

The ColoCare Study: A Paradigm of Transdisciplinary Science in Colorectal Cancer Outcomes

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Abstract

Background: Colorectal cancer is a leading cause of cancer death. Biomarkers to predict treatment outcomes are needed, as is evidence whether postdiagnosis diet and lifestyle can affect well-being and clinical outcomes. The international ColoCare Consortium aims to identify new biologic markers (e.g., metabolomic, transcriptomic, metagenomic, genetic, epigenetic, proteomic markers) that predict clinical outcomes, and to characterize associations between modifiable risk factors (e.g., diet, supplement use, physical activity) with short-term and long-term patient-reported and clinical outcomes among patients with colorectal cancer.

Methods/Results: ColoCare is recruiting newly diagnosed patients with colorectal cancer across six sites in the United States and one site in Germany. As of April 2018, we have recruited >2,000 patients across all sites. Our projected enrollment is >4,000 multiethnic patients with colorectal cancer. The study includes uniformly collected, comprehensive sets of

data and biospecimens at multiple time points up to 5 years after diagnosis. Treatment and clinical data are abstracted from medical records and centrally harmonized. Biospecimens are archived according to standardized procedures. Our initial studies demonstrated metabolic differences in adipose tissue types. We further reported on associations of biological factors (e.g., inflammation, DNA methylation, metabolomics) with lifestyle factors (e.g., adiposity, smoking, physical activity, dietary supplement use) or joint associations with clinical outcomes.

Conclusions: ColoCare is a consortium for the investigation of multilevel factors relevant to colorectal cancer survivorship.

Impact: The combination of a comprehensive set of biospecimens collected at multiple time points, jointly with detailed assessments of health behaviors and other prognostic factors, results in a unique resource that facilitates wide-ranging, innovative, and impactful research on colorectal cancer.

Introduction

Colorectal cancer is the second most frequent cancer globally (1,360,600 cases) and the third most common cause of cancer death (693,900 deaths) worldwide (1). The incidence and mortality rates among individuals below 50 years of age have increased in recent years (2). Concurrently, the number of survivors of colorectal cancer continues to increase (3) which is attributable at least in part to improved treatment regimens and to both improvements in and wider participation in colorectal cancer screening (4). However, recurrence affects nearly a third of colorectal cancer patients and is a major cause of morbidity and mortality (3, 5). The discovery of biomarkers/risk prediction models with high sensitivity and specificity for recurrence remains a high research priority. At this time, the most accurate means for predicting prognosis for colorectal cancer remains pathological stage, despite the fact that significant clinical heterogeneity in treatment response exists among patients with the same stage of cancer (6). Blood, urine, or stool-based biomarkers have the advantage that they can be examined prior to and after surgery to monitor disease status noninvasively. Studies collecting detailed patient and treatment information as well as biospecimens prior to and post-diagnosis are rare. ColoCare is an innovative and transdisciplinary cohort specifically designed to discover and validate novel prognostic biomarkers and risk

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prediction models in a highly annotated set of colorectal cancer survivors, thus addressing a clearly defined clinical and public health need.

To date, still little is known about the effects of nutritional supplements, diet, physical activity, or use of hormones and other medications on cancer outcomes. The identification of behavioral factors affecting prognosis and response to treatment is a research area ColoCare is designed to address through a series of surveys that include key health behavior research questions related to potentially modifiable exposures such as physical activity, NSAID use, alcohol consumption, dietary factors, and many more. In particular, the topics of energy balance, adipose-tumor tissue interactions and physical activity are timely and important, considering the dramatic rise in obesity worldwide, the potential for direct growth-promoting effects of adipose tissue adjacent to colon tumors, and the accumulating evidence that physical activity can positively affect cancer outcomes (7–12).

Motivating the development of the ColoCare Study was the fact that very few prospectively collected colorectal cancer patient cohorts currently exist, and those that do have multiple limitations related to sample size, comprehensiveness of exposure and outcome data, and collection of multiple types of longitudinal questionnaire data and biospecimens (13). The goal of the ColoCare Study is to provide the research infrastructure needed to identify new biologic markers (e.g., metabolomic, transcriptomic, metagenomic, genetic, epigenetic, and proteomic biomarkers) that predict clinical outcomes, and to characterize associations between potentially modifiable risk factors (e.g., diet, supplement use, NSAID use, physical activity, body composition, etc.) with short-term and long-term patient-reported and clinical outcomes (e.g., therapy-induced toxicities, recurrence, survival and quality of life, etc.) among patients with colorectal cancer. Although several of these factors have been studied in isolation, a unique feature of the ColoCare Study is its transdisciplinary approach, which enables concurrent, synergistic research on these factors within a single prospective cohort. Geographical and demographic diversity adds to the value of the study and increases generalizability. Study results leveraging ColoCare will inform potential approaches for optimizing therapies and treatment strategies for individual colorectal cancer patients and will provide evidence-based guidance for patients and clinicians on modifiable health behaviors that are associated with improved outcomes and quality of life. The collective results from the ColoCare Consortium have the potential to have an important impact on the clinical and survivorship management of this major disease.

Materials and Methods

ColoCare (ClinicalTrials.gov Identifier: NCT02328677) is an international, multicenter prospective cohort study among women and men newly diagnosed with a primary invasive colorectal cancer of any stage. ColoCare goals are to investigate predictors of cancer recurrence, survival, treatment toxicities, and health-related quality of life. The study was initially developed at the Fred Hutchinson Cancer Research Center (Seattle, WA) in 2007, with subsequent consortium sites at the H. Lee Moffitt Cancer Center and Research Institute (Tampa, FL) in 2009, National Center for Tumor Diseases and University Hospital of Heidelberg (Heidelberg, Germany) in 2010, Huntsman Cancer Institute (Salt Lake City, UT) in 2015, Cedars-Sinai Medical Center (Los Angeles, CA) in 2017, Washington University School of Medicine (WUSM;

St. Louis, MI) in 2017, and the Center for Cancer Research (Memphis, TN) in 2017.

Eligible patients are defined as follows: newly diagnosed colon (ICD-10 C18), rectum, or rectosigmoid cancer (ICD-10 C19/C20); ≥ 18 years of age at the time of diagnosis, histopathologically confirmed invasive cancer of any stage of disease based on the AJCC classification, and able to provide informed consent. ColoCare has been approved by the local institutional review boards serving each site. This study enrolls English speaking patients at all U.S. sites, except for the Cedars-Sinai Medical Center, which additionally enrolls non-English speaking individuals and the German site, which enrolls German-speaking patients. All study participants provide written informed consent (paper or electronically).

Participant recruitment and follow-up

Mechanisms are in place at each site to identify newly diagnosed patients with colorectal cancer and recruitment protocols are standardized across all sites. Patients are recruited before surgery (baseline). In brief, during a clinical appointment, preferably prior to their primary surgery to treat the cancer, patients are approached to participate in ColoCare and those willing to participate are consented. ColoCare Study participants agree to complete a baseline questionnaire and provide biological specimens at the time of enrollment and over the course of 5 years of follow-up, as outlined below. In addition, participants agree to provide access to their medical records. Figure 1 illustrates the ColoCare Study design; detailed data and sample collection procedures are described below and in Table 1. Of note, not all components are collected at each time point and across all centers.

Patients are followed up both actively and passively by study staff (in-person or remote and through medical record reviews), as well as via linkages to cancer registry and vital status records. We conduct a brief telephone assessment of physical activity and symptom measures 3 months after surgery, which for patients undergoing adjuvant therapy is approximately half-way through this treatment. Follow-up questionnaires on health behaviors, symptoms, and quality of life are administered at 6, 12, 24, 36, 48, and 60 months (details below). For patients undergoing neoadjuvant and/or adjuvant chemotherapy assessments are performed at least 2 weeks after completing a cycle.

Data collection

All questionnaires used in ColoCare are self-administered and can be completed on paper or electronically. The baseline questionnaire includes assessments of demographics (e.g., education, ethnicity, marital status), lifestyle factors known/suspected to be associated with colorectal cancer (e.g., smoking, alcohol use, and physical activity), hormone replacement therapy for women, self-reported anthropometric measures (e.g., height and weight), medical history, family history of cancer, dietary supplement use, and prescription and nonprescription medication use. General and colorectal cancer-specific quality of life questionnaires (e.g., SF-12, MDASI, EORTC QLQ-C30) are also included (see section "Patient reported outcomes" for details on quality of life assessments). We use both standardized instruments and adapted questions from ongoing studies, such as the Women's Health Initiative or the Colorectal Cancer Family Registry (14, 15). The baseline questionnaire has been designed to be relatively brief to reduce patient burden and improve completion rates.

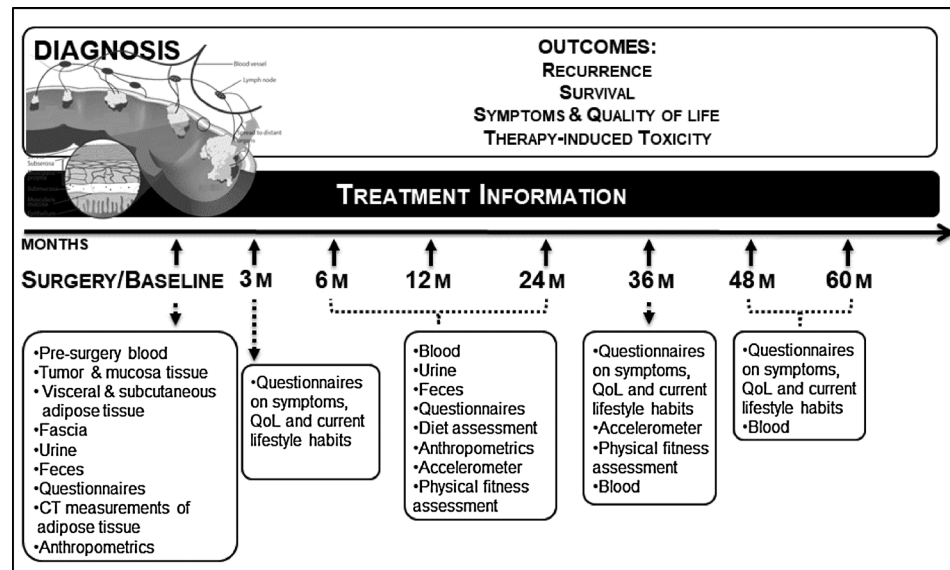


Figure 1. ColoCare Study design. Not all components are collected at each time point and across all centers.

The 6- to 60-month questionnaires include demographics, physical activity, cancer and treatment distress, work limitations, and work productivity and activity impairment questionnaires; and re-administration of the general and colorec-

tal cancer-specific quality of life and symptom measures. From the 6-month questionnaire assessment, dietary habits are measured using a food frequency questionnaire (FFQ; refs. 16, 17).

Table 1. ColoCare Study: overview of questionnaires, measurements, and biospecimen collection at each time point

	Baseline	3 months	6 months	12 months	24 months	36 months	48 months	60 months
Questionnaires								
Demographic information	X		X	X	X			
Smoking	X		X	X	X			
Alcohol consumption	X							
Medical history	X							
Family history	X							
Screening assessment	X							
Therapy and follow-up of the disease				X	X	(X)*		
Hormone replacement therapy	X		X	X	X			
Dietary supplement use	X		X	X	X			
Medication use	X		X	X	X			
Physical activity	X	X	X	X	X	X	X	X
Quality of life	X	X	X	X	X	X	X	X
Symptoms	X	X	X	X	X	X	X	X
Social network	X		X	X	X			
Sleep rhythm and quality	X	X	X	X	X	X	X	X
Work limitation assessment			X	X	X			
Dietary behavior assessment			X	X	X			
Measurements								
Height	X							
Weight	X		X	X	X	X	X	X
BMI	X		X	X	X	X	X	X
Waist-to-hip ratio	X		X	X	X	X	X	X
Waist circumference	X		X	X	X	X	X	X
Accelerometer				X	X	X		
Physical fitness testing				X	X	X		
Computed tomography scan analyses	X							
Biospecimens								
Blood	X		X	X	X	(X)**	(X)**	(X)**
Stool	X		X	X	X			
Urine	X		X	X	X			
Saliva	X		X	X	X			
Tumor and mucosa tissue	X							
Metastases	X							
Visceral fat tissue	X							
Subcutaneous fat tissue	X							
Fascia tissue	X							

*Optional follow-up of therapy and follow-up of the disease.

**Optional collection of biospecimens.

Specific assessment of dimensions of energy balance

In light of the obesity epidemic worldwide—and in lieu of the increasingly strong evidence that physical activity reduces the risk of colorectal cancer recurrence—this study includes state-of-the-art measures of physical activity and adiposity, that capture multiple dimensions of energy balance, from (i) the tumor microenvironment of tumor-adjacent adipose tissue to (ii) adipose tissue distribution and (iii) physical activity during key phases of colorectal cancer treatment and survivorship.

Physical activity measurement by accelerometry. Study participants may wear ActiGraph GT3X+ (ActiGraph, Pensacola, FL) accelerometers for a state-of-the-art, objective assessment of physical activity (18) at 6, 12, and 24 months. We have successfully tested the implementation of accelerometers and demonstrated feasibility at the German ColoCare Study site as part of a pilot study (18). Based on this initial research, study participants wear accelerometers for 4 full days. In our pilot, we have used accelerometers that have been fastened around the chest with a band. Subsequently, we have implemented accelerometers that are worn around the wrist, as they reduce participant burden. In our initial studies, we successfully demonstrated patient compliance at ColoCare Heidelberg: 59% of patients contacted agreed to wear accelerometers and, of these, 83% completed the assessment with ≥ 4 days of valid data. The implementation of accelerometers for physical activity measurement is currently ongoing at other ColoCare sites.

Physical fitness test. Participants are asked to perform a physical fitness assessment at the 12-, 24-, and 36-month time point. This is an optional component of the study. All exercises are conducted, monitored, and recorded by a certified exercise physiologist or trained study staff. The assessment consists of nine different parts: six-minute walk, hand grip, 30-seconds chair stand, the timed up and go, core endurance, leg and chest strength tests, and active range of motion testing in shoulders and hips. Pilot testing of the physical fitness testing protocol at the Wellness Center at the Huntsman Cancer Institute is currently underway, and thus far $n = 8$ patients have completed the physical fitness test. Once this pilot evaluation is complete, we will expand the physical fitness test to additional ColoCare sites.

Physical activity measurement by questionnaires. All ColoCare questionnaires assess physical activity using the VITAL questionnaire, which contains questions on light, moderate, and vigorous physical activities (19). Starting with the 6-month follow-up, the ColoCare questionnaires also contain a physical activity instrument adapted from the CHAMPS questionnaire (20). As of April 2018, 80% (range: 64%–91% across sites) of our participants have completed baseline questionnaires. These proportions continue to increase.

Anthropometric assessment. All ColoCare sites have implemented anthropometric measurements at baseline, 6, 12, and 24 months, technician-measured height, weight, waist, and hip circumferences are obtained at an in person visit. If this is not possible, height and weight are abstracted from patients' medical records or anesthesiology protocols; alternatively, self-measurement per procedures from the Iowa Women's cohort is performed (21). The overall completion rate of anthropometric assessments at baseline is 80% (August, 2018).

Adipose tissue collection. Visceral and subcutaneous adipose tissue are collected as described in section "Biospecimen collection and processing" and available for research on adipose tissue metabolomics, gene expression, and proteomics.

Radiological measures of abdominal fat deposition. Abdominal fat deposition (visceral and subcutaneous fat distribution) is assessed by using multidetector computed tomography (CT) imaging collected as part of standard of care for diagnostic purposes. The basic analysis of abdominal CT images is performed on a digital radiology workstation. Compartmental densitometry is used to quantify the total, visceral, and subcutaneous fat area (TFA, VFA, and SFA), and functional muscle mass on single axial slice of intervertebral space levels L3/4 and L4/5 by setting the CT attenuation level between 40 and 100 Hounsfield units (HU). These area-based assessments of VFA and SFA are strongly associated ($r > 0.93$) with volumetric measurements of the entire abdominal adipose compartments (22).

Biospecimen collection and processing

Biospecimens are collected and stored at each ColoCare site to facilitate future biomarker analyses, such as (i) gene expression and methylation profiling in tumor, uninvolved mucosa and fat tissue, (ii) plasma/serum biomarkers that may be associated with colorectal cancer prognosis [e.g., 25-hydroxyvitamin D₃ (25(OH) D₃) and folate-dependent one-carbon metabolites], and (iii) urinary markers of oxidative stress (e.g., 7,8-dihydro-8-oxo-2'-deoxyguanosine). Collection of stool samples at multiple time points allows studying changes in gut microbiota before and after treatment. Standardized protocols for biospecimen collection are used at all sites.

All samples are processed according to harmonized protocols and standard operating procedures across all institutions. Blood, stool, urine, and tissue samples [fresh-frozen and formalin fixed (FFPE)] are collected at all sites. At the German site additionally fascia tissue from the incisional site is collected. During the process of sample collection information on sample acquisition, processing and storage, time of sample excision, and time of freezing are documented.

Blood. Blood draws are performed at baseline as well as at 6, 12, 24, and at select sites also at 36, 48, and 60 months postsurgery. The serum, plasma, and buffy coat (or cell-rich interface) are divided into aliquots and stored at -80°C . We have successfully implemented remote collection procedures for study participants who are not able to come to the study site cancer centers for their follow-up visit.

Urine. Spot urine is obtained at each study time point during a clinic visit. Urine is immediately aliquoted (half of samples with vitamin C added) and stored at -80°C .

Stool. Stool samples are collected at baseline, and from the 6-month follow-up time point. At the baseline time point, stool collection occurs 2 to 3 days prior to bowel preparation for surgery. A plain stool specimen, as well as a specimen in RNAlater is collected at the participant's home, immediately frozen by the patient and brought to a visit or sent frozen to the lab with provided freeze packs. The stool samples are stored at -80°C .

Saliva. Saliva samples are collected for microbial studies from all participants and serve as a source of germline DNA from participants who are not willing to provide blood samples for genetic studies. Saliva is collected in RNAlater and aliquoted and stored at -80°C .

Tissue. Tumor, normal mucosa (adjacent and distant to tumor), visceral, and subcutaneous adipose tissue are collected during surgery following the standard operating procedures across all ColoCare sites. At the German site, fascia tissue is additionally collected. All tissues are collected as fresh-frozen and FFPE. Fresh-frozen samples are collected, processed, and frozen within 60 minutes of excision (cold ischemia). During the process of tissue collection, the following parameters are documented for each sample: dates of sample acquisition, processing and storage, time of sample excision, time of freezing, length of fixation, surgical procedure, facility where performed, surgeon and staff involved. For normal tissue, distance from tumor and location in relation to the tumor (proximal or distal, adjacent, or at resection margin) are recorded.

Biospecimen collection rates differ by time point and study center. This is due to the fact, that collection of urine, stool, and saliva was implemented largely after U01 funding was received (FHCRC; Moffitt Cancer Center, Cedars-Sinai, Washington University, in St. Louis, and the University of Tennessee). Blood samples are currently available for 82% of patients at baseline, 61% of patients at the 6-month time point, and 65% of patients at the 12-month time point. Fresh-frozen tissue is collected from about 50% of patients with colorectal cancer undergoing surgery, whereas FFPE tissue is generally available.

Clinical outcomes

We have implemented standardized medical record abstraction forms to obtain detailed information on surgical procedures, treatments (e.g., adjuvant chemotherapy), toxicities, recurrences, and second primaries. Information collected as part of these reviews includes detailed data on all colorectal cancer treatments (modality, timing, and dose), pathologic features, tumor molecular testing and follow-up testing results to monitor for disease recurrence (e.g., CEA test and imaging).

Toxicity. The National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE) methodology is used to grade treatment-related toxicity, using specific adverse events classified in broad categories and grading the severity of the adverse event (grades 0–5). Although clinicians themselves do not generally use the CTCAE grading to characterize toxicity, the definitions of CTCAE grades 0 to 5 are specific enough to enable our abstractors to translate information available in the medical record into these categories.

Colorectal cancer recurrence and survival. We focus on three important clinical outcomes: (i) 2-year and (ii) 5-year overall survival—which considers time of death, irrespective of cause, with appropriate censoring of loss to follow-up, (iii) recurrence loco-regional or distant metastases related to the same tumor, with censoring of deaths and loss to follow-up, and disease-free survival—which considers time to event (recurrence or death) with appropriate censoring for loss of follow-up. Detailed information on colorectal cancer recurrence is ascertained through reviews of patient medical records, pathology and imaging reports

documenting the diagnosis of a recurrence. Medical record reviews are conducted at least 2 years postdiagnosis on all patients to ensure that any recurrences diagnosed within 2 years of diagnosis—the time frame over which the vast majority of colorectal cancer recurrences present ($\sim 80\%$)—are captured. Patients' vital status, or survival, is obtained through local medical records, routine follow-up mailings, periodic requests for outside medical records, and state or national cancer and death registries. We initially review primary medical records for any signs that a patient is deceased, followed by review of outside medical records during follow-up, and any information received from routine follow-up mailings. Any informal reports of a patient's status (e.g., family member reports) are confirmed through other data sources and additional data on date and cause of death obtained. Finally, we use patient information to search national and local data sources for vital status. In the United States, these include the Social Security Death Index (SSDI), National Death Index (NDI), Cancer Surveillance System (CSS) Death Tapes in the state of Washington, state obituaries, and the Florida Cancer Data System (FCDS). In Germany, every person is registered and vital status information including date of death can be reliably obtained at no cost from the Registration Office.

Patient-reported outcomes

Health-related quality of life is assessed by the validated and widely used core questionnaire QLQ-C30 and the colorectal cancer module QLQ-CR29, developed by the European Organization for Research and Treatment of Cancer (EORTC; ref. 23) at each study time point. Moreover, at baseline and all follow-up time points, we perform the MD Anderson Symptom Inventory (MDASI), a multisymptom patient-reported outcome measure for clinical and research use (24). Chemotherapy-induced peripheral neuropathy is measured by the EORTC QLQ-CIPN20 (25). For measurement of patients' physical and mental health, the 12-item Short-Form (SF-12) health survey is used (26).

To assess the productivity impact of on-the-job work limitations due to employees' physical or mental health problems from the 6 month follow-up the Work Limitation Questionnaire (WLQ) is used (27). Additionally, the Work Productivity and Activity Impairment General Health (WPAI: GH) Questionnaire is used to ask about the effect of patients' health problems on their ability to work and perform regular activities (28). To assess distress specific to cancer and its treatment, the Cancer and Treatment Distress (CTXD) questionnaire is provided to patients (29) starting at 6 months after enrolment.

Power consideration and data analysis

The ColoCare Study provides a biorepository and resource for a multitude of research questions, including in collaboration with the other ColoCare sites, with at least 4,000 patients enrolled across the ColoCare Consortium by 2020. The study power will differ depending on the research question and the size of the study population included.

Future analyses will include cross-sectional analyses of associations between biomarkers and health behaviors, and longitudinal descriptive analyses of health behaviors over time. Repeated measures analyses will be applied to assess changes over time in lifestyle factors and molecular biomarkers in relation to recurrence and survival. Hazard ratios will be calculated for lifestyle factors and molecular characteristics at recruitment in relation to clinical outcomes.

Results

To date, in total, we recruited >2,000 patients with colorectal cancer across all ColoCare sites. Baseline characteristics of recruited ColoCare patients are given in Table 2.

Components of the ColoCare Cohort have been leveraged to support initial research; including on biologic determinants of colorectal cancer (e.g., tumor immunity, gut microbiome, epigenome), health behaviors (e.g., physical activity or dietary patterns), components of energy balance (e.g., adipose tissue distribution, accelerometry), clinical endpoints (e.g., surgical complications, quality of life), and novel biomarkers (proteomics, metabolomics, metagenomics). Furthermore, we have published on the interrelations between these factors, specifically in the context of colorectal cancer prognosis (18, 30–48). Table 3 highlights research contributions using the growing ColoCare Study cohort.

To illustrate the breadth of research supported by ColoCare, we briefly describe some key findings. For example, Skender and colleagues showed that accelerometry is a feasible method to assess physical activity in patients with colorectal cancer with three valid days of physical activity measurement sufficient for an accurate assessment; further, accelerometry-based vigorous and moderate-to-vigorous physical activities are positively associated with 25(OH)D₃ levels (18, 43). Nattenmüller and colleagues reported that the densitometric quantification of adipose tissue on CT is highly reproducible, visceral obesity is associated with

metabolic comorbidities and with increased risk of recurrence in colon and rectal cancer (41, 42, 45). As one of the first studies, Liesenfeld and colleagues comprehensively assessed differences in metabolic, lipidomic, and transcriptomic profiles between paired human VAT and SAT and their association with colorectal tumor stage. They identified markers of inflammation in VAT, which supports prior evidence regarding the role of visceral adiposity and cancer (31). Ristau and Yuan and colleagues have also investigated miRNAs as prognostic biomarkers (33, 49). We evaluated DNA methylation patterns, for example in relation to health behaviors (30, 50) and contributed to a study that showed the potential of fecal microbiota for early-stage detection of colorectal cancer (34). Recently, Gigic and colleagues showed that patients following a "Western" diet had lower chances to improve in physical functioning, constipation, and diarrhea after surgery, whereas patients following a "fruit & vegetable" diet showed improving diarrhea scores (4).

In addition, the ColoCare Cohort participant's data and samples have contributed to multiple international consortia, such as ColoRectal Transdisciplinary Study (CORECT), Genetic Associations and Mechanisms in Oncology (GAME-ON), Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO), The International Survival Analysis in Colorectal Cancer Consortium (ISACC), Consortium of Metabolomics Studies (COMETS), the Early Detection Research Network (EDRN), and several European Consortia, e.g., Metabolomic profiles throughout the continuum of colorectal carcinogenesis (MetaboCCC), and Biomarkers related to folate-dependent metabolism in colorectal cancer recurrence and survival (FOCUS).

Table 2. Patient characteristics of the ColoCare Consortium as of April 30, 2018

	<i>n</i> = 2,031	Total %
Gender		
Male	1,197	59
Female	834	41
Age		
<50	358	18
50–59	516	25
60–69	603	30
≥70	554	27
Race ^a		
American Indian/Alaska Native	16	1
Asian	52	3
Native Hawaiian/Pacific Islander	8	0
Black or African American	96	5
White	1,796	88
More than one race	12	1
Other	28	1
Unknown	23	1
Ethnicity ^a		
Not Hispanic	1,918	94
Hispanic or Latino	70	3
Unknown	43	2
AJCC stage		
I	340	17
II	482	24
III	645	32
IV	386	19
Missing ^b	178	8
Tumor site		
Colon	1,014	50
Rectum	955	47
Synchronous	36	2
Missing ^b	26	1

^aAll ColoCare patients from Heidelberg are Caucasian. Racial composition of the cohort is expected to change due to increasing enrollment at ColoCare sites with a specific focus on minorities.

^bNot abstracted yet.

Discussion

The ColoCare Study is unique in that it brings together a transdisciplinary team of clinicians, epidemiologists, and laboratory scientists to address novel questions of colorectal cancer prognosis. Multiple promising biologic and epidemiologic characteristics can be studied with cutting-edge approaches that predict outcomes among patients with colorectal cancer. Within the ColoCare Consortium at least 4,000 newly-diagnosed patients with colorectal cancer will be recruited and followed over a period of 5 years.

Strengths and limitations

Unique and innovative aspects of the ColoCare cohort include: (i) multicenter standardized recruitment of patients at the time of surgery, enabling the collection of fresh-frozen specimens and pretreatment blood samples; (ii) standardized, harmonized, and comprehensive clinical annotation; (iii) uniform protocols for collection and processing of numerous biospecimens, including tumor tissue, mucosa, fat tissue, blood, urine, stool, and saliva; (iv) serial collection of specimens at defined postdiagnosis intervals to enable assessment of changes in biomarkers in prognosis; (v) detailed measurement of health behaviors, quality of life, and symptoms at defined intervals after surgery; (vi) geographically and ethnically diverse population to enhance the applicability of the findings generated; and (vii) minority research (18, 51, 52).

Nevertheless, some limitations should be noted. The gold standard method to evaluate the effects of factors on clinical outcomes is the randomized controlled trial (RCT). ColoCare Study is an observational, nonrandomized study, which cannot prove causality. Still, the ColoCare Study design addresses

Table 3. Selected ColoCare publications

Manuscript title	Year	Full author block	Journal	PMID/PMCID
Altered RECQ helicase expression in sporadic primary colorectal cancers.	2013	Lao VV, Welsch P, Luo Y, Carter KT, Dzieciatkowski S, Dintzis S, Meza J, Sarvetnick NE, Monnat RJ, Loeb LA, Grady WM	Translational Oncology	23908689/3730021
NTRK3 is a potential tumor suppressor gene commonly inactivated by epigenetic mechanisms in colorectal cancer.	2013	Luo Y, Kaz AM, Kanngurn S, Welsch P, Morris SM, Wang J, Lutterbaugh JD, Markowitz SD, Grady WM	PLoS Genetics	23874207/3708790
RET is a potential tumor suppressor gene in colorectal cancer.	2013	Luo Y, Tsuchiya KD, II Park D, Fausel R, Dannagurn S, Welsch P, Dzieciatkowski S, Wang J, Grady WM	Oncogene	22751117/3465636
Tumor-infiltrating lymphocytes in colorectal tumors display a diversity of T cell receptor sequences that differ from the T cells in adjacent mucosal tissue.	2013	Sherwood A, Emerson R, Scherer D, Habermann N, Buck K, Staffa J, Desmarais C, Halama N, Jaeger D, Schirmacher P, Herpel E, Kloor M, Ulrich A, Schneider M, Ulrich C, Robins H	Cancer Immunotherapy and Immunology	23771160/5714563
Plasma 25-hydroxyvitamin D3, folate and vitamin B12 biomarkers among international colorectal cancer patients: a pilot study.	2013	Ulrich CM, Toriola AT, Siegel E, Brenner H, Chang-Claude J, Abbenhardt C, Kotzmann J, Song X, Owen RW, Hoffmeister M, Becher H, Shibata D, Vickers K, Rush SK, Makar K, Würtele G, Haubner R, Sellers TA, Grady W	Journal of Nutritional Science	25191595/4153124
Differences in DNA methylation signatures reveal multiple pathways of progression from adenoma to colorectal cancer.	2014	Luo Y, Wong CJ, Kaz AM, Dzieciatkowski S, Carter KT, Morris SM, Wang J, Willis JE, Makar KW, Ulrich CM, Lutterbaugh JD, Shrubsole MJ, Zheng W, Markowitz SD, Grady WM	Gastroenterology	24793120/4107146
Suitability of circulating miRNAs as potential prognostic markers in colorectal cancer.	2014	Ristau J, Staffa J, Schrotz-King P, Gigic B, Makar KW, Hoffmeister M, Brenner H, Ulrich A, Schneider M, Ulrich CM, Habermann N	Cancer Epidemiology Biomarkers and Prevention	25472670/5699859
Potential of fecal microbiota for early-stage detection of colorectal cancer.	2014	Zeller G, Tap J, Voigt AY, Sunagawa S, Kultima JR, Amiot A, Brunetti F, Costea PI, Habermann N, Hercog R, Koch M, Luciani A, Mende DR, Schneider MA, Schrotz-King P, Staffa J, Tournigand C, Van Nhieu JT, Yamada T, Zimmermann J, Benes V, Kloor M, Ulrich CM, von Knebel Doeberitz M, Sobhani I, Bork P	Molecular Systems Biology	25432777/4299606
Changes in urinary metabolic profiles of colorectal cancer patients enrolled in a prospective cohort study (ColoCare).	2015	Liesenfeld D, Habermann N, Toth R, Owen R, Frei E, Böhm J, Schrotz-King P, Klika K, Ulrich CM	Metabolomics	29250455/5730072
Repeat physical activity measurement by accelerometry among colorectal cancer patients-feasibility and minimal number of days of monitoring.	2015	Skender S, Schrotz-King P, Boehm J, Abbenhardt C, Gigic B, Chang-Claude J, Siegel EM, Steindorf K, Ulrich CM	BMC Research Notes	26048683/4456792
Methylight digital droplet PCR for detection and absolute quantification of infrequent methylated alleles.	2015	Yu M, Carter KT, Makar KW, Vickers K, Ulrich CM, Schoen RE, Markowitz SD, Grady WM	Epigenetics	26186366/4623055
Discovery of novel plasma proteins as biomarkers for the development of incisional hernias after midline incision in patients with colorectal cancer: The ColoCare study.	2016	Böhm J, Pianka F, Stüttgen N, Rho J, Gigic B, Zhang Y, Habermann N, Schrotz-King P, Abbenhardt-Martin C, Zielske L, Lampe PD, Ulrich A, Diener MK, Ulrich CM	Surgery	27745870/5560863
Genome-wide interaction analyses between genetic variants and alcohol consumption and smoking for risk of colorectal cancer.	2016	Gong J, Hutter CM, Newcomb PA, Ulrich CM, Bien SA, Campbell PT, Baron JA, Berndt SI, Bezieau S, Brenner H, Casey G, Chan AT, Chang-Claude J, Du M, Duggan D, Figueiredo JC, Schrotz-King P, Seminara D, Slattery ML, Thibodeau SN, Thornquist M, Toth R, Wallace R, White E, Jiao S, Lemire M, Hsu L, Peters U, CCFR and GECCO	PLoS Genetics	27723779/5065124

(Continued on the following page)

Table 3. Selected ColoCare publications (Cont'd)

Manuscript title	Year	Full author block	Journal	PMID/PMCID
CT-based compartmental quantification of adipose tissue versus body metrics in colorectal cancer patients.	2016	Nattenmuller J, Hoegenauer H, Boehm J, Scherer D, Paskow M, Gigic B, Schrotz-King P, Grenacher L, Ulrich CM, Kauczor HU	European Radiology	26852215/5587125
Smoking is associated with hypermethylation of the APC 1A promoter in colorectal cancer: the ColoCare Study.	2017	Barrow TM, Klett H, Toth R, Bohm J, Gigic B, Habermann N, Scherer D, Schrotz-King P, Skender S, Abbenhardt-Martin C, Zielskie L, Schneider M, Ulrich A, Schirmacher P, Herpel E, Brenner H, Busch H, Boerries M, Ulrich CM, Michels KB	Journal of Pathology	28791728/5647242
Metabolomics and transcriptomics identify pathway differences between visceral and subcutaneous adipose tissue in colorectal cancer patients: the ColoCare Study.	2017	Liesenfeld DB, Grapov D, Fahrman JF, Salou M, Scherer D, Toth R, Habermann N, Böhm J, Schrotz-King P, Gigic B, Schneider M, Ulrich A, Herpel E, Schirmacher P, Fiehn O, Lampe JW, Ulrich CM	American Journal of Clinical Nutrition	26156741/4515859
Plasma 25-hydroxyvitamin D3 levels in colorectal cancer patients and associations with physical activity.	2017	Skender S, Böhm J, Schrotz-King P, Chang-Claude J, Siegel EM, Steindorf K, Owen RW, Ose J, Hoffmeister M, Brenner H, Ulrich CM	Nutrition and Cancer: An International Journal	28094599/5587127
Dynamic plasma microRNAs are biomarkers for prognosis and early detection of recurrence in colorectal cancer.	2017	Yuan Z, Baker K, Redman MW, Wang L, Adams SV, Yu M, Dickinson B, Makar K, Ulrich N, Böhm J, Wurscher M, Westerhoff M, Medwell S, Moonka R, Sinanan M, Fichera A, Vickers K, Grady WM	British Journal of Cancer	28809863/5674097
Quantitative assessment of visceral obesity and postoperative colon cancer outcomes.	2017	Ozoya OO, Siegel EM, Srikumar T, Bloomer AM, DeRenzis A, Shibata D	Journal of Gastrointestinal Surgery	28101721/5560865
Associations between dietary patterns and longitudinal quality of life changes in colorectal cancer patients: the ColoCare Study.	2017	Gigic B, Boeing H, Toth T, Böhm J, Habermann N, Scherer D, Schrotz-King P, Abbenhardt-Martin C, Skender S, Brenner H, Chang-Claude J, Hoffmeister M, Syrjala S, Jacobsen PB, Schneider M, Ulrich A, Ulrich CM	Nutrition and Cancer: An International Journal	1397707/5867188
Associations of branched-chain amino acids with parameters of energy balance and survival in colorectal cancer patients: Results from the ColoCare Study.	2018	Delphan M, Lin T, Liesenfeld DB, Nattenmüller J, Böhm JT, Gigic B, Habermann N, Zielske L, Schrotz-King P, Schneider M, Ulrich A, Kauczor HU, Ulrich CM, Ose J	Metabolomics	29706852/5922458
Robust prediction of gene regulation in colorectal cancer tissues from DNA methylation profiles.	2018	Klett H, Balavarca Y, Toth R, Gigic B, Habermann N, Scherer D, Schrotz-King P, Ulrich A, Schirmacher P, Herpel E, Brenner H, Ulrich CM, Michels KB, Busch H, Boerries M	Epigenetics	29697014/6140810
Body fatness, adipose tissue compartments and biomarkers of inflammation and angiogenesis in colorectal cancer: the ColoCare Study.	2018	Himbert C, Ose J, Nattenmueller J, Warby CA, Holowatyj AN, Böhm J, Lin T, Haffa M, Gigic B, Hardikar S, Scherer D, Zielske L, Schrotz-King P, Koelsch T, Siegel EM, Shibata D, Ulrich A, Schneider M, Hursting SD, Kauczor HU, Ulrich CM	Cancer Epidemiology Biomarkers and Prevention	30333223/6324954
Implications of epigenetic drift in colorectal neoplasia	2018	Luebeck G, Hazelton W, Curtius K, Maden S, Yu M, Carter K, Burke W, Lampe P, Li C, Ulrich CM, Newcomb P, Westerhoff M, Kaz K, Luo Y, Inadomi J, Grady W	Cancer Research	30291105/6359943
Rare loss of function variants in candidate genes and risk of colorectal cancer.	2018	Rosenthal EA, Shirts BH, Amendola LM, Horike-Pyne M, Robertson PD, Hisama FM, Bennett RL, Dorschner MO, Nickerson, DA, Stanaway IB, Nassir, R, Vickers KA, Li C, Grady WM, Peters U, Jarvik GP on behalf of the NHLBI GO Exome Sequencing Project	Human Genetics	30267214/6283057

important clinical questions in absence of RCT data and research questions not suitable for RCTs (e.g., on alcohol consumption, smoking, and other health behaviors; ref. 53). Although an RCT can generally only test one or few specific hypotheses, the multidimensional design of the ColoCare Study allows for the simultaneous assessment of multiple factors relevant to colorectal cancer prognosis. We acknowledge the study population may not be fully representative of the general population of patients with colorectal cancer in the United States; however, at nearly all sites our participation rates are ranging between 70% and 94%, which illustrates that we capture a representative proportion of our cancer center patients. A limitation is that due to the extensive data and biospecimen collection over multiple time points, retention of participants is a challenge, the per-participant-investment is large, and study-staff time required is substantial. Therefore, a variety of retention strategies have been implemented across ColoCare sites. These include two to three newsletters to the participants each year, birthday and holiday cards, raffle of gift certificates, invitations to cancer center events, and providing participants with a summary of their physical activity testing. A further challenge in long-term follow-up of cancer patients is their postcancer identity. Patients with colorectal cancer predominantly identify themselves as survivors and with growing time since diagnosis this patient group is less likely to participate in surveys/biospecimens collections that re-label them as cancer patients (54). The consortium is currently working on tailoring strategies to ensure follow-up rates for long-term survivors. Thus, the sample size is not as large as for other consortia that have focused on lower-involvement assessments (e.g., genetic testing) or are pooling existing data. Moreover, the consistency in protocols and assessments results in fully comparable data from a diverse set of recruitment sites.

Priorities for future use and research

The ColoCare Study design is observational, which is a critical first step in colorectal cancer prognosis research, in order to inform clinical trials, each of which can focus on only a single, primary factor at considerable expense. Strong, well-designed observational studies are essential to provide information on the best intervention to test in any trial. There are many strong hypotheses tested in this transdisciplinary research, most of which have not been/cannot be addressed in trials. The ColoCare Study design enables the analysis of novel, integrated research questions, novel components of energy balance in relation to colorectal cancer outcomes, the role of dietary supplements and integrative health, the role of the gut microbiome in colorectal cancer health and prognosis, as influenced by health behaviors, and the discovery of novel biomarkers for clinical outcomes to advance precision medicine. In all these areas, we will investigate differences by race/ethnicity as we will also be positioned to assess contributors to known colorectal cancer disparities.

The epidemiologic factors being assessed are highly relevant to Western populations because they are focused on drug and supplement use and obesity and energy metabolism. Likewise the molecular studies currently funded or planned will use cutting-edge technology to assess the cancer proteome and methylo-me and will integrate these results to determine functionally-relevant patterns of molecular changes. The incorporation of the molecular results with the epidemiologic studies will permit an understanding of how specific molecular biomarkers can be used in relation to the clinical management of patients with colorectal

cancer to predict and minimize the likelihood of developing recurrent cancer.

Thus, the ColoCare Study will provide valuable insight into the effects of common, modifiable health behaviors on colorectal cancer biology (gene expression, epigenetic profile, proteomics, gut microbiome), patient well-being and clinical outcomes, and unify the predictive and prognostic potential from cutting-edge molecular tumor characterization, gut microbiome, blood biomarkers, and epidemiology in one large patient cohort and risk model. We will focus on three important clinical outcomes: (i) 2-year overall survival and (ii) 5-year overall survival, and (iii) disease recurrence. We also recognize that follow-up beyond 5 years would be beneficial especially for younger patients. Further funding will be sought to achieve this. Together, the integrative nature of the ColoCare Study will provide a critical understanding of key factors that affect response to treatment, colorectal cancer recurrence, and outcomes.

Ultimately, ColoCare Study investigators aim to identify key epidemiologic risk factors, methylation and proteomic signatures, as well as microbial patterns that influence patient survival and well-being. This research promises to lead to the discovery of cancer biomarkers that will help to optimize and personalize medical and surgical treatment of colorectal cancer and improve patient survival rates. In addition, we aim to discern new interconnections between health behaviors and molecular characteristics that will provide insight into cancer biology. We expect this study to contribute substantially to the discovery of cancer biomarkers that will help to optimize and personalize medical and surgical treatment of colorectal cancer and improve patients' clinical outcomes. Together, this information will provide guidance for clinicians and patients on how to increase survival rates, manage treatment toxicities, and improve quality of life after colorectal cancer diagnosis.

Disclosure of Potential Conflicts of Interest

C.M. Ulrich has, as cancer center director, oversight over research funded by several pharmaceutical companies, but has not received funding directly herself. W.M. Grady is a consultant/advisory board member of Freenome and SEngine. No potential conflicts of interest were disclosed for other authors.

Availability of Data and Materials

ColoCare Study data are available from the corresponding author on reasonable request and as described on the ColoCare website (<https://uofuhealth.utah.edu/huntsman/labs/colocare-consortium/>). Our data-sharing procedures are evolving and will be updated online.

Ethics Approval and Consent to Participate and For Publication

The ColoCare Study has been approved by the local institutional review boards serving each site. All participants signed a written informed consent form. This study was also registered to ClinicalTrials.gov (Identifier: NCT02328677, <https://www.clinicaltrials.gov/>).

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.M. Ulrich, B. Gigic, J. Ose, R. Viskochil, M. Schneider, G.A. Colditz, J.C. Figueiredo, W.M. Grady, C.I. Li, D. Shibata, E.M. Siegel, A.T. Toriola

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.M. Ulrich, B. Gigic, J.C. Figueiredo, C.I. Li, E.M. Siegel

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.M. Ulrich, B. Gigic, J. Ose, R. Viskochil, C.I. Li, E.M. Siegel

Study supervision: C.M. Ulrich, C.I. Li, D. Shibata, E.M. Siegel, A.T. Toriola

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