

* In order to see individualized treatment progress, there is an analysis suggesting that a clinical trial system that enrolls patients at a higher rate produces treatment advances at a faster rate and corresponding improvements in cancer population outcomes.[39]

  But there is a lot of work to do as we know that one in 20 adult patients with cancer enrolls in cancer clinical trials. Although barriers to trial participation have been the subject of frequent study, the rate of trial participation has not changed substantially over time.[39]

  Barriers to trial participation are structural, clinical, and attitudinal, and they differ according to demographic and socioeconomic factors.

OPPORTUNITIES

* Oncology is at the vanguard of precision medicine: More than 160 oncology biomarkers were approved in 2019, and more than 90% of pivotal trials are against molecular targets.[40]

  Breakthrough therapies like Pembrolizumab have been game-changers for MSI-H patients; there is considerable excitement about how these findings might apply to MSS patients to improve treatment strategies.[41]

* In President Biden's fiscal year 2022-Presidential Budget Request, a proposal was included for $6.5 billion to create the Advanced Research Project Agency for Health (ARPA-H) to "develop breakthroughs to prevent, detect, and treat diseases like Alzheimer's, diabetes, and cancer."[42]

  The proposal seeks to address the fact that many bold, high-risk, high-reward ideas do not fit into the existing research structure either at the National Institutes of Health or within the work traditionally done by the private sector and instead create a dynamic organization centered around ensuring risk tolerance, urgency, nimbleness, and innovation.

  The goal is to speed the development and implementation of health breakthroughs—from the molecular to societal level—to serve all patients.[42]

INDUSTRY CALL OUT

Colorectal cancer not only has a significant unmet need, it represents a large patient population both in the United States and globally. Industry (pharmaceutical companies) play a tremendous role in driving innovation and treatments to patients.

"Precision medicine and novel modalities, including cell therapy, offer huge potential to transform the lives of patients. However, capitalizing on this potential will require pharmaceutical companies to work in new ways as they accelerate development timelines, develop combination therapies, and—critically—find effective routes to bring these therapies to market."

The burden for patients will be advocating for faster access while bearing the economic cost of novel treatments.[43]

The global colorectal cancer therapeutics market should reach $18.5 billion by 2023 from $13.7 billion in 2018 at a compound annual growth rate (CAGR) of 6.1% for the period 2018 to 2023.[44] And if you look at global biomarker testing the market is forecasted to be 124.85 billion dollars by 2028. ($51.74 billion in 2020)[43]

OPPORTUNITIES

CHALLENGES &

FIGHT COLORECTAL CANCER™
PATH TO A CURE OBJECTIVES AND STRATEGIES

OPPORTUNITIES

PATIENTS' VOICES MATTER

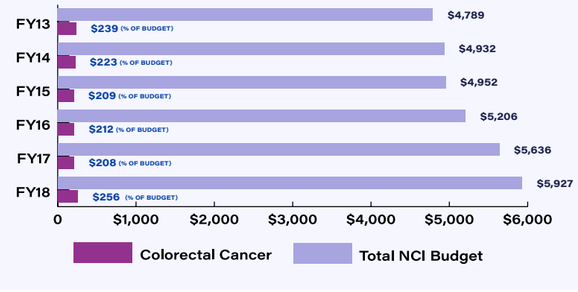
Patient Engagement Across the Clinical Trial Continuum

Pre-Discover	Pre-Clinical	Phase 1	Phase 2/3	FDA review & approval	PAS/Outcomes
* Interest of research question to patient community * Provide data on unmet need and theraputic burden * Direct funding and fundraising for research or product development * Understanding mechanisms of action relevant to disease and symptom burden	* Direct funding and fundraising for research or product development * Natural history database/registry support * Help define eligibility criteria within the study protocol * Feedback on meaningful clinical endpoints * Assist in creating the informed consent form * Advise on study recruitment * Accompany sponsor to FDA to advocate study design	* Direct funding and fundraising for trial opportunities and support * Network recruitment/outreach * Serve on a Data Safety Monitoring Board * Report on patient feedback regarding sites, investigators, and study participant experience	* Network recruitment/outreach * Direct funding and fundraising for research or product development * Infrastructure support * Provide input on safety design (barriers to participation) * Support trial awareness and recruitment * Peer advocate during informed consent procedure	* Serve on FDA advisory committees * Provide testimony at FDA hearings * Feedback on meaningful clinical endpoints	* Natural history database/registry support * Provide feedback on how the patient community views results * Help return study results to participants * Write newsletter articles or blog about results * Co-present results * Serve on post-market surveillance initiatives

Patient group engagement. CTTI. Retrieved November 4, 2021, from https://ctti-clinicaltrials.org/our-work/patient-engagement/patients-groups-clinical-trials/.

Figure 3.1

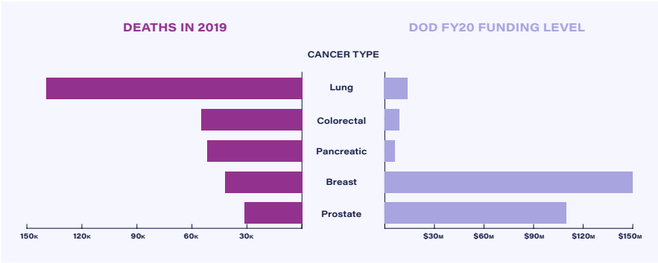
National Cancer Institute CRC funding levels by fiscal year vs. total NCI budget



Data retrieved from: 2019 NCI Budget Fact book (https://www.cancer.gov/about-nci/budget/fact-book/data/research-funding), SEER Cancer Stat Facts (https://seer.cancer.gov/statfacts/html/colorect.html Cancer of the Colon and Rectum - Cancer Stat Facts) and CDMRP Funding history (https://cdmrp.army.mil/about/fundinghistory)

Figure 3.2

Number of deaths for the top 5 deadliest cancers vs. FY20 Department of Defense Funding levels



Data retrieved from: 2019 NCI Budget Fact book (https://www.cancer.gov/about-nci/budget/fact-book/data/research-funding), SEER Cancer Stat Facts (https://seer.cancer.gov/statfacts/html/colorect.html Cancer of the Colon and Rectum - Cancer Stat Facts) and CDMRP Funding history (https://cdmrp.army.mil/about/fundinghistory)

TIME TO GET SHiT DONE

TREATMENT

PROGRESS INDICATOR:

EXPANDING TREATMENT STRATEGIES FOR COLORECTAL CANCER PATIENTS

OBJECTIVE 1

Increase clinical trial enrollment, particularly for late-stage disease, microsatellite stable, and early-age onset patients.

Strategies:

1. Collaboration with industry partners, healthcare systems, and advocacy groups to amplify education campaigns.
2. Inclusion of social determinants of health equity and other cancer care delivery issues need to be addressed in design and outreach.
3. Deliberate inclusion of patient advocates and patients in building clinical trials.
4. Strengthen incentivization of patient recruitment into open trials across and throughout the U.S. and among institutions.

OBJECTIVE 2

Increase biomarkers and molecular testing (localized versus metastatic).

Strategies:

1. Develop provider and patient education campaigns.
2. Strengthen alignment with quality and accreditation measures through National Comprehensive Cancer Network (NCCN) and Commission on Cancer.

OBJECTIVE 3

Design trials that are individualized-sequence therapies.

Strategies:

1. Integration of a multidisciplinary team for designs of next-generation trials.
2. Better contextual understanding of tumor microenvironment and circulating tumor DNA (ctDNA) for trials.
3. Implementation of clinical practice subgrouping by molecular phenotype and identifying ahead of time to preselect into clinical trials, RNA sequencing, and gene profiling.
4. Optimization of treatment strategies supported by preclinical science, specifically in:
    * Immunotherapy
    * Microbiome

OBJECTIVE 4

Strengthen infrastructure design and development to advance treatment and clinical care.

Strategies:

1. Develop stronger tracking and review of outcomes for:
    * MSS Immunotherapy and combination strategies.
    * Informative failures.
    * Pooling of rare responders for MSS trials.
2. Strengthen pre-clinical/translational collaboration, creating better overall informative opportunities, identifying molecular targets, and more closely aligning clinical relevance.
3. Support national/standardized biobanking, particularly for early-age onset colorectal cancer:
    * Standard strategy and protocols for ascertainment.
    * Routine access to samples among institutions.
4. Establish an overall survival rate goal by 2023 with relevant and pertinent data.

OBJECTIVE 5

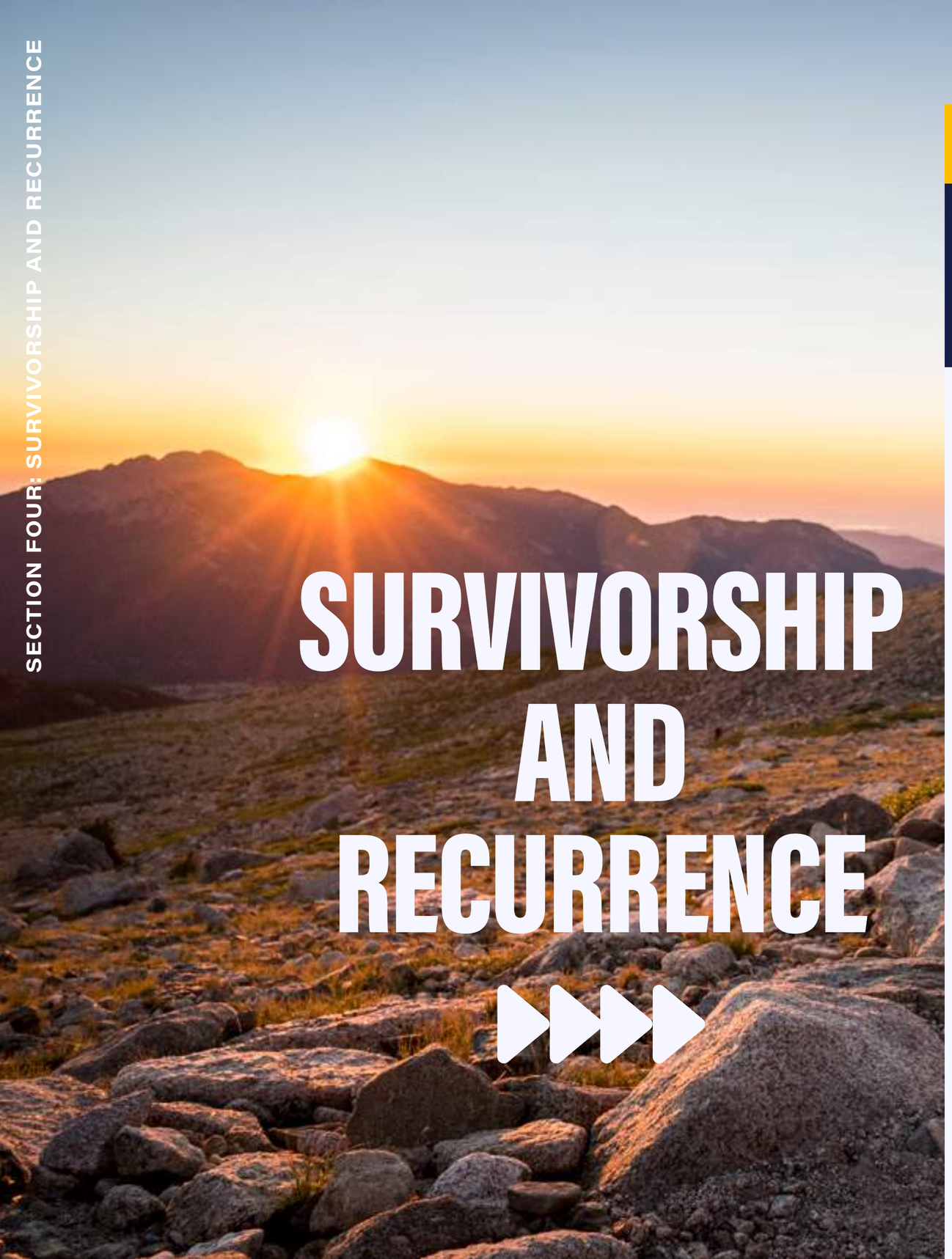
Increase federal funding for colorectal cancer research to achieve previously listed objectives.

Strategies:

1. Create a Colorectal Cancer Research Program within the DOD CDMRP.
2. Ensure colorectal cancer is prioritized in the development and implementation of ARPA-H.
3. Engage the National Cancer Institute around key areas of opportunity for colorectal cancer research to provide more dedicated dollars to colorectal cancer treatment and prevention.

SEER Stage	COLON 5-year relative survival rate	RECTAL 5-year relative survival rate
Localized	89%	91%
Regional	72%	72%
Distant	16%	14%
All SEER stages combined	67%	63%

SECTION THREE: TREATMENT



SURVIVORSHIP AND RECURRENCE

CHALLENGES & OPPORTUNITIES

4

PROGRESS INDICATOR:

ENHANCE QUALITY OF LIFE AND PREVENT RECURRENCE

SECTION FOUR: SURVIVORSHIP AND RECURRENCE

CHALLENGES & OPPORTUNITIES

ERIN & CURT
CHAMPION HIGHLIGHT

Fight CRC research advocates are helping to guide research led by Dr. Erin Van Blarigan at the University of California, San Francisco (UCSF). Dr. Van Blarigan's research, funded by the National Cancer Institute, is investigating different interventions to help colorectal cancer survivors increase exercise, and improve diet and BMI after diagnosis, following the American Cancer Society guideline score.

Four advocates with various backgrounds are informing the study design and recruitment materials to ensure that the focus of the study remains patient-centric and can positively impact the quality of life of cancer survivors post-treatment.

According to Curt Pesmen, a stage III colorectal cancer survivor and research advocate contributing to the study, *"Dr. Van Blarigan's research quickly incorporates each advocate's suggestions to add 'real-world' exercise and diet advice without creating additional survivorship burdens on the patient."*

This type of survivorship research is crucial to understanding how to best support the patient community and ensure that the tools and recommendations are actionable.

KEY MESSAGES

SECTION FOUR: SURVIVORSHIP AND RECURRENCE

CHALLENGES & OPPORTUNITIES

PATH TO A CURE

KEY MESSAGES

SURVIVORSHIP AND RECURRENCE

- There are over 1.5 million colorectal cancer survivors in the United States. The five-year survival rate for people with colorectal cancer is 65%. [44]
- Considering caregivers is also part of survivorship. There is growing research and focus on the role and needs of caregivers.
- There is an opportunity to provide guidance and consensus on colorectal cancer survivorship standards. Part of the equation is delivery of care for virtual, telehealth, or in-person visits. Let's have focused discussions on how to support the unique issues faced by young patients, late-stage patients, and those with specific tumor types and/or receiving specific types of targeted therapies.
- Our goal is for patients to live longer and enjoy their quality of life. To do this successfully, survivorship research efforts must elaborate and inform patients and their loved ones on the many issues relevant to long-term survival and risk of recurrence.
- Late-stage survivors struggle with fear of cancer recurrence/ progression and feelings of powerlessness, sadness, or frustration from the life-changing effects of treatment and surgery.

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Continuum of Colorectal Cancer Research

PREVIVORSHIP
Prevention & Early Detection

SURVIVORSHIP
Diagnosis & Treatment
Secondary Prevention & Monitoring Recurrence
Management of Recurrence

LONG-TERM SURVIVORSHIP
End-of-Life Care

CROSS-CUTTING RESEARCH
Biology
Innovative Research Designs
Intervention Development
* * *
Methods to Reduce Practice-Related Disparities
Supportive Care Research & Practice
* *

Adapted from: Warren, J. (2017, December). Achievements and Next Steps to Tackle Cancer. Grand Sciences. McGill Integrated Cancer Program Institute for Applied Cancer Science. https://slideplayer.com/slide/13852896/, https://slideplayer.com/slide/13852896/.

SECTION FOUR: SURVIVORSHIP AND RECURRENCE

CHALLENGES & OPPORTUNITIES

Funding Beyond NCI

The Department of Defense Peer Reviewed Cancer Research Program (PRCRP) supports innovative, high-impact cancer research.

The FY21 PRCRP has a focal area examining gaps in quality of life and/or survivorship that may affect the general population but have a particularly profound impact on the health and well-being of military service members, veterans, and their beneficiaries. As the military is seeing an increase in colorectal cancer in young service members, ensuring the opportunity to test models of survivorship care is an area of research focus and priority.[45]

The Centers for Disease Control and Prevention (CDC) supports, designs, implements, disseminates, and evaluates public health research to assess the needs of cancer survivors and caregivers, specifically, through work in surveillance and the National Comprehensive Cancer Control Program and dedicated research opportunities.[46]

Patient-Centered Outcomes Research Institute (PCORI) funds patient-centered outcomes research studies that also often include patient populations traditionally excluded from cancer clinical trials, such as older adults and those with comorbid health conditions.

One area emphasized by stakeholders that has been missing to date in research is the assessment of caregiver outcomes, which could be of particular benefit in colorectal cancer.[47]

SECTION FOUR: SURVIVORSHIP AND RECURRENCE

CHALLENGES &

SURVIVORSHIP

Currently, there are over 1.5 million colorectal cancer survivors in the United States. The five-year survival rate for people with colorectal cancer is 65%.[44]

The term "survivorship" covers physical, psychological, social, and financial issues affecting patients during and after treatment. Our community of colorectal cancer survivors includes people with no disease, people who continue to receive treatment to reduce their risk, and those who manage a chronic but well-controlled disease with quality of life. It is incredibly important to recognize that colorectal cancer impacts families and entire communities of people.

While there are wellness and medical guidelines for colorectal cancer patients after treatment is complete, gaps remain in *who* and *how* survivorship care is delivered. There is also variability from institution to institution about how survivorship care is delivered.

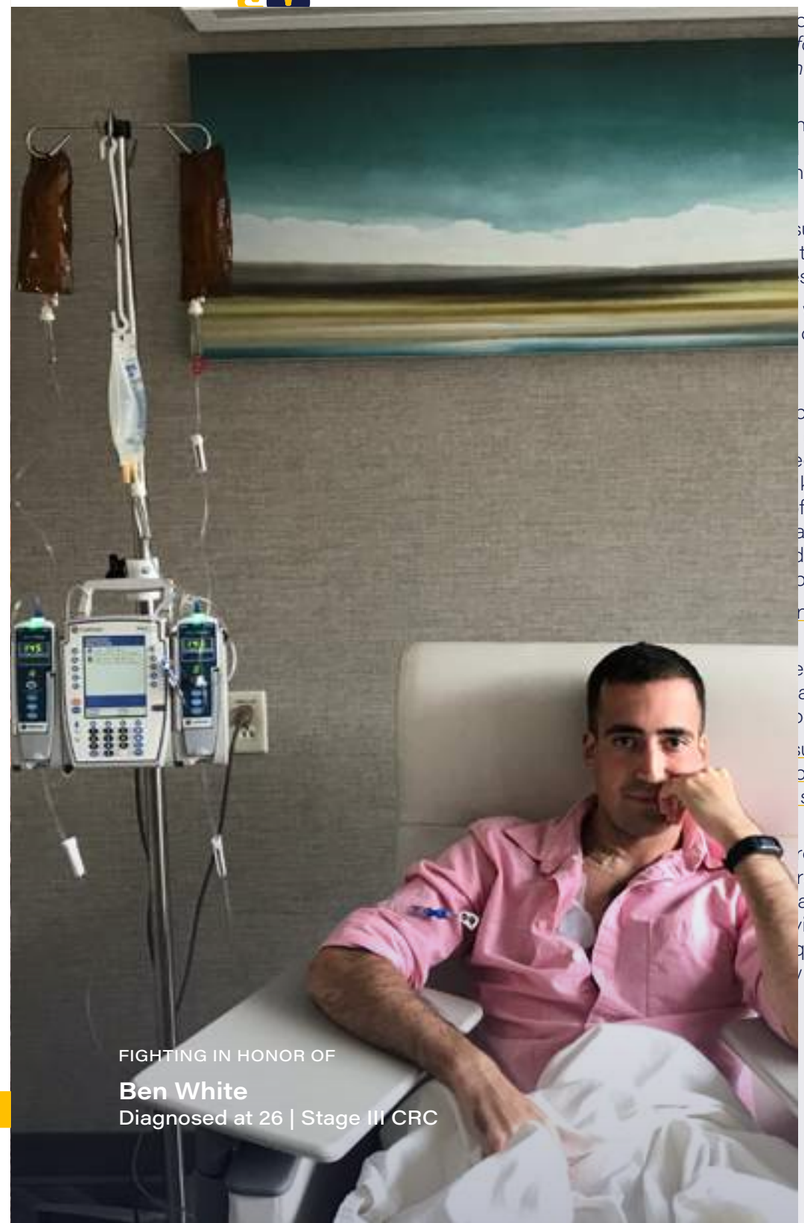
The bottom line: Colorectal cancer survivors are often lost in the transition.

> ***"An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition."***
>
> — National Cancer Institute Office of Cancer Survivorship
> (adapted from the National Coalition for Cancer Survivorship) [48]

We are devoted to understanding the etiologies of cancer and improving treatments. Yet to truly succeed in our effort to find a cure, we must seek opportunities to expand cancer research efforts to include data on survivorship through clinical trials, large cohort studies, cancer registries, and national surveys. We need to understand the unique needs of colorectal cancer survivors in order to build programs that will meet their needs and improve overall quality of life for our community.

You are alive, but are you suffering?

CHALLENGES



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OPPORTUNITIES

CHALLENGES &

SURVIVORSHIP

STRAIGHT TALK
FROM COLORECTAL CANCER SURVIVORS

Bowel dysfunction causes physical and lifestyle limitations, leading to a lesser quality of life.

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CHALLENGES

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CHALLENGES &

STRAIGHT TALK
FROM COLORECTAL CANCER SURVIVORS

Physical symptoms hinder return to work; survivors experience meaningful impairment in completing everyday tasks, which can in turn cause financial burdens.

FIGHTCRC.ORG

FIGHTING IN MEMORY OF
Robyn Schmid Tiffie
Diagnosed at 31 | Stage IV CRC

CHALLENGES

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SECTION FOUR: SURVIVORSHIP AND RECURRENCE

CHALLENGES &

SURVIVORSHIP

STRAIGHT TALK
FROM COLORECTAL CANCER SURVIVORS

Side effects and recovery can be daunting and negatively impact quality of life.

Survivors need real-world education on side effects, the surgery process, and long-term adjustments.

FIGHTCRC.ORG

Dr. Ryan Fields
CRC Surgeon

CHALLENGES

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SURVIVORSHIP

STRAIGHT TALK
FROM COLORECTAL CANCER SURVIVORS

Late-stage survivors struggle with fear of cancer recurrence/ progression and feelings of powerlessness, sadness, or frustration from the life-changing effects of treatment and surgery.

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CHALLENGES &

SURVIVORSHIP

STRAIGHT TALK
FROM COLORECTAL CANCER SURVIVORS

There are unique colorectal cancer functional limitations. Patients young and old alike face issues around sexuality.

For many, stomas can cause body image issues and reduce confidence.

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CHALLENGES

* In late 2019, the American College of Surgeons Commission on Cancer (CoC) released *Optimal Resources for Cancer Care: 2020 Standards for Cancer Program Accreditation*. This was a big win for all survivors. [49]

  This policy set a standard to require the cancer program's cancer committee to oversee the development and implementation of a survivorship program directed at meeting the needs of cancer patients treated with curative intent. [49]

  Today, there is a stronger focus on cancer survivorship and the needs of cancer patients; however, these interventions are often not reimbursed. Survivorship is an under-resourced area.

* To have a successful survivorship program, we must address the patient as a whole person. Easier said than done!

OPPORTUNITIES

* Based on the literature across all cancer types, we know treatment summaries (TS) and survivorship care plans (SCPs) are being implemented, but the data is mixed about their impact on improving patient outcomes. We know patients are riddled with challenges beyond treatment of their cancer. From mental health to nutrition, cancer patients face an avalanche of challenges, and there is a lot of thought and consideration on how to support patients in their survivorship journey.

  How can we develop research efforts that include a holistic approach to survivorship?

* There is an opportunity to provide guidance and consensus on colorectal cancer survivorship standards. Part of the equation is delivery of care for virtual, telehealth, or in-person visits.

  Let's have focused discussions on how to support the unique issues faced by young patients, late-stage patients, and those with specific tumor types, and/or receiving specific types of targeted therapies.

  Colorectal cancer survivors are a diverse group facing long-term treatment side effects. Our research efforts should encourage and empower a proactive approach to support their overall health. From implementing survivorship care plans to unpacking the real-life experiences and quality of life of survivors, we can and should use this knowledge to inform future funding opportunities.

OPPORTUNITIES

SECTION FOUR: SURVIVORSHIP AND RECURRENCE

CHALLENGES &

RECURRENCE

From surviving to thriving, you can't help but think about recurrence. Approximately 30%–40% of patients develop recurrence following surgery, and 40%–50% of recurrences are apparent within the first few years after initial surgical resection. (51)

Recurrent disease usually presents as distant metastasis in the liver or lungs or as locoregional recurrence in the pelvis or peritoneum. (51)

The following are general statistics about the chance of recurrence:

* Stage I < 10%
* Stage II 10%-15%
* Stage III 25%-40%
* Stage IV 50%-70% (after liver resection)

Adapted from: NCCN Treatment/Recurrence Staging Protocols

CHALLENGES

* Numerous studies have shown the clinical utility of ctDNA, a noninvasive biomarker which can predict minimal residual disease (MRD), and how it can help us stratify colorectal cancer patients who are more likely to relapse. (52)

  However, what this means for guiding a patients' treatment is still an active and important research question. The biggest questions are: Will patients treated with pre-surgical therapy, surgery, and post-surgical chemotherapy have additional treatments if there are signs of MRD? And how do we provide mental health support for those who do receive a positive ctDNA test?

  Research advances in this area are especially important for our metastatic and early-age onset patients. Individuals ages 25 years old and younger with colon cancer appeared to be at higher risk for relapse and death than older adults, according to data published in Journal of the American College of Surgeons.

OPPORTUNITIES

* ctDNA research is advancing rapidly, but are the study designs strong enough to change clinical practice? That's what we are striving for.

  There is strong momentum to find clinical utility for these tests to help patients with a lower risk of recurrence avoid the side effects of additional treatment and those with a higher risk receive proactive care.

  There is great promise to use ctDNA tests with current standard monitoring guidelines in the early detection of recurrence, but it will only make a difference if patients have access to these advances.

* Our goal is for patients to live longer and enjoy their quality of life. To do this successfully, survivorship research efforts must elaborate and inform patients and their loved ones on the many issues relevant to long-term survival and risk of recurrence.

POLICY SHOUT OUT

Coverage policy will play an important role when it comes to adoption of new tests. The potential clinical adoption of ctDNA assays for MRD assessment depends in part on coverage in both the commercial market and among public payers such as Medicare.

Various Medicare contractors have issued local coverage determinations (LCDs) for validated tests able to detect molecular recurrence or progression before it is evident through clinical or radiographic evaluation, but more needs to be done to ensure full coverage for all patients and clinical adoption. (53)

OPPORTUNITIES

SECTION FOUR: SURVIVORSHIP AND RECURRENCE

TIME TO GET SHiT DONE

SURVIVORSHIP AND RECURRENCE

PROGRESS INDICATOR:

ENHANCING QUALITY OF LIFE AND PREVENTING RECURRENCE

OBJECTIVE 1

Development and research of survivorship care delivery intervention and approaches, which take into account the whole person—all of one's health conditions and social conditions, not just one's colorectal cancer.

Strategies:

1. Build consensus guidelines for Commission on Cancer survivorship recommendations for colorectal cancer survivorship taking into account the following key aspects:
   - a. Integration of professional and evidence-based colorectal cancer survivorship guidelines in survivorship interventions;
   - b. Improve ways to reduce suffering and mortality among survivors, and promoting return to life, work, and school;
   - c. Focus on the needs of caregivers;
   - d. Integrate evidence-based psychosocial services into standard of care;
   - e. Enhance the education of survivors and all clinicians;
   - f. Define quality measures for colorectal cancer survivorship care;
   - g. Provide viable strategies that bridge care delivery with primary care and oncology care;
   - h. Provide survivorship care that is sustainable, accessible, affordable, and equitable.
2. Build models of care and integrate what is published, established, and known about the specific needs of the differing "types" of colorectal cancer patients.
3. Include research advocates in designing and testing models of care delivery and approaches to risk stratification for colorectal cancer survivors that consider the whole person.
4. Implement and develop quality measures for survivorship care.
5. Increase the number of grants, dollar amounts, and grant mechanisms of PCORI, NCI, DOD, and CDC to fund colorectal cancer survivorship opportunities.

SECTION FOUR: SURVIVORSHIP AND RECURRENCE

OBJECTIVE 2

Increase the capacity of healthcare delivery systems, primary care, public health, and the health workforce to bridge care needs of colorectal cancer patients post-treatment.

Strategies:

1. Focus specific strategies to educate primary care providers and help bridge care from oncologists to primary care providers for longer-term management of colorectal cancer survivors' needs and prevent recurrence.
2. Advocate with the CDC for supportive care and community-based services that must be purposefully developed for colorectal cancer survivors so they may continue their social, recreational, and vocational roles and functions in daily life.
3. Explore methods of care delivery for virtual, telehealth, in-person, or other delivery of care mechanisms to specifically support the needs of colorectal cancer patients.
4. Provide policy expertise to create sustainable patient navigation throughout the oncology care continuum, including into cancer survivorship.

OBJECTIVE 3

Expand research efforts to improve and advance development of emerging and new technologies for early detection, screening, and prevention of recurrence.

Numerous studies have shown the clinical utility of ctDNA, a noninvasive biomarker which can predict minimal residual disease (MRD), and how it can help us stratify colorectal cancer patients who are more likely to relapse. However, what this means for guiding a patient's treatment is still an active and important research question.

The biggest questions are: Will patients treated with pre-surgical therapy, surgery, and post-surgical chemotherapy have additional treatments if there are signs of MRD? And how do we provide mental health support for those who do receive a positive ctDNA test?

Research advances in this area are especially important for our metastatic and early-age onset patients. Individuals ages 25 years old and younger with colon cancer appeared to be at higher risk for relapse and death than older adults, according to data published in Journal of the American College of Surgeons.

Strategies:

1. Assess the ability and extent for ctDNA tests to guide treatment decisions and monitor for MRD and recurrence in colorectal cancer.
2. Gather stronger data from patients to monitor recurrence, ctDNA, and the correlation with clinical outcomes.
3. Identify high-risk patients with remaining microscopic disease, so that treatment and follow-ups can be tailored accordingly.

SECTION FOUR: SURVIVORSHIP AND RECURRENCE

WE CAN'T AFFORD TO WAIT.

In 1970, cancer overall was the second-leading cause of death in the United States.[11]

By 1971, President Richard Nixon signed the National Cancer Act. This effort to pass policy to initiate a war on cancer was led by an activist, Mary Lansker, personally touched by cancer.[54]

Today, colorectal cancer is the second-leading cause of cancer deaths for men and women in the U.S.[2]

Activists and advocacy groups have a rich history
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At the start of my career (1982), there was only one colorectal cancer drug available, 5-FU.

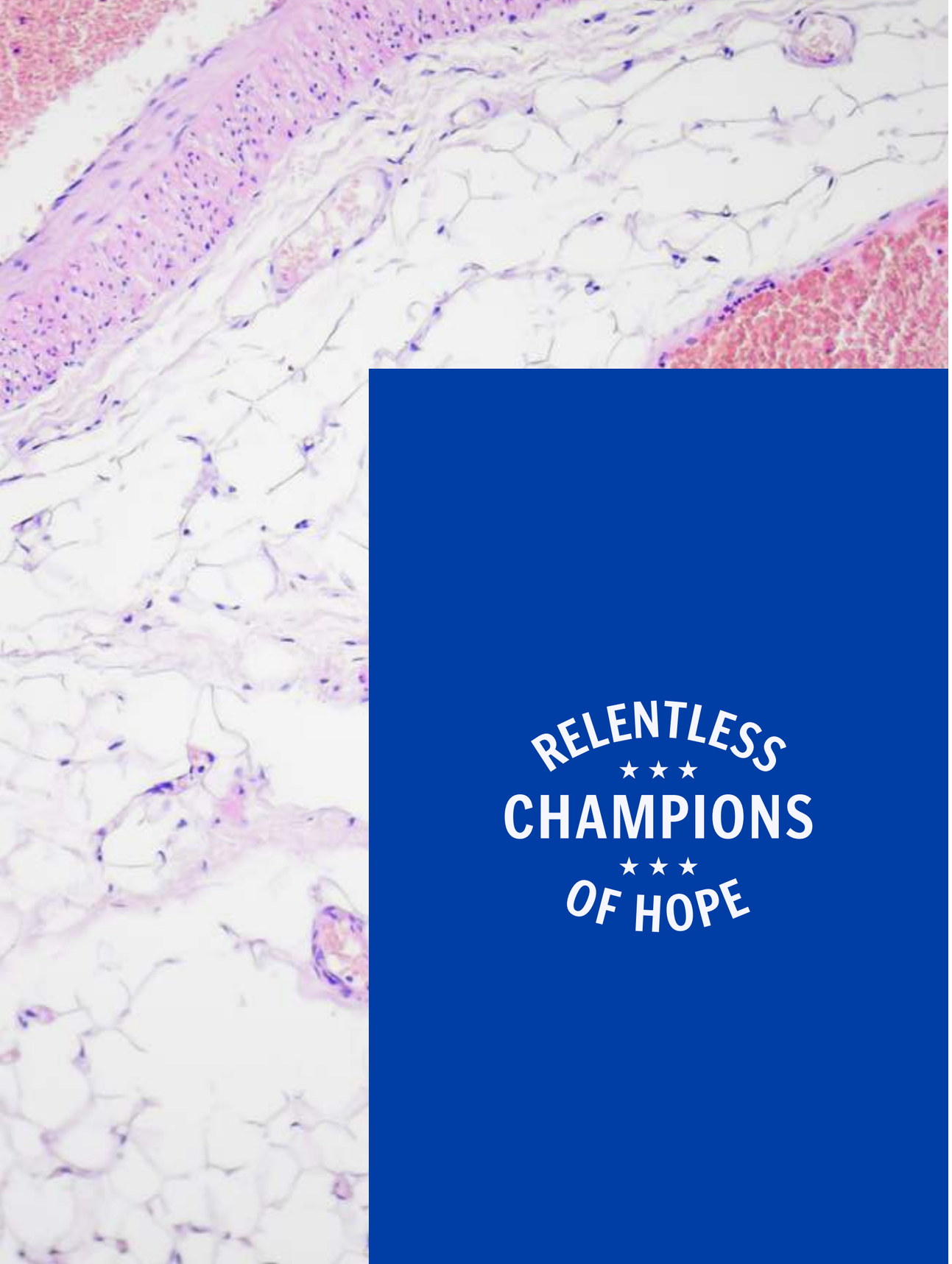
Survival for people with advanced colorectal cancer was only an average of 12 months and curing anybody with stage IV colorectal cancer seemed impossible.

Now, there are 16 drugs approved in the United States for colorectal cancer and more on the horizon.

Survival for advanced cases is currently closer to three years on average, and we're seeing a cure rate of around 15%.

I expect that rate to continue to increase for many reasons, beyond just better chemotherapy drugs.

— Dr. Richard Goldberg
GI Oncologist and Advocate



RELENTLESS CHAMPIONS OF HOPE

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Today, colorectal cancer is the second-leading cause of cancer deaths for men and women in the U.S.[2]

Activists and advocacy groups have a rich history emboldening our cancer research community to take critical steps forward. From legislation to the creation of alternative models for conducting cancer research, patients' voices have pushed us forward.

Today, across the cancer continuum, patients and advocacy organizations have made research and clinical care more of a partnership. Seeing it as a partnership is essential to understanding what patients want and need.

This report is not exhaustive. It will continue to evolve and be enriched through partnership and collaboration. But it is a bold step forward. It begins a long-term effort to incorporate patient and scientific priorities. For the colorectal cancer community, it is time to make the devastating impact of this disease a national priority.

Our future is now.

This report reflects the commitment of advocates across the country to be involved in the scientific research process and lock arms to advocate for colorectal cancer research funding and communicate research findings to the public.

We represent passionate men and women willing to push for policy change and move past the status quo. For our patients, we continue to fight with them and for them. We are giving a voice to all those impacted by colorectal cancer. We bravely hold on to hope for a cure.

Together, working hand in hand across industry, academia, advocacy, public health, government agencies, and with patients, this plan will drive and unify stakeholders to ask important questions, prioritize, and expand our scientific efforts.

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