FIGHT COLORECTAL CANCER®

PATH TO A CURE REPORT

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

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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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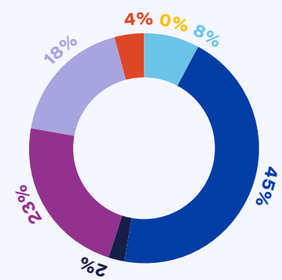


GlobalData Colorectal Cancer Development Pipeline, by Phase

- 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/.

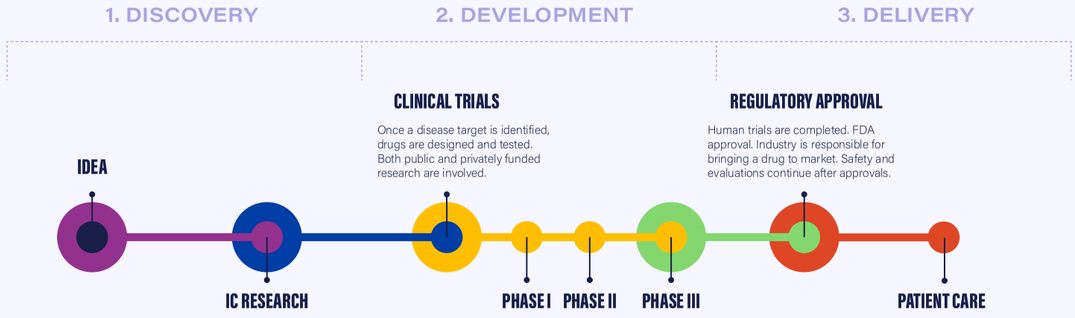
At the heart of the issue is the fact that despite being the second-leading cause of cancer deaths for men and women in the U.S., and the startling increase in diagnoses among young people, federal funding for colorectal cancer research has not kept pace.

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

FIGHT COLORECTAL CANCER™
PATH TO A CURE OBJECTIVES AND STRATEGIES

SECTION THREE: TREATMENT

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

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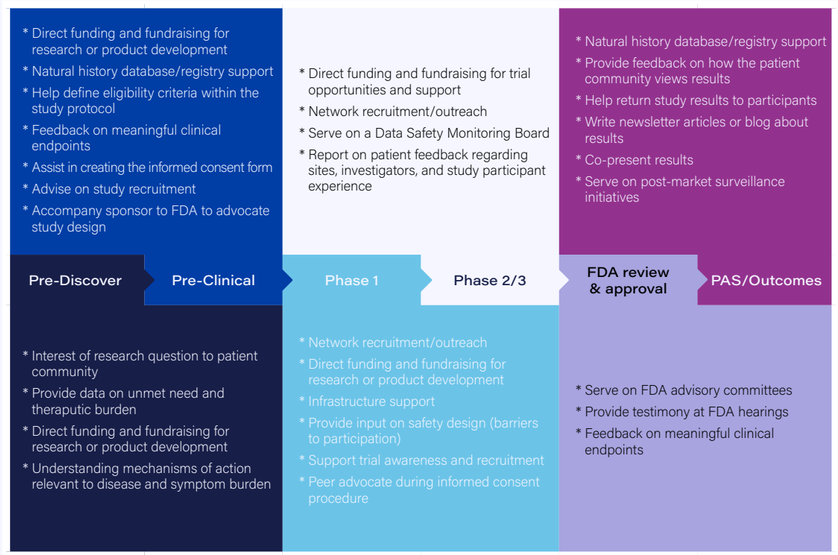
CHALLENGES &

PATIENTS' VOICES MATTER

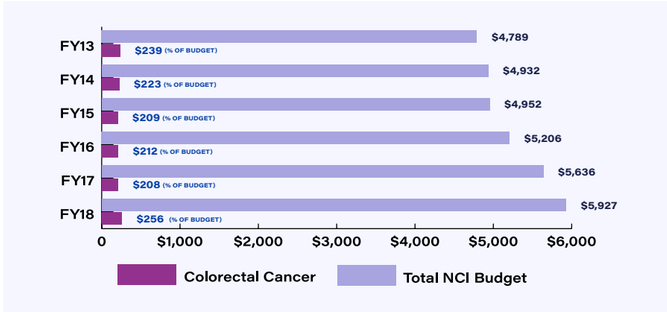
Patient Engagement Across the Clinical Trial Continuum



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

Figure 3.1

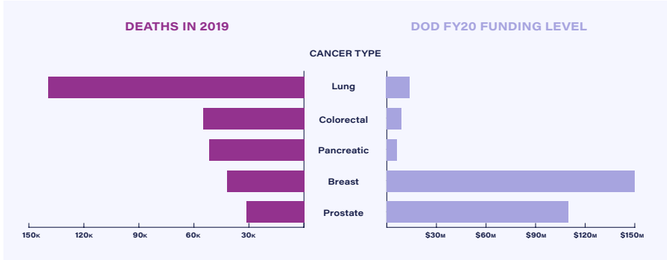
National Cancer Institute CRC funding levels by fiscal year vs. total NCI budget



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)

OPPORTUNITIES

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TIME TO GET SH*T DONE

SECTION THREE: TREATMENT

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

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