FIGHT COLORECTAL CANCER®

PATH TO A CURE REPORT

BIOLOGY AND ETIOLOGY

CHALLENGES & OPPORTUNITIES

1

PROGRESS INDICATOR:

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

SECTION ONE: BIOLOGY AND ETIOLOGY

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

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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

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CHALLENGES & OPPORTUNITIES

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]

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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.

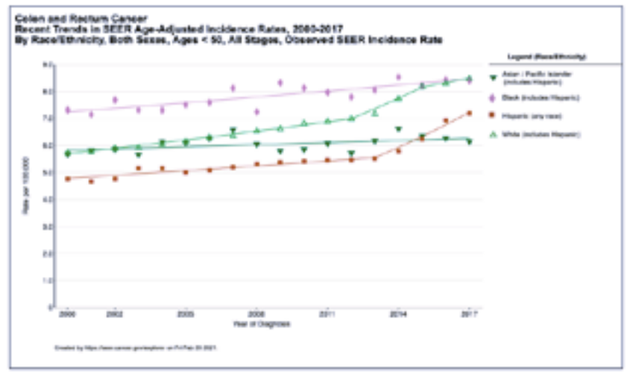
A focus for USPSTF to make guidelines for referral of patients for Lynch syndrome genetic testing routine could be explored. (12)

OPPORTUNITIES

CHALLENGES &

Figure 1.1

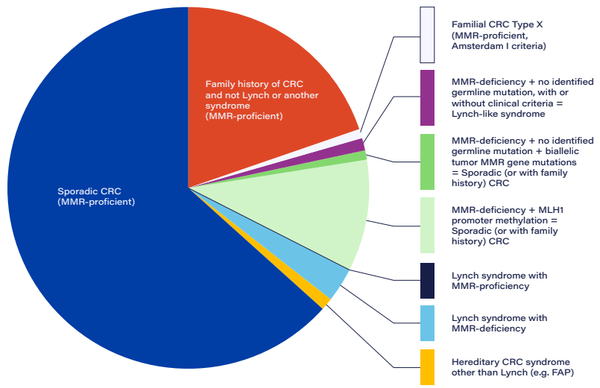
Colon and Rectum Cancer: Recent Trends in SEER Age-Adjusted Incidence Rates, 2000-2027 by Race/Ethnicity, Both Sexes, Ages < 50, Observed SEER Incidence RATES



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

Figure 1.2

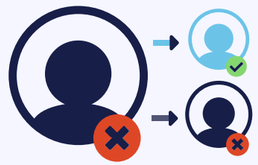
Categories of colorectal cancer (CRC) with a focus on concepts and terminology related to Lynch syndrome.



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:

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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.

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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	

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