

**Investigating the Association Between Lynch Syndrome and the Prevalence of  
Autoimmune Disorders**

by

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B.S., University of California Los Angeles, 2018

Submitted to the Graduate Faculty of the  
School of Public Health in partial fulfillment  
of the requirements for the degree of  
Master of Science

University of Pittsburgh

2022

UNIVERSITY OF PITTSBURGH

SCHOOL OF PUBLIC HEALTH

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**Background:** Lynch syndrome is caused by germline pathogenic variants in one of the mismatch repair (MMR) genes. It contributes to a significant portion of MMR deficient tumors, which are more susceptible to immune checkpoint inhibitors compared to MMR proficient tumors. MMR deficiency leads to high levels of microsatellite instability as insertion/deletion mutations are accumulated in microsatellites, leading to neoantigen production, which triggers immune responses. T-cell responses towards these neoantigens have been observed in the peripheral blood of individuals with Lynch syndrome without tumor development. These data suggest that having a germline MMR mutation may elicit an immune response, raising the question of whether patients with Lynch syndrome may be at a higher risk of developing autoimmune disorders.

**Methods:** The study included 312 patients diagnosed with Lynch syndrome who are enrolled in the UPMC Hereditary Colorectal and Associated Tumor Registry. A retrospective chart review investigated the presence of 30 autoimmune disorders in these patients. The prevalence of each autoimmune disorder was compared to that of the general population. Chi-square tests were performed on demographic/cancer data and two-sided exact binomial tests were used to assess the significance of prevalence data.

**Results:** Out of 312 patients, 35 individuals were identified to have autoimmune disorders, including 10 out of 30 autoimmune conditions assessed. Most of the identified autoimmune disorders did not show significant differences in their prevalence compared to the general

population. The prevalence of inflammatory bowel disease (IBD), however, was 1.92% in this study compared to 0.48% in the general population ( $p=0.004237$ ).

**Conclusion:** This study suggests that patients with Lynch syndrome may have higher rates of IBD, but do not seem to have significantly higher frequencies of other autoimmune disorders. Future studies should involve larger sample sizes to conduct further statistical analyses on the cancer risks in patients with Lynch syndrome with autoimmune disorders and explore potential mechanisms of an IBD overrepresentation in patients with Lynch syndrome.

**Public Health Significance:** Our investigation may contribute to the scientific community by providing knowledge that is yet to be explored and will potentially inform care and management for patients with Lynch syndrome and their providers.

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## Preface

*I would like to thank the following individuals for their support, guidance, and input to complete this research project:*

- Thesis Committee Members:
  - **Advisor:** Beth Dudley, MS, MPH, CGC
  - Andrea Durst, MS, DrPH, CGC
  - Randall Brand, MD
  - Robyn Domsic, MD
- Jonathan Chernus, PhD for the assistance with statistical analysis
- UPMC Hereditary Colorectal and Associated Tumor Registry Participants
- Classmates, the genetic counseling program leadership, and professors in the Department of Human Genetics

## 1.0 Introduction

Colorectal cancer (CRC) is a common cancer in the United States, and it is estimated that there are nearly 150,000 new cases annually with an expectation of 151,030 new cases in 2022 (Siegel et al., 2022; Siegel et al., 2017). Lynch syndrome is an autosomal dominantly inherited adult-onset hereditary cancer predisposition syndrome (Evaluation of Genomic Applications in Practice and Prevention Working Group, 2009). As the most common hereditary cause of CRC, it comprises 3-4% of all CRC and 4-13.5% of early-onset CRC (Pearlman et al., 2017; Rustgi, 2007).

Lynch syndrome is caused by a germline pathogenic variant in one of five genes – *MLH1*, *MSH2*, *MSH6*, and *PMS2*, or *EPCAM* (Pearlman et al., 2017). Mismatch repair (MMR) genes, including *MLH1*, *MSH2*, *MSH6*, and *PSM2*, are responsible for recognizing single base mismatches or small insertions/deletions and for repairing DNA damage (Lee et al., 2016). Lynch syndrome contributes to a significant portion of MMR deficient (dMMR) tumors, which have higher levels of programmed cell death-1(PD-1) and programmed cell death-ligand 1 (PD-L1) and are more susceptible to immune checkpoint inhibitors (ICIs) compared to MMR proficient (pMMR) tumors (Lee & Le, 2016). The PD-1/PD-L1 pathways are found in different immune cells, including T cells, B cells, NK cells, monocytes, and dendritic cells (Lee & Le, 2016). MMR deficiency leads to high levels of microsatellite instability (MSI-H) as insertion/deletion mutations are accumulated in microsatellites. MSI-H tumors produce neoantigens or frameshift peptides (FSPs), which are more likely to be presented as “non-self” and trigger immune responses. FSP-specific T-cell responses have been observed in MSI-H tumors as well as in the peripheral blood of individuals with germline MMR mutations without tumor development (Lee & Le, 2016; Schwitalle et al., 2008). Furthermore, autoreactive T cells play a key role in the

immunopathogenesis of numerous autoimmune disorders (Dornmair et al., 2003). These data suggest that having a germline MMR mutation may elicit immune responses and raise the question of whether patients with Lynch syndrome may be at a higher risk of developing autoimmune disorders. This study used patients enrolled in the UPMC Hereditary Colorectal and Associated Tumor Registry who have Lynch syndrome to investigate the prevalence of autoimmune disorders within these Lynch patients. The prevalence was compared to that of the general population to investigate the significance.

Assessing the association between Lynch syndrome and autoimmune disorders has yet to be fully studied in the field. Conducting the chart reviews and statistical analyses on these patients is an important first step to determining such potential associations. Our investigation may contribute to the scientific community by providing knowledge that is yet to be explored and will potentially inform care and management for patients with Lynch syndrome and their providers.

### **1.1 Specific Aims**

The following are the specific aims of this project:

1. Assess the prevalence of autoimmune disorders within the cohort of patients with Lynch syndrome in the UPMC Hereditary Colorectal and Associated Tumor Registry
2. Identify potential relationships between cancer history and autoimmune disorder diagnosis in individuals with Lynch syndrome

## **2.0 Literature Review**

### **2.1 Colon Cancer**

#### **2.1.1 Epidemiology of Colon Cancer**

Colorectal cancer (CRC) is the third most common reason for cancer-related mortality in males or females, and second when combined, in the United States. It is expected to cause approximately 52,580 deaths in 2022 (American Cancer Society, 2022; Siegel et al., 2022). Americans have a lifetime risk of CRC of about 4.3% in males and 4.0% in women. It is estimated that there would be approximately 151,000 cases identified in the year 2022, which accounts for about 8% of all cancer cases in the United States for both males and females (American Cancer Society, 2022; Siegel et al., 2022). The incidence rate of CRC has been declining both in men and women since 2000, mainly due to public health efforts in promoting colonoscopy as a preventative measure to detect precancerous polyps (Siegel et al., 2020). Colonoscopy usage in adults who are older than age 50 has increased from 20% in 2000 to 61% in 2018 (Siegel et al., 2020). According to the population screening guideline provided by the American Cancer Society, it is currently recommended individuals at average risk of CRC start screening from age 45, using either stool-based tests or visual exams, which includes colonoscopy as one of the modalities (American Cancer Society, 2020). Colonoscopy allows the detection of cancer at an earlier stage and the overall 5-year survival rate of CRC is about 63-67% (ranging from 14% to 91% depending on the stage at the time of diagnosis). While the incidence and mortality rate of CRC had a rapid decline in older adults (age  $\geq 65$  years for incidence and  $\geq 50$  years for mortality rate), the opposite was

observed among younger adults (age <65 years for incidence and <50 years for mortality rate), which speaks the importance of providing equitable preventative care and treatment in younger, especially middle-age, individuals (Siegel et al., 2020).

### **2.1.2 Hereditary Colon Cancer**

Variable risk factors are involved with the development of CRC, including different environmental and genetic factors. Only 10% of all CRCs are estimated to be hereditary, in which there is a single genetic change that increases the risk of developing cancer in a family and is passed on from generation to generation (Mao et al., 2021). Multiple pathogenic variants have been associated with CRC and polyposis risks (which ultimately leads to CRC if untreated). Lynch syndrome is the most common hereditary colorectal cancer predisposition syndrome, followed by Familial Adenomatous Polyposis (FAP), which is characterized by numerous adenomatous polyps (Kastrinos & Syngal, 2011). A hereditary form of CRC is more likely to be diagnosed at younger ages, tends to have distinct pathologic features, and needs to be followed up appropriately to prevent or reduce the risk of developing cancer.

### **2.1.3 Lynch Syndrome**

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is an autosomal dominantly inherited cancer predisposition that substantially increases the risk of developing cancer – characterized by primarily increased risks in CRC and uterine cancer. It has an overall prevalence of approximately 1 in 300 and accounts for about 3% of all colon cancer diagnoses (Jang & Chung, 2010; Win et al., 2017). The syndrome is caused by having pathogenic

or likely pathogenic variants in one of the DNA mismatch repair genes (i.e. *MLH1*, *MSH2*, *MSH6*, and *PMS2*) as well as the *EPCAM* gene, which is located upstream of *MSH2* (Jang & Chung, 2010; M. J. E. Kempers et al., 2011). Individuals with Lynch syndrome have approximately a 9-60% lifetime risk of developing CRC, which is about 2-15 times higher risk than the general population risk. Among these individuals, the average age of onset of CRC ranges between ages 42 and 69 (National Comprehensive Cancer Network, 2021). Although Lynch syndrome is primarily associated with CRC and uterine cancer risks, it can also significantly increase the risks of other cancers including ovarian, gastric, small bowel, urinary tract, pancreas/biliary tract, brain cancers, and sebaceous neoplasms (National Comprehensive Cancer Network, 2021).

Tumor formation in an autosomal dominantly inherited cancer predisposition syndrome, including Lynch syndrome, follows Knudson's two-hit model (Peltomäki, 2016). Therefore, the lack of one or more MMR protein expressions through immunohistochemistry (IHC) staining of the tumor can indicate possible etiology of tumor formation by Lynch syndrome, although it can also be due to somatic causes. Lack of functional MMR proteins also leads to microsatellite instability (MSI) as repetitive sequences called microsatellites are prone to accumulate DNA damages, such as mismatching bases and small insertion/deletion, that MMR proteins have key roles in repairing (Cunningham et al., 1998). Although clinical criteria, such as Amsterdam criteria I/II and Bethesda, can be applied to diagnose and evaluate Lynch syndrome, only about 40% and 70% of individuals with MMR gene mutations fulfill these respective diagnostic criteria, which would leave at least 25% individuals with of Lynch syndrome undiagnosed (Everett et al., 2014; Lynch Syndrome Screening Network, n.d.; Win et al., 2013). As clinical diagnostic criteria fail to identify a significant proportion of individuals with Lynch syndrome, universal screening of Lynch-associated tumors, particularly CRC and endometrial cancer, became a common public

health effort in identifying individuals with Lynch syndrome. The universal tumor screening using MSI or IHC evaluation of all newly diagnosed colorectal cancer help identify 95% of CRC caused by germline mutations (Lynch Syndrome Screening Network, n.d.). Tumors arising from Lynch syndrome have MSI or abnormal IHC staining found more than 85% of the time, while sporadic CRC tumors also display MMR deficiency about 10-15% of the time (Byers et al., 2018; Schwitalle et al., 2008). Recent studies have demonstrated that approximately 10% of all CRCs harbor MMR deficiency. Of these dMMR tumors, more than 40% are due to MLH1 hypermethylation, about 20% are due to Lynch syndrome, and about another 20 % are attributed to MMR somatic mutations with significant variability among different age groups (Eikenboom et al., 2021; Vos et al., 2020). Furthermore, the identification of MMR deficiency through tumor screening not only helps identify individuals with Lynch syndrome but also helps guide surgical and chemotherapeutic management decisions (Kawakami et al., 2015; S. B. Ye et al., 2020).

#### **2.1.4 Immunotherapy**

Microsatellite DNA is located both in coding and non-coding regions of the human genome. When there is a high mutation burden in the tumor determined by polymerase chain reaction (PCR), the tumor is considered to have MSI-high (MSI-H) phenotype. Mutations occurring at microsatellites located within coding regions of DNA (coding-microsatellites) induce the production of frameshift peptides, which get presented on the surface of the tumor as tumor-specific neoantigens and trigger an immune response (Schwitalle et al., 2008). For this reason, MSI-H tumors have enhanced immunogenicity, which is evident by the abundant lymphocyte infiltration, low metastasis frequency, and improved overall survival compared to microsatellite stable (MSS) tumors (Buckowitz et al., 2005; Popat et al., 2005). The presence of high neoantigen



frequency leads dMMR/MSI-H tumors to have an enrichment in tumor-infiltrating lymphocytes, specifically CD8+ (cytotoxic) T cells, in response to CD4+ T helper (Th) cells producing interleukins (ILs) that stimulates CD8+ T cells (Lee & Le, 2016; Randrian et al., 2021).

CD8+ T cells express immune checkpoint receptors on the cell surface in order to avoid the excessive immune response. When an immune checkpoint receptor (e.g. PD-1) on the T-cell surface binds to its ligand (e.g. PD-L1), the cytotoxic activity of the CD8+ T cell gets inhibited. PD-L1 presents in many cell types, including tumor cells as well as hematopoietic (such as macrophages, dendritic cells, and Th cells) and non-hematopoietic cells (Plesca et al., 2020; Randrian et al., 2021). A number of tumors have PD-1/PD-L1 pathway overexpression that enables the tumor to evade or tolerate the immune response (Lee & Le, 2016). Metastatic MSI tumors are the consequence of tumors escaping the immune system and about half of dMMR/MSI tumors are found to have PD-L1 overexpression (Randrian et al., 2021).

Immune checkpoint inhibitors (ICIs), forms of immunotherapy, are monoclonal antibodies (e.g. anti-PD-1, anti-PD-L1, and anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)) that block the receptor-ligand interaction that enables the evasion of the immune system, leading to apoptosis of the targeted cancer cells by tumor-infiltrating lymphocytes. Approved by the United States Food and Drug Administration (FDA) in 2017, ICI became a therapeutic tool for patients with metastatic MSI-H CRC (Gong et al., 2018; Jung et al., 2020). dMMR/MSI-H tumors are known to have a greater response to ICIs compared to pMMR/MSS tumors due to the higher frequency of PD-1/PD-L1 overexpression (Gong et al., 2018; Lee & Le, 2016). Despite the improvement made for the survival of CRC patients using chemotherapy, the majority of metastatic CRC do not respond well to conventional chemotherapy. Pembrolizumab, an ICI, has been shown to be effective as a first-line treatment for dMMR metastatic CRC compared to the

standard chemotherapy regimen (Jung et al., 2020). The inhibitory antibody drugs currently on the market for anti-PD-1 include nivolumab, pembrolizumab, and anti-PD-L1 includes atezolizumab, durvalumab, and avelumab (Jung et al., 2020; Lee & Le, 2016; Therkildsen et al., 2021).

Since tumors in individuals with Lynch syndrome typically have dMMR/MSI-H, ICI-based immunotherapy is expected to be effective in this patient population. Therkildsen et al. has investigated the efficacy of ICI treatments between dMMR/MSI tumors of patients with and without Lynch syndrome by reviewing a number of published studies (2021). The study did not identify significant differences in the response rates to immunotherapy in these patients and concluded that patients with Lynch syndrome may also benefit from ICI therapy to the same degree as sporadic dMMR/MSI tumors (Therkildsen et al., 2021).

## **2.2 Autoimmune Disorders**

### **2.2.1 Epidemiology of Autoimmune Disorders**

An autoimmune disorder is a generalized term for a wide range of disorders that are characterized by a malfunctioning of the immune system, in which the immune system mistakes self-antigens / autoantigens for foreign “non-self” antigens and can attack throughout an individual’s body (Pisetsky, 2020). There are more than 80 autoimmune disorders, affecting approximately 15 to 24 million people in the United States (Desai & Brinton, 2019; NIH, 2017). Some common conditions include rheumatoid arthritis (RA) and Sjogren’s syndrome which affect joints and muscles, Graves’ disease and Hashimoto's thyroiditis which affect the endocrine system, psoriasis that affects the skin, celiac disease and inflammatory bowel disease that affect the

digestive system, and many more with corresponding symptoms (Cleveland Clinic, 2021a). The incidence and prevalence of autoimmune disorders greatly vary among different conditions with incidence ranging from <1 to 20 cases per 100,000 person-years and prevalence ranging from 5 to >500 per 100,000 individuals (Cooper & Stroehla, 2003). Diagnoses are made by combinations of symptoms and levels of specific markers from blood tests. Autoimmune disorders have no known cure and treatment is based on symptom management such as painkillers, anti-inflammatories, immunosuppressants, etc. (Arthritis Foundation, n.d.; Cleveland Clinic, 2021a; Watson & Sampson, 2019). Anti-inflammatory drugs may include ibuprofen (Motrin, Advil) and naproxen (Naprosyn) (Watson & Sampson, 2019). There are a wide variety of immunosuppressant drugs; for example, corticosteroids such as prednisone, inosine monophosphate dehydrogenase (IMDH) inhibitors such as azathioprine (Azasan, Imuran), and biologics such as adalimumab (Humira) and infliximab (Remicade) are common drugs prescribed to patients with autoimmune disorders (Cleveland Clinic, 2021b; Giorgi & Cochrane, 2019; Moore, 2020). The triggers of autoimmune diseases can include environmental factors like climate, dietary and lifestyle factors (e.g. smoking and excessive alcohol intake), lack of exercise and adequate sleep, increased levels of stress, or hormonal changes. Controlling these factors may help prevent or lessen the severity of the disease (Angum et al., 2020; Cleveland Clinic, 2021a).

Despite a wide range of incidence and prevalence for each condition, many autoimmune disorders show clear sex biases towards women with various mean ages of onset. For instance, some of the common conditions like Sjogren's syndrome (SS) affect women in a 9:1 ratio with an average age of onset between ages 40-60; Systemic Lupus Erythematosus (SLE) affects women in a 7:1 ratio with an average age of onset between ages 15-55; and RA and systemic sclerosis affect women in 3:1 ratio with an average age of onset between ages 30-60 and 20-50, respectively

(Angum et al., 2020). It has been suggested that autoimmunity is predominantly found in females rather than males due to differences in the X chromosome – many genes on the X chromosome are involved in immune system regulation and an extra X chromosome in females may provide greater potential to trigger mutations and autoimmunity (Angum et al., 2020). Furthermore, skewed X inactivation towards one parental X chromosome is thought to produce antigens towards the less expressed X chromosome, which can be mistaken as foreign or non-self and elicit an immune response (Angum et al., 2020).

### **2.2.2 Autoimmune Disorders and Malignancies**

The bidirectional associations between autoimmune disorders and hematologic / non-hematologic malignancies have been described. Increased risks of cancer have been identified with various autoimmune disorders, such as SS, SLE, RA, and myositis (Franks & Slansky, 2012; Giat et al., 2017; Labrador-Horrillo & Selva-O'Callaghan, 2018; Liang et al., 2014; Mao et al., 2016). While some malignancies have clearly increased risk under specific autoimmune disorders, some cancer-autoimmune disorder association remains controversial among various studies (Franks & Slansky, 2012; Giat et al., 2017). Conversely, a number of studies have reported that pre-existing malignancies induce autoimmunity (Franks & Slansky, 2012; Giat et al., 2017). This phenomenon is called a paraneoplastic syndrome, where immune cells attack healthy cells due to the cross-reaction of tumor antigens that mimics self-antigens. The paraneoplastic syndrome can affect various body systems – nervous, endocrine, dermatologic, hematologic, and rheumatologic systems – which is most commonly caused by breast, ovarian, GI, lung, and lymphoproliferative cancers (Franks & Slansky, 2012; Mayo Clinic, 2022).

As immunomodulatory treatments can influence the fine balance between immune conditions and tumor formation, the relationship between malignancies and treatments of autoimmune conditions has been a focus of research studies. Anti-TNF therapy, for instance, is frequently used for the treatment of RA, psoriasis, ankylosing spondylitis, and inflammatory bowel disease. It is still controversial whether anti-TNF therapy is associated with higher risks of developing cancer. Some studies have suggested no association, whereas others have shown a significantly increased risk for melanoma and hematologic cancers such as lymphoma under the context of RA, but the results of these studies are not necessarily applicable to other autoimmune disorders and warrant further investigations (Giat et al., 2017; Vial & Descotes, 2003).

As discussed earlier, ICIs have drastically influenced the treatment of metastatic solid tumors, which activates the anti-tumor immunity in the tumor microenvironment. Individuals with autoimmune disorders may more frequently and severely experience immune-related adverse events (irAEs) as a result of enhanced activity of the immune system using ICIs. Therefore, these individuals have traditionally been excluded from clinical trials due to potentially increased toxicity. For this reason, although many patients diagnosed with cancer have pre-existing autoimmune disorders, the efficacy and safety of ICIs in these individuals are understudied. Recent studies have shown the potential benefits of ICIs in individuals with pre-existing autoimmune disorders despite a potentially higher incidence of irAEs, which were mostly mild and manageable (Tang et al., 2021). The current recommendation is to weigh the benefits and risks to the individual patient in a multidisciplinary approach, including oncologists and rheumatologists, to consider the severity of an autoimmune disorder, cancer type and its prognosis, the possible alternative therapies, and the patient's desire. The patient must be closely monitored for adverse reactions for

optimal care, from which additional clinical insights can also be gained in order to learn more about such complex interactions (Kennedy et al., 2019; Tang et al., 2021).

## **2.3 Lynch Syndrome and Autoimmune Disorders**

A previous study has demonstrated that circulating T lymphocytes isolated from peripheral blood of patients with Lynch syndrome were able to elicit an immune response against tumor-specific frameshift peptides regardless of the development of tumors (Schwitalle et al., 2008). Studies have also shown the presence of dMMR non-neoplastic intestinal mucosa of colonic crypts and non-neoplastic endometrial glands in the surgical samples of individuals with Lynch syndrome but none in sporadic or pMMR tumor groups (Hegazy et al., 2021; Niskakoski et al., 2018; Pai et al., 2018; Staffa et al., 2015; Wong et al., 2020). Combined with the fact that autoreactive T cells play a key role in the immunopathogenesis of numerous autoimmune disorders (Dornmair et al., 2003), these data suggest that having a germline MMR mutation may elicit immune responses and a higher risk of developing autoimmune disorders. However, co-occurrence of Lynch syndrome and autoimmune disorders has yet to be fully explored. To date, the co-occurrence of Lynch syndrome and autoimmune disorders has only been documented with inflammatory bowel disease (IBD) (Laharie et al., 2001; Nambu & Muise, 2021; Nambu et al., 2021; Shim, 2019; Snapper & McGovern, 2021).

### **2.3.1 Epidemiology of Inflammatory Bowel Disease**

IBD is a type of autoimmune disorder that is characterized by chronic inflammation of the gastrointestinal (GI) tract due to malfunctioning of the immune system. There are two major disorders of IBD: ulcerative colitis (UC) and Crohn's disease (CD) (Peppercorn & Cheifetz, 2021). Chronic inflammation in the digestive tract can cause abdominal pain, blood in the stool, fatigue, diarrhea, reduced appetite and weight loss, and malnutrition (Centers for Disease Control and Prevention, 2018). UC strictly affects the mucosal layer of the colon and often starts at the rectum and then spreads into the colon. CD affects transmural or several layers of the wall of the GI tract, often starting in portions of the small intestine prior to affecting the colon (Centers for Disease Control and Prevention, 2018; Peppercorn & Cheifetz, 2021). Diagnosis of IBD requires combinations of multiple methodologies: laboratory testing, endoscopic testing, and imaging. Laboratory testing such as complete blood count and stool samples can identify the signs of inflammation or infections. Endoscopic evaluation including colonoscopies and upper endoscopies can determine the presence of inflammation and its location and severity through imaging and biopsies. Biopsies can help confirm the diagnosis of IBD and distinguish between CD and UC. Imaging tools such as X-ray, CT, and MRI can be utilized for the areas that are difficult to analyze through endoscopies and can determine the presence of inflammation and complications such as fistulas, abscesses, and obstructions (Cleveland Clinic, 2021c; Feakins, 2013; Mayo Clinic, 2020). Treatment of IBD aims to reduce inflammation through diet and lifestyle modulation, drug therapy, or surgery. Individuals with IBD may use medication such as anti-inflammatory drugs, immunosuppressors, biologics, and other medications. Approximately 2/3 of individuals with CD and 1/3 of individuals living more than 30 years with UC undergo surgical treatment to manage their symptoms (Cleveland Clinic, 2021c; Mayo Clinic, 2020).

Among adults in the United States, the prevalence of IBD is estimated to be around 478.4 per 100,000 persons – 181.1 per 100,000 persons for UC and 197.7 per 100,000 persons for CD (Ye et al., 2019). Both UC and CD have been reported to have small differences between sexes with slight female predominance (Peppercorn & Cheifetz, 2021; Ye et al., 2019). IBD can affect individuals of any age, yet the peak age of diagnosis ranges between 15 to 35 years of age (CCFA, 2014; Centers for Disease Control and Prevention, 2021; Peppercorn & Cheifetz, 2021). Although the etiology of IBD has not been clearly understood to this date, risk factors for IBD include various environmental factors such as lifestyle (e.g. smoking, physical inactivity, certain dietary intakes, and sleep deprivation), infections (e.g. acute gastroenteritis caused by pathogens leading to IBD due to inappropriate immune response to microbes), and certain medications (e.g. antibiotics, nonsteroidal anti-inflammatory drugs, etc.) (CCFA, 2014; Peppercorn & Cheifetz, 2021).

Although many individuals diagnosed with IBD do not have a family history, studies have demonstrated genetic factors that increase susceptibility to IBD. In most affected individuals, IBD appears to follow multifactorial inheritance – having a first-degree relative with an IBD diagnosis puts an individual at approximately a 3- to 20-fold increased risk of developing IBD compared to the general population (Snapper & McGovern, 2021). A study has demonstrated that an individual is more likely to develop the same kind of IBD, either UC or CD, that is diagnosed in the family (Laharie et al., 2001). Theoretically, an offspring has a higher risk of IBD when both parents are affected by IBD. The same study has shown that an individual who has both parents affected with IBD has a 33% likelihood of developing IBD by the age of 28 (Laharie et al., 2001).

More than 200 loci associated with IBD have been identified by Genome-wide association studies (GWAS), which are involved in various pathways such as the innate and adaptive immune



pathways, the autophagy pathway, and epithelial barrier functional pathways (Nambu & Muise, 2021; Snapper & McGovern, 2021). These loci detected by GWAS are mostly located in introns or intragenic regions and have small effect sizes (Nambu & Muise, 2021).

Approximately 60 Mendelian forms of very-early onset IBD have also been reported – most frequently reported mutations in *IL10RA/B*, *XIAP*, *CYBB*, *LRBA*, and *TTC7A*, affecting immune function and intestinal barrier function (Nambu et al., 2021; Shim, 2019). Nambu et al. reviewed over 300 articles from January 2000 to December 2020 and observed that more than 60% of patients with monogenic IBD developed the disease by the age of six and about 10% are over the age of 18 (Nambu et al., 2021).

### **2.3.2 Inflammatory Bowel Disease and Colorectal Cancer**

Individuals with IBD have a 1.5-to 2-fold increased risk of developing CRC compared to the general population without IBD (Greuter et al., 2020; Herrinton et al., 2012). CRC accounts for approximately 10-15% of all mortality related to IBD (Stidham & Higgins, 2018). Chronic inflammation is thought to cause oxidative stress that induces DNA damage and carcinogenesis by activating protooncogenes or silencing tumor suppressors (Beaugerie & Itzkowitz, 2015). Under chronic inflammation and oxidative stress, the progression of IBD-CRC follows the sequence of no dysplasia, to low-grade dysplasia, high-grade dysplasia, and finally adenocarcinoma (Baker et al., 2018; Stidham & Higgins, 2018). It has also been suggested that prolonged exposure to immunosuppressants as a treatment of IBD itself may be carcinogenic by causing DNA alteration, hindering immune response to chronic mutagenic virus infection, or impairing the immunosurveillance of cancerous cells (Beaugerie & Itzkowitz, 2015). Molecularly, the chromosome instability pathway (i.e. p53 mutations) contributes to up to 85% of colitis-

associated tumors (Sebastian et al., 2014). While the MSI pathway has been reported in IBD-CRC by a number of studies, its role is less clear (Brentnall et al., 1996; Fleisher et al., 2000; Lyda et al., 2000; Rajamaki et al., 2021). Interestingly, MSI has been reported in the non-neoplastic colonic mucosa of patients with UC, which may have the potential to become a prognostic indicator for these subsets of individuals (Brentnall et al., 1996; Sebastian et al., 2014).

### **2.3.3 Co-occurrence of Lynch Syndrome and Inflammatory Bowel Disease**

Five studies have documented confirmed co-occurrence of Lynch syndrome and IBD. Two of the studies are case reports, one of which is a 28-year-old female with UC, systemic lupus erythematosus, and *MSH2* pathogenic variant who was diagnosed with colon (showing signet ring cell carcinoma), uterine, and ovarian cancer (Minami et al., 2014). Another case is a 51-year-old female with CD and *MLH1* pathogenic variant diagnosed with uterine, colon, and duodenal cancer. This study addressed the necessity of careful consideration with the treatment of IBD with immunosuppressants in patients with Lynch syndrome (Lourensz & Jones, 2015).

A 2016 McNamara et al. publication included 12 case reports and studied whether Lynch syndrome and concurrent IBD increase the risk for CRC development and warranted prophylactic colectomy. Eight individuals had UC and four of them had CD. Four out of 12 cases have developed CRC, and additional five individuals had prophylactic colectomy due to severe colitis or non-malignant low-grade dysplasia indication. The study did not establish a significant enough increased risk of CRC with concurrent Lynch syndrome and IBD to recommend prophylactic surgery, which the authors claimed was partly due to the small sample size of the study (McNamara et al., 2016).

Aronson et al. (2010) investigated the impact of co-occurrence of Lynch syndrome and IBD on the risk or the age of onset of CRC. The study included 329 patients with Lynch syndrome and observed five (1.5%) individuals concurrently diagnosed with IBD. This study did not establish earlier-onset CRC due to the comorbidity of these two disorders, which also claimed to be partly due to the small sample size of the study (Aronson et al., 2010).

An article by Derikx et al. published a study in 2017 that investigated 1046 Dutch patients and studied the risk of CRC with the patient having a combination of both disorders. Fifteen out of 1046 patients (1.4%) with Lynch syndrome were confirmed to have concurrent IBD diagnoses. Among 15 patients who had both confirmed diagnoses, the study did not observe significantly increased risks of CRC, yet it observed younger ages of CRC development in the patients with both conditions compared to patients with Lynch syndrome without IBD (Derikx et al., 2017).

The IBD prevalence in Lynch syndrome in the two studies is about 4 to 5 times higher than that of the estimated global prevalence of more than 0.3% (Ng et al., 2017). Further investigations with larger sample sizes are needed to enable further statistical analyses on the risks of various types of cancer risks with comorbidity of Lynch syndrome and IBD.

In summary, there have only been two studies that investigated the prevalence of co-occurrence of Lynch syndrome and IBD, with the primary goal of describing colorectal cancer risk. Both studies have demonstrated a higher prevalence of IBD compared to the estimated general population prevalence, although this was not the goal of their research. The studies did not demonstrate that the comorbidity of Lynch syndrome and IBD affects the risk of developing CRC, yet one study observed a significantly younger age of CRC diagnosis in these patients. Further investigations and replication of these observations in a diverse population are critical in establishing the clinical significance.

### 3.0 Manuscript

#### 3.1 Background

Colorectal cancer (CRC) is a common cancer in the United States. It is estimated that there are nearly 150,000 new cases annually (Siegel et al., 2022). Lynch syndrome, having an estimated prevalence of 1 in 300, is the most common hereditary cause of CRC, comprising approximately 3-4% of all CRC and 4-13.5% of early-onset CRC (Evaluation of Genomic Applications in Practice and Prevention Working Group, 2009; Pearlman et al., 2017; Rustgi, 2007; Win et al., 2017). It is inherited in an autosomal dominant pattern. Lynch syndrome is also referred to as hereditary non-polyposis colorectal cancer (HNPCC). Individuals with Lynch syndrome have about a 9-60% lifetime risk of developing CRC (National Comprehensive Cancer Network, 2021).

Lynch syndrome is caused by a germline pathogenic variant in the mismatch repair (MMR) genes or germline 3' deletion of *EPCAM* that epigenetically silences *MSH2* (M. J. Kempers et al., 2011; Pearlman et al., 2017). Mismatch repair (MMR) genes, including *MLH1*, *MSH2*, *MSH6*, and *PSM2*, are responsible for recognizing single base mismatches or small insertions/deletions and for repairing that DNA damage (Lee et al., 2016). Due to a lack of proper MMR gene function, tumors in individuals with Lynch syndrome are MMR deficient (dMMR) more than 85% of the time, whereas it is found in about 10-15% of sporadic CRC (Byers et al., 2018; Schwitalle et al., 2008). MMR deficiency can be indicated by the loss of one or more MMR protein expressions on immunohistochemistry (IHC) staining and/or high levels of microsatellite instability (MSI-H) determined by polymerase chain reaction (PCR) (Evaluation of Genomic Applications in Practice and Prevention Working Group, 2009; Vos et al., 2020). dMMR tumors have higher levels of

programmed cell death-1(PD-1) and programmed cell death-ligand 1 (PD-L1) and are more susceptible to immune checkpoint inhibitors (ICI) compared to MMR-proficient (pMMR) tumors (Lee & Le, 2016). The PD-1/PD-L1 pathways are found in different immune cells, including T cells, B cells, NK cells, monocytes, and dendritic cells (Lee & Le, 2016). MSI-H tumors produce neoantigens that are more likely to display themselves as “non-self” and trigger immune responses. T-cell responses specific to these neoantigens have been observed in MSI-H tumors as well as in the peripheral blood of individuals with germline MMR mutations without tumor development (Lee & Le, 2016; Schwitalle et al., 2008). Studies have also shown the presence of dMMR non-neoplastic intestinal mucosa of colonic crypts and non-neoplastic endometrial glands in the surgical samples of individuals with Lynch syndrome but none in sporadic dMMR or pMMR tumor groups (Hegazy et al., 2021; Niskakoski et al., 2018; Pai et al., 2018; Staffa et al., 2015; Wong et al., 2020). Furthermore, autoreactive T cells play a key role in the immunopathogenesis of numerous autoimmune disorders (Dornmair et al., 2003). These data suggest that having a germline MMR mutation may elicit immune responses and raises the question of whether individuals with Lynch syndrome may be at a higher risk of developing autoimmune disorders.

The primary goal of this study is to understand the prevalence of autoimmune disorders within the cohort of patients with Lynch syndrome. The study involved patients enrolled in the UPMC Hereditary Colorectal and Associated Tumor Registry who have Lynch syndrome. The prevalence of selected autoimmune disorders was determined through an electronic medical record review of these patients. The study prevalence of each autoimmune disorder was compared to that of the general population to determine the significance.

The association between Lynch syndrome and autoimmune disorders has yet to be fully assessed in the field. Conducting the chart reviews and statistical analyses on these patients is an

important first step to determining such potential associations. Our investigation may contribute to the scientific community by providing knowledge that is yet to be explored and will potentially inform care and management for patients with Lynch syndrome and their providers.

## **3.2 Methods**

### **3.2.1 Data Collection – Study Design and Participants**

The study included patients with Lynch syndrome from the UPMC Hereditary Colorectal and Associated Tumor Registry between 2012 to 2021 (IRB Approval Number: STUDY19050027). The IRB approval letter is included in the appendix. These individuals received Lynch syndrome diagnoses through the identification of pathogenic or likely pathogenic variants in MMR genes (*MLH1*, *MHS2*, *MHS6*, and *PMS2*) as well as the EPCAM gene. All study participants are 18 years of age or older. A retrospective chart review was conducted to determine the presence of 30 autoimmune disorders in our patients (Table 1). A total of 43 terms were used in the medical record search bar to capture these 30 autoimmune conditions (Table 2). The documentation of an autoimmune disease diagnosis was audited by a gastroenterologist and a rheumatologist for each patient and used for further analysis – demographic, prevalence, and cancer history associations.

**Table 1. List of 30 autoimmune disorders assessed**

Autoimmune Disorders Investigated	
Addison's disease	<b>Inflammatory bowel disease</b>
Ankylosing spondylitis	Multiple sclerosis
Aplastic anemia	Myasthenia gravis
Behcet's disease	Myositis
<b>Celiac disease</b>	Pemphigus vulgaris
Chronic inflammatory demyelinating polyneuropathy	<b>Pernicious anemia</b>
Cutaneous lupus	Polyarteritis nodosa
Eosinophilic granulomatous polyangiitis	<b>Psoriasis</b>
Giant cell arteritis	<b>Psoriatic arthritis</b>
Granuloma annulare	<b>Rheumatoid arthritis</b>
<b>Graves' disease</b>	Scleroderma
Guillain-Barre syndrome	<b>Sjogren's syndrome</b>
<b>Hashimoto's thyroiditis</b>	Systemic lupus erythematosus
Henoch-Schonlein purpura	<b>Type 1 diabetes mellitus</b>
IgA nephropathy	Vasculitis

\*Bolded texts indicate the conditions identified in our Lynch syndrome cohort

**Table 2. List of 43 terms used in the medical record research box**

Search Terms	
Addison's disease	IgA
Ankylosing spondylitis	IgA nephropathy
Aplastic anemia	Inflammatory bowel disease
Arthritis	Lupus
Autoimmun	Multiple sclerosis
Behcets disease	Myasthenia gravis
Celiac disease	Myositis
Chronic inflammatory demyelinating polyneuropathy	Pemphigus vulgaris
Churg-Strauss	Pernicious anemia
Crohn's	Polyarteritis nodosa
Cutaneous lupus	Polymyositis
Dermatomyositis	Polyneuropathy
EGPA	Psoriasis
Eosinophilic granulomatous polyangiitis	Psoriatic arthritis
Giant cell arteritis	Rheumatoid arthritis
Granuloma annulare	Scleroderma
Granulomatous polyangiitis	Sjogren's syndrome
Graves' disease	Small vessel vasculitis
Guillain-Barre syndrome	Systemic lupus erythematosus
Hashimoto's thyroiditis	Type 1 diabetes mellitus
Henoch schonlein purpura	Ulcerative colitis
	Vasculitis

### 3.2.2 Statistical Analysis

Demographic Data: To understand our participants' demographics, the data were divided by sex, age, race, prior cancer history, and gene mutation type. Chi-squared tests investigated the distribution difference between participants with and without the diagnosis of autoimmune disorders for each category. Chi-squared tests were performed manually using an excel sheet.

Prevalence Data: The prevalence of each autoimmune disorder obtained in this study was compared to that of the estimated United States general population prevalence. IBD study prevalence was further compared to previously published IBD prevalence in patients with Lynch syndrome. Two-sided exact binomial tests implemented in R (R Development Core Team, 2021) were used to determine the significance of the prevalence data.

Cancer Association: Association between cancer history and autoimmune disorders in patients with Lynch syndrome was analyzed. The presence of cancer histories was stratified by gene and the presence of autoimmune disorder diagnosis. Chi-squared tests investigated the distribution difference in cancer history between participants with and without the diagnosis of autoimmune disorders for each gene type. Chi-squared tests were performed manually using an excel sheet.



### 3.3 Results

#### 3.3.1 Registry Demographics

Using the registry, we identified 312 patients with confirmed diagnoses of Lynch syndrome. Of these 312 individuals, 109 (27%) individuals were males and 203 (73%) individuals were females, reflecting the patient population of the UPMC Gastrointestinal Clinic (Table 3 Registry demographics). The majority of the study participants were White (94%). There were more individuals over 50 years of age and about two-thirds of the participants had prior cancer history at the time of the enrollment into the registry. Pathogenic variants in *MSH2/EPCAM* (37%) are most represented in this study cohort, followed by *MSH6* (25%), *MLH1* (22%), and *PMS2* (16%) pathogenic variant carriers.

**Table 3. Demographic breakdown by various categories overall vs the presence of autoimmune disorders**

Variable	Categories	Registry demographics		Without autoimmune disorders		With autoimmune disorders		$X^2$	$p$
		n=312	(%)	n=277	(%)	n=35	(%)		
Sex	Male	109	(27%)	101	(36%)	8	(23%)	2.796	0.094
	Female	203	(73%)	176	(64%)	27	(77%)		
Age*	<50	138	(44%)	125	(45%)	13	(37%)	0.901	0.343
	≥50	174	(56%)	152	(54%)	22	(63%)		
Race	American Indian or Alaska Native	4	(1%)	3	(1%)	1	(3%)	0.421	0.516
	Asian	4	(1%)	4	(1%)	0	(0%)		
	Black or African American	7	(3%)	7	(3%)	0	(0%)		
	Hispanic	1	(0%)	1	(0%)	0	(0%)		
	Native Hawaiian or Other Pacific Islander	0	(0%)	0	(0%)	0	(0%)		
	White	294	(94%)	260	(94%)	34	(97%)		
	Other**	2	(1%)	2	(1%)	0	(0%)		
Prior Cancer Hx*	Yes	193	(62%)	173	(62%)	20	(57%)	6.786	0.079
	No	119	(38%)	104	(38%)	15	(43%)		
Mutation Type	MLH1	70	(22%)	65	(23%)	5	(14%)	6.786	0.079
	MSH2/EPCAM	114	(37%)	105	(38%)	9	(26%)		

MSH6	78	(25%)	65	(23%)	13	(37%)
PMS2	50	(16%)	42	(15%)	8	(23%)

Hx history

\*Age and cancer history are based on the time of the enrollment

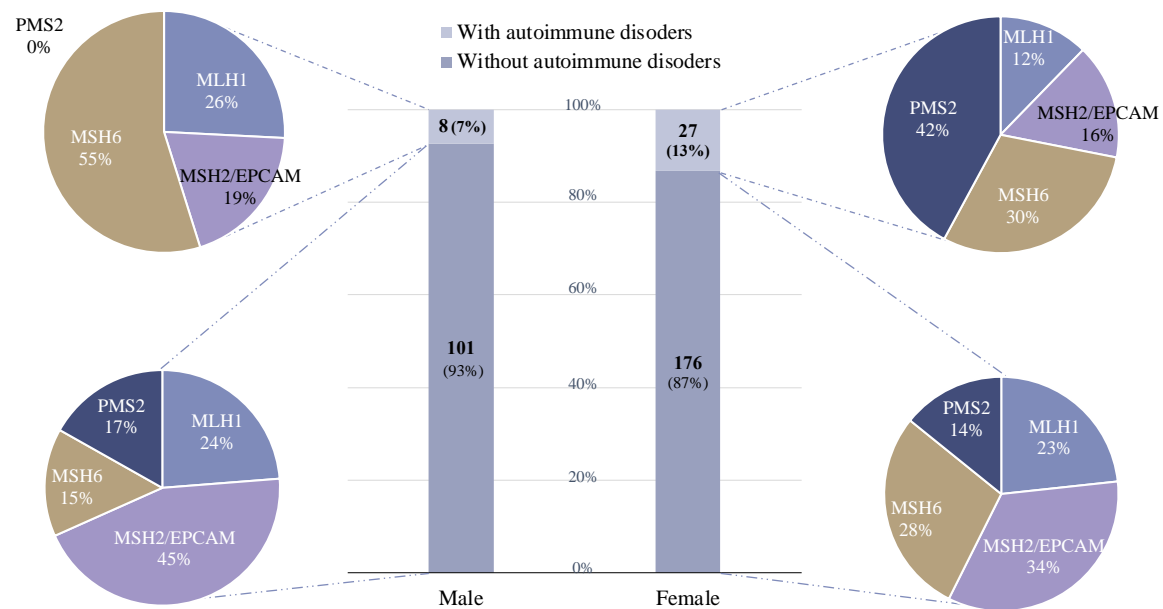
\*\*Other: mixed racial group

### 3.3.2 Lynch Syndrome and Autoimmune Disorders

Among 312 participants with Lynch syndrome, a total of 35 patients had autoimmune disorder diagnoses. The demographic variables were also stratified by the presence of autoimmune disorder diagnoses. Chi-squared tests were performed on the demographic data between the groups of patients with and without autoimmune disorders among various categories including sex, age, prior cancer history, and mutation type. No significant differences were identified between the groups, indicating that a history of the immune disorder was not associated with these categories in our cohort (Table 3). Although there is no statistically significant result, individuals with *MSH6* and *PMS2* pathogenic variants are overrepresented in the group with autoimmune disorders (Table 3. Mutation Type).

This study identified 10 out of 30 autoimmune conditions that were assessed: celiac disease (n=2), Graves' disease (n=6), Hashimoto's thyroiditis (n=8), inflammatory bowel disease (n=6), pernicious anemia (n=1), psoriasis (n=3), psoriatic arthritis (n=1), rheumatoid arthritis (n=3), Sjogren's syndrome (n=3), and type 1 diabetes mellitus (n=2) (Table 1. bolded conditions). Of these individuals, 27 of them were female (13%) and eight of them were male (7%), occurring at an overall rate of approximately 2 to 1 (Table 3; Figure 1), which is consistent with previously published female to male ratio (Angum et al., 2020). When comparing the ratio by the gene in males and females, patients without autoimmune disorders have similar mutation distribution among both sexes. In the groups with autoimmune disorder diagnoses, *MSH6* mutation carriers are represented the most in males and *PMS2* mutation carriers are represented the most in females

(Figure 1). No *PMS2* mutation carriers were represented by the males who had autoimmune disorder diagnoses. Although further statistical analysis is warranted, the small sample size of autoimmune disorder groups makes the statistical analysis have little power to detect any significant differences.



**Figure 1. Prevalence of autoimmune disorders by sex and variant**

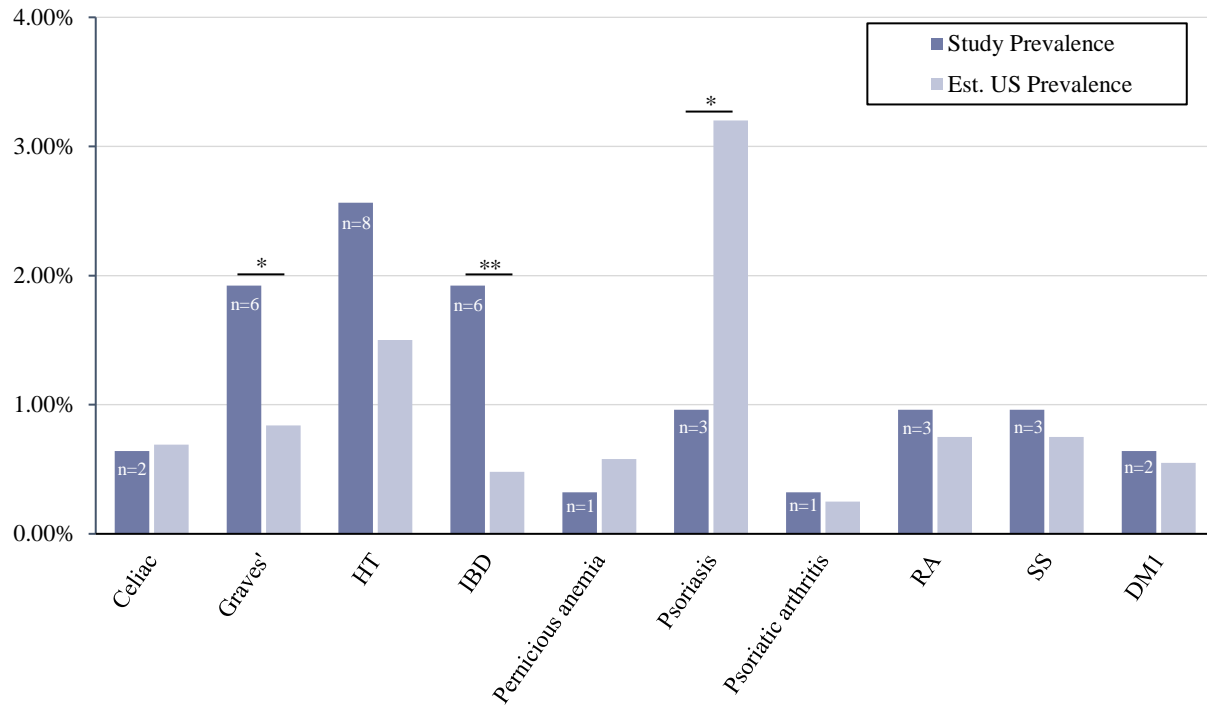
The prevalence of autoimmune disorders was broken down by sex as females and males have differences in the frequency of autoimmune disorders. Autoimmune disorders are present in 7% of males and 13% of females, occurring at an overall rate of approximately 2 to 1. The ratios of each gene in males and females with and without autoimmune disorders are represented in the pie charts. When comparing by gene, patients without autoimmune disorders have similar mutation distribution among both sexes. In the groups with autoimmune disorder diagnoses, *MSH6* mutation carriers are represented the most in males and *PMS2* mutation carriers are represented the most in females.

The prevalence of 10 autoimmune disorder diagnoses in our study participants was compared to those of the estimated general population prevalence in the United States using two-sided exact binomial tests implemented in R (R Development Core Team, 2021). Table 4 lists the reference prevalence used for this analysis; mean values were utilized for the prevalence that was estimated in ranges.

**Table 4. Estimated United States prevalence of autoimmune disorders and the referenced resources**

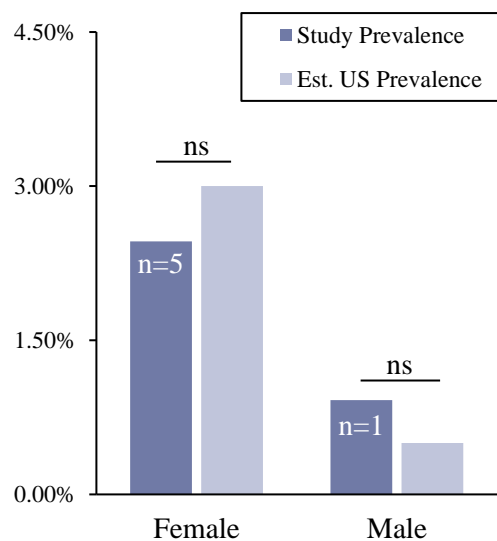
<b>Disease</b>	<b>Est. US Prevalence</b>	<b>Mean value used for analysis</b>	<b>Sources</b>
Celiac disease	0.34 - 1.04%	0.69%	(Schuppan & Dieterich, 2020)
Graves' disease	0.72–0.96%	0.84%	(Pokhrel & Bhusal, 2021)
Graves' disease – Female	3.0%		
Graves' disease – Male	0.5%		
Hashimoto's thyroiditis	1-2%	1.5%	(MedlinePlus [Internet], 2020)
Inflammatory bowel disease	0.4784%		(Y. Ye et al., 2020)
Pernicious anemia	0.15 - 1%	0.575%	(Jensen & Feldman, 2020)
Psoriasis	3.2%		(Rachakonda et al., 2014)
Psoriatic arthritis	0.25%		(Gelfand et al., 2005)
Rheumatoid arthritis	0.5 - 1%	0.75%	(England & Mikuls, 2021)
Sjogren's syndrome	0.30-1.21%	0.755%	(NIH, 2019)
Type 1 diabetes mellitus	0.55%		(Bullard et al., 2018)

Graves' disease ( $p=0.04983$ ) and psoriasis ( $p=0.02229$ ) showed nominally significant differences in the prevalence between our cohort and the general population (Figure 2). While Graves' disease showed enrichment in its prevalence, psoriasis showed lower prevalence when compared to the general population. Notably, inflammatory bowel disease (IBD) showed a significant difference ( $p= 0.004237$ ) even after Bonferroni correction of  $p<0.005$  (Figure 2). Based on the known differences in Graves' disease prevalence between males and females, the prevalence of Graves' disease was stratified by sex. The general population prevalence of Graves' disease is estimated at 3.0% in females and 0.5% in males (Pokhrel & Bhusal, 2021). The Graves' disease prevalence in this study cohort is 2.46% in females and 0.92% in males. The prevalence after stratification is no longer significant (Figure 3). As IBD and psoriasis do not have established prevalence differences based on sex, stratification by males and females was not performed for IBD and psoriasis. Additionally, our patients with a concurrent diagnosis of IBD and Lynch syndrome were all females, which could be attributed to our skewed sample population towards females.



**Figure 2. Prevalence of autoimmune disorders per condition**

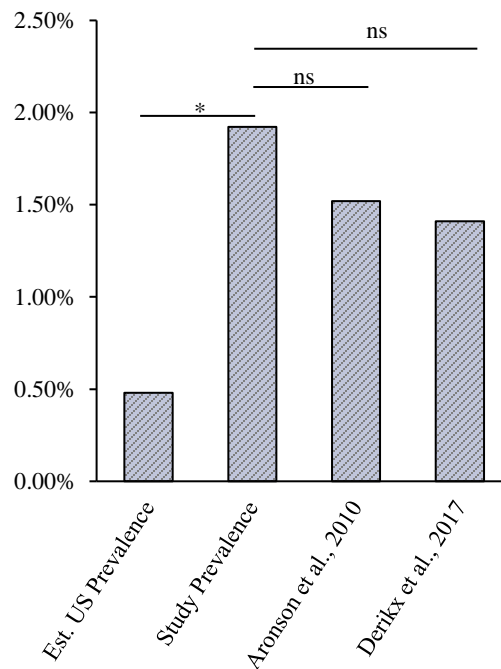
The prevalence of each autoimmune disorder in this study was compared to that of the estimated United States general population. Significant differences were obtained for Graves' disease ( $p=0.04983$ ), IBD ( $p=0.004237$ ), and psoriasis ( $p=0.02229$ ). \* represents a nominally significant difference ( $p<0.05$ ) and \*\* represents a significant difference after Bonferroni correction ( $p<0.005$ ). HT= Hashimoto's Thyroiditis, IBD= Inflammatory Bowel Disease, RA= Rheumatoid Arthritis, SS= Sjogren's syndrome, DM1= Type1 Diabetes Mellitus.



**Figure 3. Sex stratified prevalence of Graves' disease compared to general population frequencies**

The general population prevalence of Graves' disease (3.0% in female and 0.5% in males) were compared to our data of 2.46% in female and 0.92% in male, which no longer shows significant differences (female:  $p=0.8371$ ; male:  $p=0.421$ ).

IBD was the only autoimmune disease in our cohort that showed a significant difference in prevalence after correction compared to the population. Our study prevalence was further compared to the prevalence estimates that were previously reported in other Lynch syndrome cohorts (Figure 4). The study prevalence did not show significant differences when compared to the previous studies (1.43 % and 1.52%).



**Figure 4. Prevalence of IBD: our study vs estimated United States prevalence; our study vs previously studies**  
The study prevalence of 1.92% (6/312) and the previously published prevalence of 1.52% (5/329) by Aronson et al. (2010) and 1.43% (15/1044) by Derikx et al. (2017) do not show statistically significant differences ( $p=0.4846$  and  $p=0.4658$ , respectively).

### 3.3.3 Overview of Patients with Lynch Syndrome with IBD in Our Study

Table 5 shows information about patients with Lynch syndrome with IBD, including their demographic and smoking history, Lynch syndrome and IBD diagnoses, presence of other autoimmune disorders, and prior neoplasm histories. All six of these patients are white females,

ages ranging from 37 to 68 years. Four out of six individuals carry *MSH6* mutations and two carry *MSH2* mutations. Four of them are diagnosed with Crohn's disease (CD) and two are diagnosed with ulcerative colitis (UC). Three developed Lynch syndrome-associated cancers, including colon cancer, uterine cancer, and small bowel cancer; additionally, one individual had a gastric adenoma with high-grade dysplasia and sebaceous neoplasms. Among four individuals who used immunosuppressants as their treatment of IBD, only one patient developed tumors.

**Table 5. Overview of patients with Lynch syndrome with IBD**

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
<b>Demographic</b>						
Current Age	38	58	37	68	48	53
Ethnicity	White	White	White	White	White	White
Sex	F	F	F	F	F	F
Smoking Hx	Past Total: 5 yrs (3 cig/d)	Past Total: 15yrs (40cig/d)	Never	Never	Never	Past Total: 3 yrs (10 cig/d)
<b>Lynch Syndrome</b>						
MMR gene mutation	MSH6 c.3847_3850dupATTA	MSH6 c.2680C>T	MSH6 c.3439-2A>G	MSH2 del exon 1	MSH2 c.518T>C	MSH6 c.1108_1109delTT
LS diagnosis Age	30	52	33	54	30	37
Indication LS diagnostics	FHx LS	Abn. IHC	FHx LS	PHx sebaceous neoplasms & uterine ca	Strong FHx & PHx of cancer	FHx LS
<b>IBD</b>						
Type	CD	CD	CD	CD	UC	UC
Age at IDB diagnosis	19	55	26	49	18	35
Immunosuppression	Azathioprine Uceris Mercaptopurine (6-MP) Infliximab (Remicade) Vedolizumab (Entyvio) Mesalamine (Apriso)	No	Azathioprine (Imuran) Mercaptopurine (6-MP) Methotrexate Infliximab (Remicade)	No	Prednisone Mercaptopurine (6-MP) Azathioprine (Imuran) Hydrocortisone	Hydrocortisone (Cortifoam)
Anti-inflammatory		Mesalamine (Lialda)		Mesalamine (Pentasa; Asacol)	Sulfasalazine (Azulfidine) Mesalamine (Asacol) Balsalazide (Colazal)	Mesalamine (Canasa; Asacol)
Other Tx (age: tx)	Bowel resection (24)					
<b>Other autoimmune disorder diagnoses</b>						
	NA	NA	NA	Graves' disease	NA	Psoriasis
<b>Cancer Hx</b>						
Age at cancer	NA	52		39	30	32
Location/Grade		Uterine p.T1aNx		Uterine NA	Transverse Colon pT4aN0M1	Small Bowel pT1NxMx
Stage (TNM)						
Histology classification / differentiation		Endometrioid adenocarcinoma / well-differentiated (FIGO1)		Severely atypical complex adenomatous hyperplasia of the endometrium focally approaching the level of well-differentiated adenocarcinoma in situ	Invasive, moderately differentiated adenocarcinoma arising from a background of active mucosal ulcerative colitis	Invasive well-differentiated adenocarcinoma arising in serrated adenoma invading just through muscularis mucosa into the submucosa
Genetics						
IHC		MSH6 loss		MSH2 & MSH6 loss	MLH1 loss	
MSI		NA		High	Present	
Surgery		TAH-BSO		TAH-BSO	Total colectomy TAH-BSO	Segmental small bowel resection
<b>Polyp Hx</b>						
(Age: type of polyps)	None	58: HPP (sigmoid) 52: SSA (transverse)	None	59: TA/TVAs (hemicolectomy) 58: gastric adenoma with HGD 55: TA (cecum)	42: small bowel polyp 29: polyroids in right/transverse colon	49: HPP (sigmoid) 46: endometrial polyp 42: frag HPP (rectum) 40: endometrial polyp 39: HPP (rectum)
<b>Other neoplasms</b>						
(Age: neoplasm)				53: sebaceous neoplasm 42: sebaceous neoplasm		

TAH-BSO total abdominal hysterectomy with bilateral salpingo-oophorectomy, TA tubular adenoma, TVA tubulovillous adenoma, HPP hyperplastic polyps, SSA sessile serrated adenoma, HGD high-grade dysplasia, Abn abnormal, Hx history, Tx treatment



### 3.3.4 Cancer History in Patients with Lynch Syndrome with Autoimmune Disorders Versus without Autoimmune Disorders

The frequencies of cancer diagnoses were compared between groups with and without autoimmune disorders (Table 6). Chi-squared tests did not yield significant differences in cancer frequencies between these two groups either when pooled or stratified by mutation type. The strongest association was seen for *MSH6* mutation carriers ( $p=0.051$ ) – patients with *MSH6* mutations appeared to show a higher autoimmune disorder frequency and a lower cancer frequency (Table 3 & 6). Note that age was not adjusted for as a potential confounder due to the small sample size.

**Table 6. Association between cancer history and autoimmune disorders in patients with Lynch syndrome, stratified by the mutation type**

Variant	Prior Cancer Hx*	Median Age* (min-max)	Without autoimmune disorders			With autoimmune disorders			$X^2$	$p$
			n=277	(%)	Median Age* (min-max)	n=35	(%)	Median Age* (min-max)		
Pooled	Yes	51	173	(62%)	51	20	(57%)	51	0.421	0.516
	No	(18-93)	104	(38%)	(18-88)	15	(43%)	(22-93)		
MLH1	Yes	46.5	39	(60%)	46	4	(80%)	51	0.833	0.361
	No	(18-78)	26	(40%)	(18-78)	1	(20%)	(24-64)		
MSH2/EPCAM	Yes	48.5	66	(63%)	47	8	(89%)	56	2.612	0.106
	No	(18-82)	39	(37%)	(18-82)	1	(11%)	(22-70)		
MSH6	Yes	55.5	46	(71%)	58	6	(46%)	49	3.808	0.051
	No	(21-93)	19	(29%)	(21-88)	7	(54%)	(35-71)		
PSM2	Yes	54.5	22	(52%)	53	2	(25%)	62.5	2.405	0.121
	No	(21-80)	20	(48%)	(21-80)	6	(75%)	(46-71)		

Hx history

\*Age and cancer history are based on the time of the enrollment

### 3.3.5 Overview of Lynch syndrome, IBD, and Cancer History

Table 7 shows the comparison between patients with Lynch syndrome with and without IBD in various categories – sex, median age, mutation types, presence of CRC history and the median age of first CRC diagnosis, as well as any cancer history and their median age of the first diagnosis. Having a small sample size and yielding only six patients with IBD diagnoses makes it low power; thus, no statistical analysis was conducted. The individuals in the case group have a younger age of first cancer diagnosis and first CRC diagnosis compared to the LS controls (median age of 39 vs 50 and 44.5 vs 50, respectively). However, also note that the median age of the case groups is younger than the LS control group overall.

**Table 7. Overview of patients with Lynch syndrome with and without IBD**

Variable	IBD & LS (n = 6)		LS controls (n = 306)	
Female sex, n (%)	6	(100%)	197	(64%)
Age*, median (min-max), y	42	(31-64)	51.5	(18-93)
MMR mutation				
MLH1, n (%)	0	(0%)	70	(23%)
MSH2, n (%)	2	(33%)	112	(37%)
MSH6, n (%)	4	(67%)	74	(24%)
PMS2, n (%)	0	(0%)	50	(16%)
CRC cancer**, n (%)	2	(33%)	113	(37%)
multiple CRCs, n (%)	0	(0%)	17	(6%)
Age at 1st CRC diagnosis median, (min-max), y	44.5	(36, 59)	50	(21-93)
Age at 1st cancer diagnosis median, (min-max), y	39	(30-52)	50	(21-93)
<i>LS</i> Lynch syndrome				
*Age = age of enrollment				
**number of diagnoses not considered				

The IBD data from our study, Aronson et al. (2010), and Derikx et al. (2017) are compiled in Table 8. As mentioned previously, the prevalence of IBD among patients with Lynch syndrome ranges from 1.4% to 1.9%. Across three studies, 26 individuals were diagnosed with IBD, with pathogenic variants in all of the mismatch repair genes being observed. While patients diagnosed with both Lynch syndrome and IBD in our study are all female, the other two studies have more even distributions of biological sexes, further supporting that our findings arose from the skewed sample population of the registry. Seven of 26 patients with IBD developed CRC. Three of them had their cancer diagnosis prior to the development of IBD. The rest of the individuals developed IBD before cancer diagnosis, and only one individual had a history of immunosuppressant usage as IBD treatment. A total of four individuals were diagnosed with uterine cancer. Among the patients who developed uterine cancer in our study and Aronson et al. (2010), two individuals developed cancer prior to the diagnosis of IBD and one developed cancer after the diagnosis of IBD (unknown status of immunosuppressant usage). Although Derikx et al. (2017) also observed one individual with uterine cancer; however, no other information such as the age of diagnosis or the chronological relationship between cancer and IBD is available from the article.

**Table 8. Comparison between our study and previously published studies**

Our Study				Aronson et al. (2010)			Derikx et al. (2017)					
Participants Obtained from				UPMC Hereditary Colorectal and Associated Tumor Registry, US			Familial GI Cancer registry at Mount Sinai Hospital in Toronto, Canada			LS: Radboud University Medical Center and Academic Medical Center, Netherlands IBD: Dutch Nationwide Network and Registry of Histopathology and Cytopathology		
Participants, n				312			329			1046		
IBD dx, n (%), median age of dx (max-min), y				6	(1.92%)	30.5 (18-55)	5	(1.52%)	27 (20-32)	15	(1.43%)	30 (10-63)
Sex												
Female, n (%)				6	(100%)		3	(60%)		8	(53%)	
Mutation distribution												
MLH1, n (%)				0	(0%)		1	(20%)		5	(33%)	
MSH2/EPCAM, n (%)				2	(33%)		3	(60%)		2	(13%)	
MSH6, n (%)				4	(67%)		1	(20%)		7	(47%)	
PMS2, n (%)				0	(0%)		n/a	n/a		1	(7%)	
Cancer Hx												
CRC, n (%), median age of 1 <sup>st</sup> dx (max-min), y				2	(33%)	44.5 (30, 59)	1	(20%)	21	4	(27%)	36 (34-42)
Cancer dx before IBD dx, n				0			1 (MLH1)			2 (MLH1 & MSH6)		
IBD dx before cancer dx, n ( <i>no</i> hx of ISx)				1 (MSH2)			0			2 (MLH1 & PMS2)		
IBD dx before cancer dx, n ( <i>with</i> hx of ISx)				1 (MSH2)			0			0		
Uterine, n (%), median age of dx (max-min), y				2	(33%)	45.5 (39, 52)	1	(20%)	57	1	(7%)	n/a
Cancer dx before IBD dx, n				2 (MSH2 & MSH6)			0			n/a		
IBD dx before cancer dx, n				0			1 (MSH6)			n/a		

Hx history, dx diagnosis, ISx immunosuppressants

### 3.4 Discussion

Our study demonstrated IBD overrepresentation in patients with Lynch syndrome, but these individuals do not have higher frequencies of other autoimmune disorders. When compared to the estimated United States general population prevalence, IBD was significantly enriched in our patients with Lynch syndrome even after Bonferroni correction (1.92% vs 0.48%,  $p=0.004237$ ). This suggests that patients with Lynch syndrome may have a higher risk of developing IBD than the general population.

The UPMC Hereditary Colorectal and Associated Tumor Registry included 312 patients with Lynch syndrome. A retrospective chart review identified 35 individuals diagnosed with autoimmune disorders. In our cohort, 10 conditions out of 30 disorders assessed were identified. Demographic data showed no significant differences between patients with and without autoimmune disorders. The study cohort is predominantly composed of white females, who are over 50 years of age. Individuals with *MSH2/EPCAM* mutations are most represented in this study cohort. Autoimmune disorders were observed with a female to male ratio of 2:1, consistent with previously published data in the general population (Angum et al., 2020). When comparing gene mutation distributions, patients without autoimmune disorders had similar distribution among both sexes; whereas, in the groups with autoimmune disorder diagnoses, *MSH6* mutations are represented the most in males and *PMS2* mutations are represented the most in females. Further studies with larger sample sizes are needed to determine the significance of these differences. Patients with co-occurrence of Lynch syndrome and autoimmune disorder did not show significant differences in the frequencies of cancer histories. Further investigation such as the prescription histories of immunosuppressant drugs in relation to the diagnosis of autoimmune disorders and cancer still needs to be performed to further analyze the role of such medication in the history of

cancer diagnoses in these patients. As studies reviewing Lynch syndrome and various autoimmune conditions are scarce in the literature, this study provides new insight into this relationship.

The co-occurrence of Lynch syndrome and autoimmune disorders has yet to be fully explored. To date, this has only been documented in relation to IBD. Five studies have documented confirmed co-occurrence of Lynch syndrome and IBD, three of which are case reports and two of which have provided the prevalence of IBD in Lynch syndrome cohorts. Our study is unique as its primary purpose was to determine the prevalence of autoimmune diseases (including IBD) within patients with Lynch syndrome, while these other studies have aimed to investigate the impact of comorbidity of IBD and Lynch syndrome.

Aronson et al. published a study in 2010 that investigated whether the co-occurrence of Lynch syndrome and IBD leads to cumulatively higher risk or earlier age of onset of CRC diagnoses. The study included 329 patients with Lynch syndrome from Familial GI Cancer Registry at Mount Sinai Hospital in Toronto, Canada. This study observed five individuals (1.52%) with concurrent diagnoses of Lynch syndrome and IBD, which did not establish an increased risk for early-onset CRC due to the comorbidity of these two disorders, potentially due to having a low power because of the small sample size (Aronson et al., 2010). In 2017, Derikx et al. investigated 1046 Dutch patients among two medical centers in the Netherlands and studied the risk of CRC in individuals with LS and IBD. Fifteen out of 1046 patients (1.43%) with Lynch syndrome were confirmed to have concurrent IBD diagnoses. Among 15 patients who had both confirmed diagnoses, the study did not observe significantly increased risks of CRC, yet it observed younger ages of CRC development in the patients with both conditions compared to patients with Lynch syndrome without IBD (Derikx et al., 2017). The IBD prevalence in patients with Lynch syndrome in the two studies is about 4 to 5 times higher than that of the estimated global prevalence of more

than 0.3% (Ng et al., 2017). Our study showed a similar prevalence of IBD among patients with Lynch syndrome: 1.92%, which did not have significant differences in the frequencies from these previous studies. Like Derikx et al. (2017), our study also saw a trend toward younger age of the first cancer diagnosis compared to the non-IBD Lynch syndrome control group: median ages of 39 vs 50 for any cancer and 44.5 vs 50 for CRC. Across these three studies, pathogenic variants in all of the mismatch repair genes were observed in the individuals who developed IBD.

Our study has a number of limitations, some of which include a lack of racial diversity within the study sample, sample size, completeness of the medical record, and the age and cancer history used at the time of the enrollment. Having underrepresentation of other racial and ethnic groups makes it difficult to generalize the result of this study to people of color. Considering the rarity of autoimmune disorders in the general population, the small sample size leads to low numbers of autoimmune disorders identified in the study, which makes it difficult to perform statistical comparisons. The uncertainty of the completeness of study participants' medical records, especially for patients who primarily receive their care outside of our health system, can lead to an under-representation of existing autoimmune disorders in the cohort. Using the age and cancer history at the time of the enrollment does not reflect the most recent medical history of our participants, which may influence our analysis of cancer risks. The estimated United States prevalence of each autoimmune disorder is another limitation. Some conditions have estimated numbers that are not well established or are controversial. This study utilized up-to-date information to the best of our ability.

Future studies should involve prospective studies with larger samples sizes to 1) ascertain the true significance of the association seen between autoimmune disorders and Lynch syndrome, 2) further analyze the risks of various cancer types with comorbidity of Lynch syndrome and IBD,

3) explore potential mechanisms of an IBD overrepresentation in patients with Lynch syndrome, and 4) analyze the association between cancer history and autoimmune disorders adjusted for multiple possible confounders such as age and immunosuppressants usage. Prospective studies will enable us to follow participants more closely and to understand the relationship between autoimmune disorders and cancer risks under the impact of various confounding factors.

### **3.5 Conclusions**

This study suggests that patients with Lynch syndrome may have an increased risk for IBD, but do not seem to have an increased risk for other autoimmune disorders. The frequency of IBD observed in the study cohort was similar to what was previously published in Canadian and Dutch cohorts. The prevalence of IBD in patients with Lynch syndrome should be replicated and explored further in different populations to capture a wider picture of the possibility of IBD overrepresentation. It is still unclear how patients' cancer risks are affected by comorbidity of Lynch syndrome and autoimmune disorders, considering the number of potential cofounders and the need for matched control groups. Future studies should involve prospective studies with larger sample sizes to conduct further statistical analyses on the cancer risks and explore potential mechanisms of an IBD overrepresentation in patients with Lynch syndrome.



#### **4.0 Research Significance to Genetic Counseling and Public Health**

This study is relevant to public health as this is one of the first studies to investigate the possible association between Lynch syndrome and autoimmune disorders. In relation to the 10 essential services of public health, the study addresses the last portion of the assessment component: to diagnose and investigate. By exploring the potential health hazard or health problems within a community, this service allows for increased knowledge of certain diseases and conditions of concern within its community. The finding of no significant association between Lynch syndrome and most autoimmune disorders, with the exception of IBD, is a novel insight obtained in our study.

As Lynch syndrome is a common and highly penetrant genetic condition that has established clinical guidelines, the Centers for Disease Control and Prevention (CDC) Office of Genomics and Precision Public Health (OGPPH) has classified Lynch syndrome as one of the Tier 1 Genomic Applications. Tier 1 applications have systematic evidence that supports implementation in routine practice. Lynch syndrome is not only widely screened by universal tumor screening in all CRC in many institutions, but also starting to gain attention to be screened by population screening programs in healthy individuals. With such effort in identifying the individuals with Lynch syndrome, more and more individuals will be diagnosed with this condition and the demand for studies like this will increase to fill in the gaps of knowledge that exist for this syndrome.

This study was initially driven by patients with Lynch syndrome in our clinic asking whether they are more susceptible to developing autoimmune disorders. With the lack of studies addressing these potential problems in the scientific community, their questions are unanswered

until today. Although this is a fundamental and exploratory study, our finding has the potential to be explored in a larger and more inclusive population, with the goal to protect, promote, and inform the health of a wider community. Genetic counselors and other healthcare providers may be able to provide an answer to these patients, who are wondering about their risks for health problems other than the development of cancers. Our investigation contributes to the community of patients with Lynch syndrome and the scientific community by providing knowledge that is yet to be explored and potentially informs care and management for these patients and their providers in the future.

## Appendix A : IRB Approval



### APPROVAL OF SUBMISSION (Expedited)

Date:	March 31, 2021
IRB:	CR19050027-007
PI:	Randall Brand
Title:	Hereditary Colorectal and Associated Tumor Study - A prospective family study
Funding:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may continue as outlined in the University of Pittsburgh approved application and documents.

#### Approval Documentation

Review type:	Continuing Review
Approval Date:	3/31/2021
Expiration Date:	3/30/2022
Expedited Category	(9) Convened IRB determined minimal risk

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at <http://www.hrpo.pitt.edu/>.

Continuing review (CR) can be submitted by clicking "Create Modification/CR" from the active study at least 5 weeks prior to the expiration date.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, [Emily Bird](#).

Please take a moment to complete our [Satisfaction Survey](#) as we appreciate your feedback.

## Appendix B : R Commands Used for Prevalence Analyses

### Celiac Study Prevalence vs Estimated US Prevalence

# Run exact binomial test for reference proportion = 0.69% (Lynch syndrome population)

```
p_reference <- 0.0069
binom.test(x=2,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

Exact binomial test

```
data: 2 and 312
number of successes = 2, number of trials = 312, p-value = 1
alternative hypothesis: true probability of success is not equal to 0.0069
95 percent confidence interval:
 0.0007772567 0.0229629756
sample estimates:
probability of success
      0.006410256
```

### Graves' Study Prevalence vs Estimated US Prevalence

# Run exact binomial test for reference proportion = 0.84% (us general population)

```
p_reference <- 0.0084
binom.test(x=6,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

Exact binomial test

```
data: 6 and 312
number of successes = 6, number of trials = 312, p-value = 0.04983
alternative hypothesis: true probability of success is not equal to 0.0084
95 percent confidence interval:
 0.007089254 0.041385245
sample estimates:
probability of success
      0.01923077
```

### Graves' Study Prevalence (Female) vs Estimated US Prevalence

# Run exact binomial test for reference proportion = 3.00% (us general population)

```
p_reference <- 0.03
binom.test(x=5,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

```
Exact binomial test

data: 5 and 203
number of successes = 5, number of trials = 203, p-value = 0.8371
alternative hypothesis: true probability of success is not equal to 0.03
95 percent confidence interval:
 0.008044767 0.056540463
sample estimates:
probability of success
 0.02463054
```

### Graves' Study Prevalence (Male) vs Estimated US Prevalence

# Run exact binomial test for reference proportion = 0.50% (us general population)

```
p_reference <- 0.005
binom.test(x=1,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

```
Exact binomial test

data: 1 and 109
number of successes = 1, number of trials = 109, p-value = 0.421
alternative hypothesis: true probability of success is not equal to 0.005
95 percent confidence interval:
 0.0002322465 0.0500568231
sample estimates:
probability of success
 0.009174312
```

### Hashimoto's Thyroiditis Study Prevalence (Male) vs Estimated US Prevalence

# Run exact binomial test for reference proportion = 1.50% (us general population)

```
p_reference <- 0.015
binom.test(x=1,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

```

Exact binomial test

data: 8 and 312
number of successes = 8, number of trials = 312, p-value = 0.1521
alternative hypothesis: true probability of success is not equal to 0.015
95 percent confidence interval:
 0.01113355 0.04989599
sample estimates:
probability of success
      0.02564103

```

### IBD Study Prevalence vs Estimated US Prevalence

# Run exact binomial test for reference proportion = 0.4784% (us general population)

```
p_reference <- 0.004784
```

```
binom.test(x=6,
```

```
n=312,
```

```
p = p_reference,
```

```
alternative = "two.sided",
```

```
conf.level = 0.95)
```

```

Exact binomial test

data: 6 and 312
number of successes = 6, number of trials = 312, p-value = 0.004237
alternative hypothesis: true probability of success is not equal to 0.004784
95 percent confidence interval:
 0.007089254 0.041385245
sample estimates:
probability of success
      0.01923077

```

### IBD Study Prevalence vs Previously Published Prevalence – Aronson et al. (2010)

# Run exact binomial test for reference proportion = 1.52% (Previous Lynch syndrome population)

```
p_reference <- 0.0152
```

```
binom.test(x=6,
```

```
n=312,
```

```
p = p_reference,
```

```
alternative = "two.sided",
```

```
conf.level = 0.95)
```

```

Exact binomial test

data: 6 and 312
number of successes = 6, number of trials = 312, p-value = 0.4846
alternative hypothesis: true probability of success is not equal to 0.0152
95 percent confidence interval:
 0.007089254 0.041385245
sample estimates:
probability of success
      0.01923077

```

### **IBD Study Prevalence vs Previously Published Prevalence – Derikx et al. (2017)**

# Run exact binomial test for reference proportion = 1.43% (Previous Lynch syndrome population)

```
p_reference <- 0.0143
binom.test(x=6,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

```
Exact binomial test

data: 6 and 312
number of successes = 6, number of trials = 312, p-value = 0.4658
alternative hypothesis: true probability of success is not equal to 0.0143
95 percent confidence interval:
 0.007089254 0.041385245
sample estimates:
probability of success
      0.01923077
```

### **Pernicious anemia vs Previously Published Prevalence**

# Run exact binomial test for reference proportion = 0.575% (us general population)

```
p_reference <- 0.00575
binom.test(x=1,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

```
Exact binomial test

data: 1 and 312
number of successes = 1, number of trials = 312, p-value = 1
alternative hypothesis: true probability of success is not equal to 0.00575
95 percent confidence interval:
 8.114353e-05 1.772755e-02
sample estimates:
probability of success
      0.003205128
```

### **Psoriasis vs Previously Published Prevalence**

# Run exact binomial test for reference proportion = 3.2% (us general population)

```
p_reference <- 0.032
binom.test(x=3,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

Exact binomial test

```
data: 3 and 312
number of successes = 3, number of trials = 312, p-value = 0.02229
alternative hypothesis: true probability of success is not equal to 0.032
95 percent confidence interval:
 0.00198733 0.02784156
sample estimates:
probability of success
 0.009615385
```

### Psoriatic Arthritis vs Previously Published Prevalence

# Run exact binomial test for reference proportion = 0.25% (us general population)

```
p_reference <- 0.0025
binom.test(x=1,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

Exact binomial test

```
data: 1 and 312
number of successes = 1, number of trials = 312, p-value = 0.542
alternative hypothesis: true probability of success is not equal to 0.0025
95 percent confidence interval:
 8.114353e-05 1.772755e-02
sample estimates:
probability of success
 0.003205128
```

### Rheumatoid Arthritis vs Previously Published Prevalence

# Run exact binomial test for reference proportion = 0.75% (us general population)

```
p_reference <- 0.0075
binom.test(x=3,
n=312,
p = p_reference,
alternative = "two.sided",
conf.level = 0.95)
```

Exact binomial test

```
data: 3 and 312
number of successes = 3, number of trials = 312, p-value = 0.5104
alternative hypothesis: true probability of success is not equal to 0.0075
95 percent confidence interval:
 0.00198733 0.02784156
sample estimates:
probability of success
 0.009615385
```



### **Sjogren's syndrome vs Previously Published Prevalence**

# Run exact binomial test for reference proportion = 0.755% (us general population)

```
p_reference <- 0.00755
```

```
binom.test(x=3,
```

```
n=312,
```

```
p = p_reference,
```

```
alternative = "two.sided",
```

```
conf.level = 0.95)
```

```
Exact binomial test

data: 3 and 312
number of successes = 3, number of trials = 312, p-value = 0.513
alternative hypothesis: true probability of success is not equal to 0.00755
95 percent confidence interval:
 0.00198733 0.02784156
sample estimates:
probability of success
      0.009615385
```

### **Type 1 Diabete Millitus vs Study Prevalence vs Estimated US Prevalence**

# Run exact binomial test for reference proportion = 0.55% (Lynch syndrome population)

```
p_reference <- 0.0055
```

```
binom.test(x=2,
```

```
n=312,
```

```
p = p_reference,
```

```
alternative = "two.sided",
```

```
conf.level = 0.95)
```

```
Exact binomial test

data: 2 and 312
number of successes = 2, number of trials = 312, p-value = 0.6913
alternative hypothesis: true probability of success is not equal to 0.0055
95 percent confidence interval:
 0.0007772567 0.0229629756
sample estimates:
probability of success
      0.006410256
```

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