**RELATIONSHIP BETWEEN GENETIC-RELATED OBJECTIVES AMONG STATE CANCER CONTROL PLANS AND COLORECTAL CANCER INCIDENCE AND MORTALITY**

by

Emma Gyurisin

BS, University of Pittsburgh, 2017

Submitted to the Graduate Faculty of

Human Genetics

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2019

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This essay is submitted

by

Emma Gyurisin

on

April 18, 2019

and approved by

**Essay Advisor:**

Candace Kammerer, PhD

Associate Professor

Human Genetics

Graduate School of Public Health

University of Pittsburgh

**Essay Reader:**

Gerald Mark Barron, MPH

Associate Professor

Health Policy and Management, Behavioral and Community Health Sciences

Graduate School of Public Health

University of Pittsburgh

Copyright © by Emma Gyurisin

2019

Candace Kammerer, PhD

**RELATIONSHIP BETWEEN GENETIC-RELATED OBJECTIVES AMONG STATE CANCER CONTROL PLANS AND COLORECTAL CANCER INCIDENCE AND MORTALITY**

Emma Gyurisin, MPH

University of Pittsburgh, 2019

**ABSTRACT**

**Introduction:** Colorectal cancer is the third most deadly cancer in the United States and Lynch syndrome (LS) is the most common hereditary colorectal cancer, therefore identifying interventions that reduce the incidence and mortality is a critical public health issue. Current guidelines recommend screening all individuals with newly diagnosed colorectal cancer tumors for LS to reduce morbidity and mortality among relatives. However, states vary in their inclusion of genetic-related strategies in their cancer control plans and the relationship between these strategies and incidence, and incidence-based mortality for LS is unclear.

**Methods:** I categorized 51 state cancer control plans by five levels of evidence-based genetic strategies. For each state, I obtained incidence and Incidence-based mortality for colorectal cancers diagnosed before age 50 through the National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology, and the End Results (SEER) program from 2001-2015. I next assessed possible relationships between cancer control plan categories and each state’s incidence of colorectal cancer and incidence-based mortality for LS.

**Results:** Seven states (14%) had no genetics mentioned in their plan, 9 (18%) state plans included a genetics-related term, 13 (25%) plans had a genetics-related objective, 16 (31%) plans had a LS specific objective, and 6 (12%) of state plans had an objective related to screening all individuals with newly diagnosed colorectal cancers for Lynch syndrome. Overall, the inclusion of genetics in a state cancer control plan was not related to colorectal cancer incidence (p=0.90) nor incidence-based mortality (p=0.50) of colorectal cancer diagnosed before age 50.

**Conclusion:** I observed no relationship between measures of colorectal cancer incidence or mortality and state cancer control plan objectives, most likely because most state cancer plans that incorporated genetic screening were only developed within the past 10 years. However, 68% of states included a genetics-related goal in their cancer control plans. Furthermore, plans developed after 2015 were more likely to include goals related to universal screening, genetic testing, or genetic counseling. Future analyses should focus on evaluating shorter term outcomes such as earlier age of colorectal cancer diagnosis, as well as the number of at-risk individuals identified via cascade screening of relatives.

TABLE OF CONTENTS

[1.0 Introduction 1](#_Toc7088336)

[1.1 Colorectal cancer 1](#_Toc7088337)

[1.1.1 Environment/Lifestyle Risk Factors 3](#_Toc7088338)

[1.1.2 Comorbidities 5](#_Toc7088339)

[1.2 genetic Factors: LYNCH SYNDROME 6](#_Toc7088340)

[1.2.1 Clinical characteristics & Epidemiology 6](#_Toc7088341)

[1.2.2 Genetics 7](#_Toc7088342)

[1.2.3 MSI & IHC screening, family history screening 8](#_Toc7088343)

[1.3 Lynch Syndrome & Public Health Initiatives 10](#_Toc7088344)

[1.3.1 Universal LS screening 11](#_Toc7088345)

[1.3.2 Cascade Screening 12](#_Toc7088346)

[1.3.3 Cancer Registries 13](#_Toc7088347)

[1.3.4 Bidirectional Reporting 14](#_Toc7088348)

[1.3.5 Cancer Control Plans 14](#_Toc7088349)

[1.4 Project 16](#_Toc7088350)

[2.0 METHODS 18](#_Toc7088351)

[3.0 RESULTS 20](#_Toc7088352)

[3.1 State Cancer Genomic Plans 20](#_Toc7088353)

[3.2 Incidence, Mortality, poverty, medicare 25](#_Toc7088354)

[4.0 Discussion 29](#_Toc7088355)

[bibliography 32](#_Toc7088356)

List of Tables

[Table 1 Genetics Related Term 21](#_Toc7088357)

[Table 2 Genetics Related Goals/Objectives 22](#_Toc7088358)

[Table 3 Lynch Syndrome Specific Goals/Objectives 23](#_Toc7088359)

[Table 4 Screening All Newly Diagnosed Colorectal Cancer for Lynch Syndrome Goals/Objectives 24](#_Toc7088360)

[Table 5 Genetics Plan and ANOVA Test Results 25](#_Toc7088361)

List of Figures

[Figure 1 Incidence Rate by Cancer Plan Category for Cases Diagnosed <50 years from 2001-2015 26](#_Toc7088362)

[Figure 2 Mortality Rae by Cancer Plan Category for Cases Diagnosed <50 years from 2001-2015 26](#_Toc7088363)

[Figure 3 Percent of State Population in Poverty by Cancer Plan Category for Cases Diagnosed < 50 years from 2001-2015 27](#_Toc7088364)

[Figure 4 Percent of State Population on Medicare by Cancer Plan Category for Cases Diagnosed < 50 years from 2001-2015 28](#_Toc7088365)

# Introduction

## Colorectal cancer

Colorectal cancer occurs in the colon or rectum. Most colorectal carcinomas derive from abnormal growths (called adenomatous polyps) that originate in the colorectal mucosa (Fleming et al. 2018) and may form adenocarcinomas over time. Other types of colorectal carcinomas include squamous cell, neuroendocrine adenosquamous, spindle cell, and undifferentiated carcinomas (Fleming et al. 2012).

In 2018, an estimated 140,250 individuals in the United States of America were diagnosed with colorectal cancer and, furthermore, an estimated 50,630 individuals died from colorectal cancer (Jemal et al. 2018). In men, colorectal cancer is the third most common newly diagnosed cancer (8% of all newly diagnosed cancers in men), behind prostate and lung cancers. In women, colorectal cancer is the third most common newly diagnosed cancer (8% of all newly diagnosed cancers in women) after breast and lung cancers (Marley and Nan 2016).

Although the prevalence of colorectal cancer is high in the United States, national statistics from the Surveillance, Epidemiology, and End Results (SEER) program revealed that between the 1975 to 2015, the age-adjusted incidence rate for both sexes and all races dropped from 60 cases per 100,000 individuals to 36.98 new cases per 100,000 individuals. For men of all races, the age-adjusted incidence rate dropped 39.2% from 68.45 new cases per 100,000 individuals in 1975 to 41.61 new cases per 100,000 individuals in 2015. Over this time frame, the age-adjusted incidence rate across all women dropped 38.7% (from 53.66 to 32.92 new cases per 100,000 individuals). The age-adjusted incidence rate decreased 40% among all individuals of European ancestry (from 60.20 to 36.17 new cases per 100,000. Among all individuals of African ancestry, the decrease in age-adjusted incidence rate from 1975-2015 was less, 21.3% (that is, 56.85 new cases per 100,000 individuals in 1975 to 44.70 new cases per 100,000 individuals in 2015). Thus, although the age-adjusted incidence rates decreased among individuals of African ancestry, the rate of decrease was substantially less, and African Americans still have higher rates of colorectal cancer and mortality than other U.S. populations. (SEER Cancer Statistics Review 1975-2015).

With respect to changes in mortality rates, the age-adjusted death rate across both sexes and all races decreased approximately 50% between 1975 and 2015 decreased (i.e., 28.09 deaths per 100,000 individuals in 1975 to 13.99 deaths per 100,000 individuals in 2015). The age-adjusted death rate decreased 49.3% over all men (from 32.84 deaths to 16.65 deaths per 100,000), and 52.6% over all women (from 24.96 deaths to 11.84 deaths per 100,000 individuals). Age-adjusted mortality rates also decreased within different ancestry groups, but the magnitude of change was higher among individuals of European versus African ancestry of both sexes, 51.7% versus 30.4% respectively. Although the age-adjusted mortality rate was 6% higher among European American versus African Americans in 1975 (28.3 versus 26.7 deaths per 100,000 individuals, respectively), in 2015, the mortality rate was 27% lower among European Americans versus African Americans (13.67 versus 18.64 deaths per 100,000 individuals, respectively) (SEER Cancer Statistics Review 1975-2015). Thus, disparities between ethnic groups have increased within the last 45 years.

For colorectal cancer, the Surveillance, Epidemiology, and End Results (SEER) program revealed that between the 1975 to 2015, the age-adjusted incidence rate for both sexes and all races dropped from 60 cases per 100,000 individuals to 36.98 new cases per 100,000 individuals (SEER Cancer Statistics Review 1975-2015). This compares to the age-adjusted incidence rate for female breast cancer that increased from 105.08 new cases per 100,000 individuals in 1975 to 131.10 new cases per 100,000 individuals in 2015, and the age-adjusted rate for male prostate cancer that increased from 93.99 new cases per 100,000 individuals in 1975 to 105.00 new cases per 1000,000 individuals in 2015 (SEER Cancer Statistics Review 1975-2015).

As described above, colorectal cancer incidence and mortality rates have decreased substantially from the mid-70s, however, the economic burden of colorectal cancer remains substantial. The annualized mean net costs of colorectal cancer in 2010 US dollars for women younger than 65 is $61,593 initially, $3,159 annually for continuing care, and $126,778 during the last year of life due to colorectal cancer (Mariotto et al., 2011). For women older than 65, the cost is $51,327 initially, $3,159 annually for continuing care, and $84, 519 during the last year of life due to colorectal cancer. The annualized mean net costs of colorectal cancer in 2010 US dollars for men younger than 65 is $62,174 initially, $4,595 annually for continuing care, and $128,507 during the last year of life due to colorectal cancer. For men older than 65, the cost is $51,812 initially, $4,595 annually for continuing care, and $85,671 during the last year of life due to colorectal cancer (Mariotto et al., 2011).

### Environment/Lifestyle Risk Factors

In addition to overall differences in incidence and mortality rates between ethnic groups (described above), numerous studies in different populations have revealed several environmental and lifestyle factors that are associated with colorectal cancer.

FIND stuff about frequency of each type and if the different types differ by group.

Increased risk of colorectal cancer is commonly attributed to higher obesity levels and a sedentary lifestyle. Higher obesity levels are also associated with a diet consisting of high-meat, high-calorie, high-fat, and low-fiber (Bishehsari et al., 2014). High fat diets are hypothesized to promote carcinogenesis by forming bile acids in the liver, such as deoxycholic acid and lithocholic acid (Harris 2015). Furthermore, cooking meat at very high temperatures is an additional risk factor for colorectal cancer. Charcoal grilling, frying, and boiling meat often produces mutagenic heterocyclic amines and polycyclic aromatic hydrocarbons. Over time, these molecules may form the carcinogen N-nitroso (Harris 2015).

Increased alcohol consumption is another risk factor for colorectal cancer. In a meta-analysis of 7 cohort and 12 case-control studies, individuals who consumed four or more alcoholic beverages per day were at a 52% (95% CI= 27-81%) increased risk for colorectal cancer (Pelucchi et al., 2011). The RR was 1.43 (CI=1.23-1.67) for colon cancer, and 1.59 (95% CI= 1.18-2.15) for rectal cancers. The authors found no differences in risk by sex, however the association was strongest in studies completed in Asian countries (RR= 1.81; 95% CI=1.33-2.46), and lowest among participants from European countries (RR=1.16; 95% CI= .95-1.43). Acetaldehyde (a metabolic product of alcohol consumption and known carcinogen) which is critical for DNA stability, especially during DNA replication and repair. Adequate folate levels prevent chromosome breakage and uracil misappropriation that may lead to carcinogenesis (Seitz and Stickel 2010).

Individuals who smoke cigarettes are also more likely to develop colorectal cancer. In a meta-analysis of 15 studies including 7,433 colorectal cancers, the relative risk of cigarette smoking versus non-smoking was 1.06 (95% CI:1.03-1.08) for 5 pack-years, 1.11 (95% CI: 1.07-1.16) for 10 pack-years, 1.21 (95% CI: 1.13-1.29) for 20 pack-years, 1.26 (95% CI: 1.17-1.36) for 30 pack-years. The authors found no significant heterogeneity between the studies included (Johnson et al., 2013). Common carcinogens in cigarettes are easily absorbed throughout the gastrointestinal tract and over time this process may lead to inflammation, mutagenesis, and carcinogenesis in the colorectal mucosa (Harris 2015).

The United States Preventative Task Force (USPSTF) recommends low-dose aspirin use to reduce the risk of colorectal cancer when used consistently (at least two times per week) (Chan et al 2007). Aspirin works by inhibiting cyclooxygenase-2 (COX-2)Overexpression of COX-2 can cause inflammation and cell proliferation, and many colorectal tumors express this enzyme (Chan et al., 2007).

### Comorbidities

Several comorbidities, such as hyperinsulemia, have been associated with a 26% (HR=1.26 CI: 1.12-1.42) increased risk for colorectal cancer (Tabung et al., 2018). Guyara (2015) reported that individuals with type 2 diabetes mellitus were at an increased risk for developing colorectal cancer due to enhanced angiogenesis.

Chronic inflammation in the colon due to ulcerative colitis is also associated with increased risk of colorectal cancer (Yashiro 2014). Colorectal cancer that develops as a result of ulcerative colitis is often mucinous or signet ring carcinoma (Yashiro 2014). These patients are younger, may have multiple cancer lesions and, consequently, a worse prognosis. Colorectal cancer in patients with ulcerative colitis accounts for 1% of all colorectal cancer diagnosis (Yashiro 2014). Individuals with Crohn’s disease, another disease with chronic inflammation of the colon, are also more likely to develop colorectal cancer (Yashiro 2014).

## genetic Factors: LYNCH SYNDROME

As described above, many environmental and life-style causes have been associated with increased risk of colorectal cancer. Genetic variants have also been associated with risk of developing colorectal cancers; Lynch syndrome is the most common form of these hereditary colorectal cancers.

### Clinical characteristics & Epidemiology

Hereditary nonpolyposis colorectal cancer, also called Lynch syndrome (LS) is the most common type of hereditary colorectal (colon) cancer. Lynch syndrome represents approximately 3% of all colorectal cancers (~4,000 individuals per year) and 3% of uterine (endometrial) cancers (~1,800 women per year) (Krovachuck and Church 2017). Individuals with Lynch syndrome are more likely to develop colorectal cancer including endometrial, stomach, ovary, small bowel, hepatobiliary tract, urinary tract, brain, and skin cancers, and at a younger age (before 50). (Krovachuck and Church 2017). The lifetime risk for developing colorectal cancer in those with LS ranges from 52%-82%, with a mean age at diagnosis of 44-61 years. For example, Aarnio and colleagues studied a Finnish cohort of 1763 members of 50 families in which some family members had been genetically diagnosed with Lynch Syndrome. The investigators reported that the cumulative incidence rate (up to 70 years of age) of mutation carriers for colorectal cancer was 82% compared to 1.6% for the general Finnish population (Aarnio et al. 1999).

In addition to colorectal cancer, LS carriers are at risk of developing other cancers. The lifetime risk of developing gastric cancer for LS patients is 6%-13%, with a mean age at diagnosis of 56 years (REF). Among women with LS, the lifetime risk of developing endometrial cancer is 25%-60% (mean age at diagnosis of 48-62 years), whereas the lifetime risk for developing ovarian cancer is lower: 4%-12%. Although the mean age at diagnosis of ovarian cancer is 42.5 years, approximately 30% of cases of ovarian cancer are diagnosed before the age of 30 years old.

Several medical options are recommended to identify cancerous tumors early among at-risk individuals in order to reduce morbidity and mortality. The National Comprehensive Cancer Network (NCCN) recommended that individuals with LS have colonoscopies every 1-2 years starting between the ages of 20-25, or 2-5 years before the earliest colorectal cancer in the family. To detect endometrial cancer, women at risk for LS may undergo transvaginal ultrasound and endometrial biopsy every 1-2 years, beginning at age 30-35 years of age (NCCN 2018). To detect ovarian cancer, CA-125 blood tests can be utilized every year. In addition, the guidelines state that patients with LS may receive upper endoscopies every 3-5 years starting between the ages of 30-35 to detect stomach and small bowel cancer, while urinalysis every year can be utilized between the ages of 30-35 to detect bladder cancer. Neurological exams starting between the ages of 25-30 can be utilized to detect cancer in the central nervous system (NCCN 2018).

### Genetics

Lynch syndrome is caused by germline mutations in the genes mutL homologue 1 (*MLH1*), mutS homologue 2 (*MSH2)*, mutS homologue 6 (*MSH6*), or postmeiotic segregation 1 homolog 2 (*PMS2*). The *MLH1*, *MSH2*, *MSH5*, and *PMS2* locicode for mismatch repair enzymes that repair errors during DNA replications. Although the epithelial cell adhesion molecule (*EPCAM*) is not a mismatch repair locus, individuals with a deletion in the *EPCAM* locus lso have LS (Goverde et al., 2018). Deletions in the *EPCAM* locus result in a non-functioning enzyme which results in downstream silencing of *MSH2* by hypermethylation (Niessen et al., 2009).

Protein products of the mismatch repair (MMR) genes maintain DNA stability by proofreading for errors made as part of the DNA replication process (Lynch et al. 2015). LS-associated cancers arise from loss of function of the remaining wild-type allele of the affected mismatch repair gene (Lynch et al. 2015). The wild-type allele may lose function via inactivation from somatic mutation or loss of heterozygosity (Martin-Lopez and Fishel 2013). Promotors in *MLH1*, *MSH2*, *MSH5*, or *PMS2* may also be hypermethylated to silence protein production (Martin-Lopez and Fishel 2013). Loss of function in MMR genes results in a failure to repair the DNA mismatches that arise during DNA synthesis, and consequently leads to an increased error rate. Regions in the DNA that contain repetitive nucleotide sequences (called microsatellites) are more highly prone to mismatch errors and are usually a target for mismatch repair (Martin-Lopez and Fishel 2013). In LS-associated tumors, the microsatellite region is more likely to be expanded or minimized, as compared to normal tissue. The consequent microsatellite instability (MSI) impacts cell growth, as well as apoptosis or cell death (Martin-Lopez and Fishel 2013). Because of its association with colorectal cancer, MSI testing is used for diagnosis (discussed below).

### MSI & IHC screening, family history screening

While LS is the most common form of hereditary colorectal and endometrial cancers, it is vastly under-identified in clinical practice. Whereas the gold standard by which to diagnose an individual with LS is by germline genetic testing, individuals at risk for LS may be identified by analysis of family history or by screening tumor tissue.

The Amsterdam I and II criteria are clinical guidelines used to identify individuals who are likely to be mutation carriers of LS based on their family history (Vasen et al., 1999). An individual is considered to be at-risk for LS if they have colorectal cancer or any other Lynch syndrome associated cancer, and three or more relatives with a histologically verified LS-associated cancer provided these criteria are met: One relative should be a first-degree relative of the proband, at least two successive generations should be affected, and at least one affected relative should be diagnosed with colorectal cancer before 50 years of age. For colorectal carcinoma, Amsterdam II criteria do not include familial adenomatous polyposis (FAP) (Vasen et al., 1999).

Bethesda guidelines are used to determine when individuals should have their tumors tested by MSI testing (Umar et al. 2004). The criteria are as follows “(1) colorectal cancer diagnosed in a patient who is less than 50 years old, (2) the presence of synchronous, metachronous colorectal, or other LS-associated tumors, at any age, (3) colorectal cancer with MSI-H histology (tumor infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern), diagnosed in a patient who is less than 60 years of age, (4) colorectal cancer diagnosed in one or more first-degree relatives with a LS-related tumor – at least one cancer must be diagnosed before 50 years of age, or (5) colorectal cancer diagnosed in two or more first or second-degree relatives with LS-related tumors, at any age” (Umar et al. 2004). Meeting any one of these criteria is sufficient to proceed with MSI testing of tumors.

Microsatellite instability (MSI) testing uses polymerase chain reaction (PCR) to show expansion or minimization of repetitive sequences in the tumor DNA, as compared to normal tissue DNA. A test result of labelled “MSI high (MSI-H)” indicates the individual is likely to have LS, whereas a test result labelled “MSI stable (MSI-S)” indicates the individual is unlikely to have LS. A test result of MSI-L is inconclusive.

Immunohistochemistry tumor screening utilizes molecular staining to detect absent or truncated MMR proteins. If both the MSH2 and MSH6 proteins are absent, an individual is likely to have LS. Similarly, if both of the MSH6 or PSM2 protein are absent, the individual is likely to have LS. If the MLH1 and PMS2 proteins are absent, the test is inconclusive. If all proteins are present, the individual is unlikely to have LS.

Although the microsatellite instability and immunohistochemistry tumor screening indicate possible at-risk individuals, germline genetic testing is needed to confirm a diagnosis of LS. If a patient meets the Amsterdam criteria, germline genetic testing may be performed without tumor screening. Pathogenic germline genetic mutations in *MSH2*, *MSH6*, *MLH1*, *PMS2*, or *EPCAM* are required for an absolute diagnosis of LS.

## Lynch Syndrome & Public Health Initiatives

Earlier detection of colorectal cancer is associated with reduced morbidity, mortality (Järvinen et al., 2000), as well as decreased medical costs (Ladabaum et al., 2011), thus, implementation of public health interventions is critical to enable identification of at-risk individuals. In a 15-year Finland trial of 22 families at risk for LS, 1 cohort was screened at 3-year intervals, while the other underwent no screening. 8 screened participants developed CRC (16%), while 19 control participants (16 %; P = 0.014) developed CRC (Järvinen et al., 2000). Throughout the 15-year trial, genetic testing became available, and in LS mutation-positive individuals, the CRC rates were 18% in screened subjects and 41% in controls (P = 0.02). The CRC rate was reduced by 62% through the removal of adenomas. The overall mortality rates was was lower in the screening group (P = 0.003) (Järvinen et al., 2000).

A variety of public health interventions have been implemented locally (as part of different hospital systems), state-wide, and nationally. These interventions include universal LS screening in a hospital system like Cleveland Clinic (Heald et al., 2013) , cascade screening of relatives, cancer registries, and cancer control plans.

### Universal LS screening

Universal tumor screening of all newly diagnosed colorectal cancers identifies those at risk for LS by gene sequencing the tumor cells, and has been reported to be an effective way to identify those at risk for LS (Heald et al., 2013). In a universal LS screening program at Cleveland Clinic, 178 (16%) of 1,708 patients had abnormal screening results, and only 20.3% of those patients met Amsterdam criteria, and 66.1% met Bethesda criteria (Heald et al., 2013). In 2009, the CDC-sponsored Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group recommended that all individuals with newly diagnosed colorectal cancer should be offered genetic testing for Lynch syndrome (Green et al., 2018). The EGAPP working group was established in 2005 to utilize a systematic process for recommending new genetic tests based on clinical utility and legitimacy. Previously, eligibility for genetic testing among individuals with newly diagnosed colorectal cancer was determined by age and/or family health history. One of the goals of Healthy People 2020, a science-based 10 year public health objective by the Office of Disease Prevention and Health Promotion, is to expand the proportion of patients with newly diagnosed colorectal cancer who have genetic testing for Lynch syndrome.

### Cascade Screening

Cascade screening is an intervention designed to reduce morbidity and mortality among relatives of individuals with LS. First degree relatives of individuals with LS each have a 50% chance of also having LS. Therefore, as soon as a patient with colorectal cancer is diagnosed with LS, all first-degree relatives over 18 years of age (that is, parents, siblings, and children) should receive genetic testing for the specific genetic mutation observed in the patient. For those relatives who are subsequently identified to carry the specific LS mutation, their first-degree relatives should receive genetic testing. Thus, cascade screening enables the identification of family members at high risk for LS who will need intensive cancer surveillance. The intervention also identifies family members who are not at high risk of developing LS; these family members should follow the general population guidelines for screening and prevention.

The cascade-screening intervention is most effective if most family members participate. Extensive efforts and research are being done to improve participation of family members in the cascade screening process, especially for adult-onset conditions. As an example, genetic counselors developed a website, *Kintalk* (https://kintalk.org), in which individuals with hereditary cancer syndromes are able to securely share diagnosis and test results with their family members. Other examples include developing materials for individuals with LS to give to their family members, or to direct communication between the LS patient’s clinician and the patient’s family members. However, large-scale expansion of cascade screening requires a change in national public policy to enable the development of the necessary nationwide infrastructure (Hampel 2016).

### Cancer Registries

Public health interventions also focus on cancer surveillance, that is, the continuous and systematic collection of data on colorectal cancer through registries. The National Cancer Registries Amendment Act of 1992 provided funds for states to improve cancer registries, create and new cancer registries in states that lack them, and set data reporting standards. This act established the National Program of Cancer Registries, requiring that states send cancer data to a central registry. Before this law was enacted, 10 states had no cancer registries, and most states did not have the resources to develop and maintain an accurate (and useful) registry.

Data for cancer registries is collected from the medical record of patients diagnosed with cancer in accordance with the North American Association of Central Cancer Registries’ (NAACCR) data standards. Medical record data are collected by trained cancer registrars for individuals who receive cancer care in hospitals, outpatient clinics, radiology departments, doctors’ offices, laboratories, pharmacies, or surgical centers. Cancer registry data are commonly used to monitor cancer trends over time within different populations, develop cancer control plans, allocate health resources, and advance epidemiological and clinical cancer research.

The National Cancer Institute’s (NCI) Surveillance, Epidemiology, and End Results (SEER) Program is a cancer registry that collects population cancer data such as patient demographics, type(s) of tumors, and stage of diagnosis. SEER is meant to be representative of the US populating covering approximately 36.6% of the US population.

### Bidirectional Reporting

Some states utilize bidirectional reporting in cancer registries to identify individuals at risk for LS, and then contact them for further genetic testing. For example, based on cancer registry information, these programs identify individuals with colorectal (or endometrial) cancer diagnosed at a young age (before 50), and reach out to them for genetic testing. The Maryland cancer genomics program identified 10,340 cases of colorectal cancer diagnosed before age 50, 1,985 cases with multiple hereditary breast or ovarian cancer (HBOC-) related or Lynch syndrome-related cancers, and 459 cases with endometrial cancers diagnosed before age 50 (Green et al. 2018). Bidirectional reporting is one way state cancer plans can comply with the EGAPP recommendation, that is, contacting individuals with newly diagnosed cancers to encourage follow-up genetic testing.

### Cancer Control Plans

The Centers for Disease Control and Prevention’s (CDC) National Comprehensive Cancer Control Plan oversees each state’s cancer control plans. Cancer control plans identify how an organization or agency implements changes to reduce cancer incidence, morbidity and mortality within their geographic area. Plans implement goals and objectives related to preventing new cancer cases and deaths, as well as improving the quality of life of patients and survivors. Plans are specific to the geographic region and are created utilizing data from the population residing there. All 50 states and the District of Columbia have plans. Additionally, plans have been developed for Puerto Rico, six Pacific Island jurisdictions (American Samoa, Commonwealth of Northern Mariana Islands, Federated States of Micronesia, Guam, Republic of the Marshall Islands, Republic of Palau), and 8 Native American tribes (Alaska Native Tribal Health Consortium, American Indian Cancer Foundation, California Rural Indian Health Board, Inc, Cherokee Nation, Fond du Lac Reservation, Inter-Tribal Council of Michigan, Inc, Northwest Portland Area Indian Health Board, South Puget Intertribal Planning Agency) (Centers for Disease Control and Prevention). Thus, a total of 66 plans exist within the jurisdiction of the U.S.

State cancer control plans function by engaging a variety of stakeholders to implement their plans. The state partners with various stakeholders including: local cancer registries, health-care providers, health systems, policymakers, insurance companies, other public health programs, academia, industry, community organizations, and advocacy groups (Green et al. 2015).

The current 66 cancer control plans vary considerably, especially with regards to emerging topics, such as genetics. In 2012, Laufman and colleagues reported that 64% of state cancer plans included genetics-related goals, or objectives (Laufman et al., 2012). Nineteen state cancer programs include strategies for Lynch syndrome or family health history of colorectal cancer (Laufman et al. 2012). Five state cancer plans included specific goals related to screening of all newly diagnosed colorectal cancers for LS, consistent with EGAPP recommendations (Laufman et al. 2012). In 2018, Green et al. (2018) reported that 72% of state cancer plans included genetics-related goals or objectives. Nineteen state plans included goals, objectives, or strategies that cover family history of colorectal cancer of LS, whereas only five state plans had goals consistent with EGAPP recommendations for screening all newly diagnosed colorectal cancers for LS (Green et al. 2018). Although these investigators assessed the state cancer control plans, neither group assessed whether the different cancer control plans were achieving their goals.

## Project

As part of this study, I categorized the most recent state cancer control plans and assessed whether the different types of plans were associated with measures of prevalence, morbidity, and mortality from colorectal cancer. State cancer control plans were categorized based on different levels of genetic inclusion: (1) no genetics mentioned, (2) genetics-related term used, (3) genetics related goal or objective state, (4) LS specific goal or objective stated, or (5) contained a goal related to screening of all newly diagnosed colorectal cancers for LS (that is, the current EGAPP recommendation).

National Program of Cancer Registries (NPCR) from 50 states and Washington DC was utilized to obtain data on the incidence and mortality from colorectal cancer diagnosed before 50 years of age. Information on poverty and Medicare rate for all 50 states and Washington DC were obtained from the US Census data. I next performed analyses to determine whether the state cancer control plan category was associated with cancer incidence, mortality, poverty, and Medicare rates.

I hypothesized that states with goals or objectives related to Lynch syndrome would have a lower incidence of colorectal cancer diagnosed before the age of 50. I also hypothesized that states with Lynch syndrome related goals or objectives included in their cancer control plan would have a lower incidence-based mortality from colorectal cancer diagnosed before the age of 50.

Specific Aims

Aim 1: Systematically search state cancer control plans and categorize them into a following group: (1) No genetics mentioned in plan, (2) genetic related term, (3) genetic related goal or objective, (4) LS specific goal or objective, or (5) Goal related to screening all newly diagnosed colorectal cancers for LS.

Aim 2: Utilize the National Program of Cancer Registry colorectal cancer dataset to obtain each state’s incidence rate, and mortality rate for colorectal cancer diagnosed before the age of 50.

Aim 3: Analyze differences between states in incidence, and mortality rate of colorectal cancer diagnosed before the age of 50 and how that relates to the states’ cancer control plan containing more/less genomic goals/objectives.

Aim 4: Analyze differences between states in demographic information of colorectal cancer diagnosed before the age of 50 and how that relates to the states’ cancer control plan containing more/less genomics to assess health disparities.

Aim 5: Describe current trends in genetics related goals/objectives in comprehensive cancer control plans.

# METHODS

The cancer control plans for all fifty states, and Washington DC area, were categorized based on the level of genetics and hereditary colorectal cancer incorporated into the plan. Cancer control plans were read and searched for by genetic-related terms such as gene, genetic, genomics, and DNA. They were then additionally searched for by hereditary, heritability, family health history, high risk, and risk assessment. This is consistent with previous search terms utilized by (Green et al., 2018) and (Laufman et al,. 2012). Cancer control plans were categorized into the following categories: (1) No genetics mentioned in plan, (2) Genetic related term, (3) Genetic related goal or objective, (4) LS specific goal or objective, or (5) Goal related to screening all newly diagnosed colorectal cancers for LS.

National Program of Cancer Registries (NPCR) from 50 states and Washington DC was used to identify colorectal cancer incidence diagnosed before 50 between the years 2001-2015. NPCR and Surveillance Epidemiology and End Results (SEER) data was also used to calculate incidence-based mortality in cases diagnosed before the age of 50 between the years 2001-2015.

Census data from April 1st 2010-July 1st 2017 was used to obtain each state’s population size, % persons in poverty, % Medicare beneficiaries. NPCR and SEER data was analyzed using SEER\*stat software to find incidence, and incidence-based mortality. Incidence, incidence-based mortality utilized age-adjusted rates from the 2000 U.S Standard Population. All colon and rectal cancer cases were included. Microsoft Excel was used to compile incidence, incidence-based mortality, U.S Census, and state cancer genomic plans data.

One-way ANOVA were done to test if the means of incidence, incidence-based mortality, % poverty, % Medicare, % ethnicities, and public health department accreditation status were different among the categories of genomics. Bartlett’s test was used to check for equal variances among the groups. Pairwise comparisons were used to see p-values for individual group comparisons. All statistical analyses were done using STATA (add a reference and link).

# RESULTS

## State Cancer Genomic Plans

Seven states (14%) had no genetics mentioned in their plan, 9 (18%) state plans included a genetics-related term, 13 (25%) plans had a genetics-related objective, 16 (31%) plans had a LS specific objective, and 6 (12%) of state plans had an objective related to screening all individuals with newly diagnosed colorectal cancers for Lynch syndrome. 68% of states included a genetics-related goal in their cancer control plans. Furthermore, plans developed after 2015 were more likely to include goals related to universal screening, genetic testing, or genetic counseling.

Examples of state cancer plans that contained “genetics-related terms” include those from Maine, Indiana, and North Caroline (Table 1). All three plans describe “risk factors” for cancer and state that “family history” (a genetics-related term) is one risk factor. But they do not have any goals or objectives regarding “family history”.

Table 1 Genetics Related Term

|  |  |
| --- | --- |
| Maine | “Individuals and their health care providers should make the determination of screening for these cancers based on personal risk factors and individual medical and family history.” |
| Indiana | “Experts agree that cancer can be caused by both internal and external factors. These factors can sometimes act together, or in sequence, to cause cancer. While risk factors such as family history or age cannot be avoided, many cancers can be prevented through changes in lifestyle and behavior.” |
| North Carolina | “Risk factors increase a person’s chances of developing cancers.  In addition to the risk factors listed in the chart, additional factors are growing older and gender. Risk factors such as growing older, gender and family history of cancer are beyond a person’s control. However, knowledge of family history may help with early detection of cancers with a strong genetic link. Cancers known to run in families include melanoma skin cancer and cancers of the breast, ovary, prostate and colon.” |

The descriptions of “genetics” in the goal/objective among states varied extensively (Table 2). Both the Iowa and Kansas plans referred to cancer (of any kind), whereas the Washington plan focused on prostate cancer. The Iowa plan also proposed to increase access to cancer risk assessment and the Kansas plan focused on increasing knowledge of cancer family history.

Table 2 Genetics Related Goals/Objectives

|  |  |
| --- | --- |
| Iowa | “Increase access to cancer risk assessment and genetic counseling services.” |
| Kansas | “Increase the number of adult Kansans who know their family history of cancer back through second-degree relatives (parents, siblings, children, grandparents, aunts, uncles). “ |
| Washington | “Encourage men with a family history of prostate cancer or of African-American descent to consult their health care provider and participate in shared decision making regarding prostate cancer screening.” |

Lynch syndrome specific goals/objectives were specifically related to hereditary colorectal cancer, or a family history of colorectal cancer (Table 3). The Virginia plan mentions a “high risk population younger than 50” and the national colorectal cancer screening guidelines that state individuals with a “family history” of colorectal cancer should under preventative screening sooner. The Hawaii and Tennessee plans focus on genetic counseling and risk assessment for those with a “family history”.

Table 3 Lynch Syndrome Specific Goals/Objectives

|  |  |
| --- | --- |
| Virginia | “Provide education to physicians, other healthcare providers, and the public about current national colorectal cancer screening guidelines, including high risk population younger than 50.” |
| Hawaii | “Increase by 10 percent the proportion of individuals with a family history of Colorectal Cancer who receives evidence based genetic risk assessment and appropriate screening.” |
| Tennessee | “Increase utilization and awareness of genetic counseling for families with high risk CRC and primary care providers (PCP) awareness of genetic counseling.” |

Finally, examples of state plans containing goals relating to screening all newly diagnosed colorectal cancer for Lynch syndrome are presented in Table 4. The Colorado plan specifically states that MMR and MSI testing should be used to identify individuals at risk for Lynch syndrome, whereas the Louisiana and New York state plans state “genetic testing”, but do not mention a specific test.

Table 4 Screening All Newly Diagnosed Colorectal Cancer for Lynch Syndrome Goals/Objectives

|  |  |
| --- | --- |
| Colorado | “Advocate for universal MSI or MMR protein testing for colorectal and endometrial cancers and for guideline-based molecular profiling of cancers when applicable.” |
| Louisiana | “Increase knowledge of and appropriate care for those at risk of genetic cancers. Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic counseling and testing to identify Lynch syndrome (or familial colorectal cancer syndromes)” |
| New York | By 2023, assess available data sources to measure items such as:  a. The number of moderate- and high-risk individuals who receive appropriate screening and referral to cancer genetic services.  b. The use of hereditary cancer risk assessment, including genetic counseling and appropriate genetic testing.  c. The percentage of colorectal tumors tested for inherited gene mutations. |

## Incidence, Mortality, poverty, medicare

Across the five categories of state cancer control plans, median incidence of colorectal cancer ranged from 6.9 to 7.25 cases per 100,000 individuals for categories 1 to 4 and category 5, respectively, (Table 5). Recall that category 5 plans contained the most specific genetics goals. As can be seen in Figure 1, colorectal cancer incidence varied widely within each cancer control plan category, and the difference between categories was not significant (p=0.90). Median mortality rate varied from 1.5 deaths per 100,000 individuals (category 3 plans) to 1.75 deaths per 100,000 individuals (category 5 plans), but again the range of mortality rates was wide within each category (Figure 2) and this difference was not significant (p=0.50, Table 5).

Table 5 Genetics Plan and ANOVA Test Results

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Plan Category | No genetics mentioned | Genetics related term | Genetics related goal/objective | LS specific goal/objective | Goal related to screening all newly diagnosed colorectal cancers for LS | ANOVA test statistic | ANOVA  p-value |
| Number of states in the Category | 7 | 9 | 13 | 16 | 6 |  |  |
| Incidence (Median, Range) | 6.95  (6.7-7.4) | 6.9  (5.9-7.5) | 6.9  (5.8-8.6) | 6.9  (5.7-9.2) | 7.25  (5.5-8.1) | 0.27 | 0.8989 |
| Mortality (Median, Range) | 1.55  (1.4-1.7) | 1.61  (1.1-1.9) | 1.5  (1.3-2.2) | 1.6  (1.2-2.8) | 1.75  (1.2-2.2) | 0.85 | 0.5013 |
| % Poverty (Median, Range) | 13.6  (9.2-15.2) | 14  (10.6-17.2) | 14.8  (10.8-19) | 16.1  (10.4-21.9) | 16.4  (12.1-19.9) | 1.50 | 0.2167 |
| % Medicare Beneficiaries  (Median, Range) | 19  (16-20) | 18  (13-23) | 17  (14-20) | 18  (11-23) | 17  (14-19) | 0.79 | 0.5379 |



Figure 1 Incidence Rate by Cancer Plan Category for Cases Diagnosed <50 years from 2001-2015

Figure 2 Mortality Rae by Cancer Plan Category for Cases Diagnosed <50 years from 2001-2015

I next assessed possible differences between cancer control plan category and two state-wide demographic measures: percent of state population in poverty and percent of the state population who were Medicare beneficiaries. The median percent of individuals in poverty ranged from 13.6 to 16.4%. across state cancer control plan categories; the lowest median poverty rate was among category 1 plans (no genetics mentioned) and the maximum median poverty rate was among category 5 plans (specific genetics goals). Although there seems to be a trend in median poverty rate across plan categories (Figure 3), the range within each category was wide and the differences were not significant, p=0.22 (Table 5). Finally, the median percent of Medicare beneficiaries in each category ranged brom 17 to 19%. Again, the range of percent beneficiaries for states within each cancer control plan category was wide, and the differences among categories was not significant, (p=0.5379; Figure 4).



Figure 3 Percent of State Population in Poverty by Cancer Plan Category for Cases Diagnosed < 50 years from 2001-2015



Figure 4 Percent of State Population on Medicare by Cancer Plan Category for Cases Diagnosed < 50 years from 2001-2015

# Discussion

One of the long-term goals of policy-makers and citizens of states is the reduction cancer morbidity and mortality in their population. Currently, 71% of states and Washington, DC have a genetics-related goal/objective included in their cancer control plan - an increase from a study in 2012 that reported only 64% of states had a goal related to genetics in their cancer control plan (Laufman et al.,2012). Consistent with the 2012 results, I observed that most state cancer plans that incorporated genetic screening were developed within the past 10 years; concomitantly, older state cancer control plans were less likely to have genetics included in their plans. Although only six state plans included specific goals to screen all newly diagnosed colorectal cancers for LS, state plans developed after 2015 were consistently more likely to include goals related to universal screening, genetic testing, or genetic counseling. In addition, more cancer control plans included hereditary breast and ovarian cancer specific goals/objectives, and some plans include family history risk-assessment for prostate, skin, and pancreatic cancer. The incorporation of these genetics-related goals into state cancer control plans may indicate that state health professionals have used clinical evidence-based recommendations (e.g., from EGAPP) when developing state cancer control plans. It also indicates that health care professionals, policy makers, and the public support the identification of individuals at risk for LS and other colorectal cancers, with the goal of reducing morbidity and mortality among relatives of patients with LS.

Six states, Delaware, Illinois, Nebraska, New Hampshire, Rhode Island, and Pennsylvania, had no genetics included in their cancer control plans. This lack may result in harm to individuals in these states who might benefit from additional education or genetic screening of all newly diagnosed colorectal cancers to prevent morbidity and mortality in relatives who may have a higher risk of developing CRC. However, even among states whose plans recommend universal screening for LS (that is, Colorado, Georgia, Louisiana, Michigan, and Oklahoma) progress toward implementing the plan goals is not clear. In 2011 in Louisiana, Green and colleagues (2019) reported that only 23% of individuals diagnosed before 50 with colorectal cancer were subsequently screened.

To assess whether cancer control plans with more genetics-related goals resulted in reduction of colorectal cancer incidence and mortality (a long-term outcome), I tested for differences in incidence and mortality across 5 control plan categories. I observed no relationship between state cancer control plan category and colorectal cancer incidence or mortality among states. The lack of a relationship likely reflects the relatively recent development of cancer control plans and consequently the short time period in which interventions could be implemented to achieve the goals of the plan. Furthermore, because the average age of diagnosis is approximately 50 years old, the time between identification of at-risk individuals and their development of cancer is long. I assessed incidence and mortality because these measures were readily available. However, to better assess whether implementation of cancer control plans are meeting their objectives, measurement of shorter term outcomes (e.g., an increase in the number of at-risk individuals identified) need to be done in future studies.

I also observed no relationship between cancer control plan category and percent poverty or percent of Medicare beneficiaries across states. This result may be beneficial from a health disparities standpoint because states with higher percentage of their population on Medicare or with higher percentage of poverty did not differ from other states with regards to proposing genetic screening of their population. Therefore, theoretically, citizens of states with an older or less financially secure population also can benefit from advances in genetic screening for individuals at-risk for cancers. However, as described above, states with fewer resources may have more difficulty implementing their plan goals.

*Conclusions.* A majority of states (71%) include genetics-related goals and objectives in their state cancer control plans. However, cancer incidence and mortality, as well as percent poverty, or Medicare rate did not differ significantly among states with more genetics-related strategies included in their plan.

Future analyses should focus on evaluating shorter term outcomes such as earlier age of colorectal cancer diagnosis, as well as the number of at-risk individuals identified via cascade screening of relatives.In addition, future studies should also include plans from six Pacific Island jurisdictions (American Samoa, Commonwealth of Northern Mariana Islands, Federated States of Micronesia, Guam, Republic of the Marshall Islands, Republic of Palau), Puerto Rico, and 8 Native American tribes (Alaska Native Tribal Health Consortium, American Indian Cancer Foundation, California Rural Indian Health Board, Inc, Cherokee Nation, Fond du Lac Reservation, Inter-Tribal Council of Michigan, Inc, Northwest Portland Area Indian Health Board, South Puget Intertribal Planning Agency) (Centers for Disease Control and Prevention).

Although the incorporation of genomics in public health is still emerging, evaluations of current efforts are necessary to provide evidence to inform and support future initiatives.

*Limitations.* This study had several limitations. First, development and implementation of the state cancer control plans covered a wide range of years. Second, incidence, mortality, and census data did not match the implementation years. Furthermore, the sizes of some of the control plan categories was small, for example, only 5 states screen all newly diagnosed colorectal cancer for LS. The small sample size reduces the statistical power. Analyses of shorter term outcomes and longitudinal trends may increase power.

# bibliography

Aarnio, M., Sankila, R., Pukkala, E., Salovaara, R., Aaltonen, L. A., de la Chapelle, A., ... & Järvinen, H. J. (1999). Cancer risk in mutation carriers of DNA‐mismatch‐repair genes. International journal of cancer, 81(2), 214-218.

Ben, Q., Sun, Y., Chai, R., Qian, A., Xu, B., & Yuan, Y. (2014). Dietary fiber intake reduces risk for colorectal adenoma: a meta-analysis. *Gastroenterology*, *146*(3), 689-699.

Bishehsari, F., Mahdavinia, M., Vacca, M., Malekzadeh, R., & Mariani-Costantini, R. (2014). Epidemiological transition of colorectal cancer in developing countries: environmental factors, molecular pathways, and opportunities for prevention. *World journal of gastroenterology: WJG*, *20*(20), 6055.

Chan, A. T., Ogino, S., & Fuchs, C. S. (2007). Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *New England Journal of Medicine*, *356*(21), 2131-2142.

Dreher, M. L. (2018). Fiber and Colorectal Cancer. In *Dietary Fiber in Health and Disease* (pp. 333-365). Humana Press, Cham.

Fleming, M., Ravula, S., Tatishchev, S. F., & Wang, H. L. (2012). Colorectal carcinoma: pathologic aspects. Journal of gastrointestinal oncology, 3(3), 153.

Giovannucci, E. (2001). An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiology and Prevention Biomarkers*, *10*(7), 725-731.

Gorham, E. D., Garland, C. F., Garland, F. C., Grant, W. B., Mohr, S. B., Lipkin, M., ... & Holick, M. F. (2005). Vitamin D and prevention of colorectal cancer. The Journal of steroid biochemistry and molecular biology, 97(1-2), 179-194.

Goverde, A., Wagner, A., Bruno, M. J., Hofstra, R. M. W., Doukas, M., van der Weiden, M. M., ... & Spaander, M. C. W. (2018). Routine molecular analysis for Lynch syndrome among adenomas or colorectal cancer within a national screening program. *Gastroenterology*.

Green, R. F., Ari, M., Kolor, K., Dotson, W. D., Bowen, S., Habarta, N., ... & Khoury, M. J. (2018). Evaluating the role of public health in implementation of genomics-related recommendations: a case study of hereditary cancers using the CDC Science Impact Framework. *Genetics in Medicine*, 1.

Guraya, S. Y. (2015). Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. *World Journal of Gastroenterology: WJG*, *21*(19), 6026.

Hampel, H. (2016). Genetic counseling and cascade genetic testing in Lynch syndrome. *Familial cancer*, *15*(3), 423-427.

Harris, R. E. (2015). *Global epidemiology of cancer*. Jones & Bartlett Publishers.

Heald, B., Plesec, T., Liu, X., Pai, R., Patil, D., Moline, J., ... & Eng, C. (2013). Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing lynch syndrome in a large academic medical center. Journal of clinical oncology, 31(10), 1336.

Healthy People 2020 Progress Review: Cancer and Genomics. https://www.healthypeople.gov/sites/default/files/HP2020\_Cancer\_and\_Genomics\_Progress\_Review\_Slides.pdf. Accessed 26 September 2018.

Järvinen, H. J., Aarnio, M., Mustonen, H., Aktan–Collan, K., Aaltonen, L. A., Peltomäki, P., ... & Mecklin, J. P. (2000). Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology, 118(5), 829-834.

Johnson, C. M., Wei, C., Ensor, J. E., Smolenski, D. J., Amos, C. I., Levin, B., & Berry, D. A. (2013). Meta-analyses of colorectal cancer risk factors. Cancer causes & control, 24(6), 1207-1222.

Kravochuck, S. E., & Church, J. M. (2017). Hereditary non‐polyposis colorectal cancerPelucchi, C., Tramacere, I., Boffetta, P., Negri, E., & Vecchia, C. L. (2011). Alcohol consumption and cancer risk. *Nutrition and cancer*, *63*(7), 983-990.

Ladabaum, U., Wang, G., Terdiman, J., Blanco, A., Kuppermann, M., Boland, C. R., ... & Phillips, K. A. (2011). Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Annals of internal medicine, 155(2), 69-79.

Lynch, H. T., Snyder, C. L., Shaw, T. G., Heinen, C. D., & Hitchins, M. P. (2015). Milestones of Lynch syndrome: 1895–2015. Nature Reviews Cancer, 15(3), 181.

Martín-López, J. V., & Fishel, R. (2013). The mechanism of mismatch repair and the functional analysis of mismatch repair defects in Lynch syndrome. Familial cancer, 12(2), 159-168.

Mariotto, A. B., Robin Yabroff, K., Shao, Y., Feuer, E. J., & Brown, M. L. (2011). Projections of the cost of cancer care in the United States: 2010–2020. Journal of the National Cancer Institute, 103(2), 117-128.

Muller, C., Lee, S. M., Barge, W., Siddique, S. M., Berera, S., Wideroff, G., ... & Katona, B. W. (2018). Low Referral Rate for Genetic Testing in Racially and Ethnically Diverse Patients Despite Universal Colorectal Cancer Screening. Clinical Gastroenterology and Hepatology.

National Comprehensive Cancer Network. (2018). NCCN clinical practice guidelines in oncology (NCCN guidelines TM): Genetic/Familial high risk assessment: Colorectal Cancer

Niessen, R. C., Hofstra, R. M., Westers, H., Ligtenberg, M. J., Kooi, K., Jager, P. O., ... & Kleibeuker, J. H. (2009). Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. *Genes, Chromosomes and Cancer*, *48*(8), 737-744.

Seitz, H. K., & Stickel, F. (2010). Acetaldehyde as an underestimated risk factor for cancer development: role of genetics in ethanol metabolism. Genes & nutrition, 5(2), 121.

Siegel, R. L., Miller, K. D. and Jemal, A. (2018). Cancer statistics, 2018. CA: A Cancer Journal for Clinicians, 68: 7-30.

Tabung, F. K., Wang, W., Fung, T. T., Smith-Warner, S. A., Keum, N., Wu, K., ... & Giovannucci, E. L. (2018). Association of dietary insulinemic potential and colorectal cancer risk in men and women. The American journal of clinical nutrition.

Vasen, H. F., Watson, P., Mecklin, J. P., & Lynch, H. T. (1999). New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology*, *116*(6), 1453-1456.

Yashiro, M. (2014). Ulcerative colitis-associated colorectal cancer. *World Journal of Gastroenterology: WJG*, *20*(44), 16389.