Universal Tumor Screening for Lynch Syndrome: Investigation of Patient Reported Distress Levels

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Abstract

Lynch syndrome is a hereditary cancer predisposition from pathogenic variants in mismatch repair (MMR) genes, conferring an increased lifetime risk of colorectal cancer up to 70%. Many healthcare facilities utilize universal tumor screening (UTS) of colorectal tumors through microsatellite instability (MSI) testing or immunohistochemistry (IHC) staining for MMR protein expression. These screening tests identify individuals at risk to carry a pathogenic variant in a Lynch related gene. This pilot study analyzed levels of patient distress among colorectal cancer patients who had UTS or who had been diagnosed with colorectal cancer before the age of 50, and subsequently underwent genetic counseling at the University of Pittsburgh Medical Center (UPMC) Hereditary GI Tumor Program, and patients with normal UTS who were seen in the surgical oncology center without genetic counseling. Patients were asked to complete a series of validated questionnaires (PHQ-8, GAD-7, IES-R) to evaluate their levels of depression, generalized anxiety, and trauma associated with their diagnosis of cancer at three points. For those who received genetic testing, the MICRA questionnaire was completed after receiving genetic test results to evaluate impact of the results on distress. Given the small number of participants (n=23), nonparametric tests were used to assess the differences in patient distress over time. Levels of distress were measured in both groups at all three time points. For a given individual, there was no statistically significant difference in any distress scores across the three time points within the case group. Analysis of baseline distress between patients in the case group and the control groups were not statistically significant, however the mean values of patient distress trended higher across the

case sample compared to the control sample. The impact of test result type on distress levels did not identify a statistically significant difference ($p=0.727$). While not statistically significant, increased levels of uncertainty were observed in the case group after receiving genetic testing results as compared to controls. Understanding the impact of UTS on patient-associated distress has important public health implications and may assist in patient support to alleviate psychological distress and further the assessment of UTS as a public health application.

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Preface

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1.0 Literature Review

1.1 Colon Cancer

1.1.1 Epidemiology of Colon Cancer

Worldwide, colorectal cancer (CRC) accounts for more than 880,000 deaths per year and is the third most common malignancy in the United States.[1] As the most preventable, but least prevented type of cancer, the 5-year relative survival rate of CRC is between 64-67%.[2; 3] Early-detection through public health screening (beginning at age 50 years) has had a role in the reduction in the prevalence and mortality of CRC through both the early removal of precancerous growths known as polyps, and the increased detection of CRC at early more treatable stages.[3] Although CRC remains a common cancer, the incidence and mortality rates from CRC in older populations have seen dramatic decline within the past 30 years.[4] However, while older populations have seen a continued decline in the incidence of invasive CRC, those aged 40-49 have seen an increase in incidence and mortality from CRC.[3; 4]

1.1.2 Hereditary Colon Cancer

Hereditary cancer syndromes are caused by inherited mutations that increase an individual's susceptibility to cancer development. When considering all CRC, approximately 10% are due to a hereditary predisposition.[5] Inherited forms of CRC are seen in multiple generations,

present with distinct histological features, and are more likely to be diagnosed before the age of 50, which is the recommended age to begin screening through colonoscopies.[5]

1.1.3 Lynch Syndrome

Lynch Syndrome (LS) is the most common form of hereditary CRC.[5] Lynch Syndrome accounts for approximately 3% of all hereditary CRC and has been shown to be present in about 8% patients diagnosed with CRC before the age of 50. [5] Four DNA mismatch repair (MMR) genes are associated with LS: *MLH1, MSH2, MSH6, PMS2* as well as a gene associated with the *MSH2* promoter hypermethylation: *EPCAM*.

Lynch syndrome is an autosomal dominant condition and therefore, patients with Lynch syndrome have a 50% chance of passing the affected gene to their children, and there is a 50% chance that their siblings carry the same variant. Individuals with a pathogenic variant in a Lynch syndrome related gene are not only at an increased lifetime risk for colon cancer but are also at increased risk for several other cancers.

Lynch syndrome conveys a risk of colon cancer as high as 70%, with uterine (also known as endometrial) cancer risks following between 40-60%.[6] Patients with Lynch syndrome are also at a 5-8% risk of stomach cancer, a 7% risk of ovarian cancer, a 6% risk of urinary tract cancers and a 2-4% risk of small bowel, pancreatic, or brain cancer.[6] Risks associated with pathogenic variants in the *MSH6* and *PMS2* genes are lower than those associated with *MSH2* and *MLH1*. There are also variant forms of Lynch syndrome, such as Muir Torre, and Turcot syndrome that are associated with extra dermatologic and CNS findings respectively. Given these known increased lifetime cancer risks, preventative screening and guidelines have been established to increase early detection.

For early detection of colon cancers, colonoscopies repeated every 1-2 years are recommended beginning at 20-25 years or 2-5 years prior to the earliest diagnosis of CRC in the family if before 25 years of age. Daily intake of 81mg of Aspirin has also been recommended as a chemopreventive agent to reduce risk of colonic adenomas, but the optimal dose and duration is uncertain.[7] Prevention and screening guidelines similarly exist for the risk associated with extra-colonic Lynch associated cancers.[8] Endometrial biopsies, transvaginal ultrasounds, and serum CA-125 levels may be recommended for women every 1-2 years, until a hysterectomy and bilateral-salpingo oophorectomy can be completed.[8] Oral contraception has also been indicated as a risk reducing agent for uterine and ovarian cancers.[8] Annual urinalysis beginning at 30-35 years old for urinary tract cancer screening and upper endoscopy beginning at 40, every 3-5 years for stomach and small bowel cancer screening are also recommended for individuals with Lynch syndrome.[8] If there is a history of a first degree relative with pancreatic cancer, then MRI or endoscopic ultrasound can be considered as a screening tool for pancreatic cancer.[9] Treatment for Lynch related cancers can also differ based on the presence of tumor related histological features. These features are assessed as a part of the tumor screening program.

1.1.4 Tumor Screening Techniques for Lynch Syndrome

The loss of these MMR protein expression in solid tumors causes microsatellite instability (MSI), which could result from a germline mutation or acquired deficiency, so MSI testing can serve as a screening test for Lynch Syndrome. Similarly, immunohistochemistry (IHC) studies performed on a tumor can evaluate for loss of MMR protein expression.

Historically, cases of LS were clinically diagnosed using the Amsterdam criteria, but nearly three-quarters of LS patients with an identifiable germline mutation fail to meet Amsterdam

criteria.[10; 11] The use of MSI testing or IHC studies to identify MMR deficiency has been found to detect >90% of LS patients. [10; 12] As a result, the cancer genetics community has widely adopted universal tumor screening (UTS) of colorectal cancers for MMR deficiency.[13]

In 2009, the Evaluation of Genetic Applications in Practice and Prevention (EGAPP) working group made the recommendation of UTS for all patients newly diagnosed with CRC, through MSI and/or IHC testing. These methods have been acknowledged as cost-effective and beneficial to patients.[14] Routine analysis of other Lynch syndrome-related cancers such as ovarian, or sebaceous neoplasms have been studied and have found to be effective methods of identifying individuals requiring further genetic evaluation.[15; 16] UTS through IHC has been found to have a diagnostic yield of 2.2% with a specificity and sensitivity of 93% and 100% respectively.[17] Even with the recommendation for UTS by EGAPP, it has not been widely embraced.[18; 19] A study of 106 respondents within the Familial Cancer Risk Counseling Special Interest Group of the National Society of Genetic Counselors identified that only 42.9% (24/59) of newly diagnosed endometrial or colorectal tumors were being automatically screened for Lynch Syndrome at their institutions.[18] Additionally, some groups such as the NCCN indicate that histology is acceptable as a first line analysis to reduce the number of unnecessarily tested tumors, despite the fact that data has found that histologic features of MMR deficiency do not reliably predict the status of MMR proteins by IHC.[20]

With the advent of UTS, there has been an increase in the number of patients being identified as having LS that lack obvious clinical features.[18; 21; 22] This has important implications for the identification of families with increased risks for Lynch associated cancers. When a pathogenic variant is identified in an individual, cascade testing can begin to identify other family members at increased risk. Early identification of Lynch Syndrome can result in initiation of

appropriate screening and prevention, leading to an increase in Lynch-cancer survival rates.[15; 16] Still, the identification of Lynch tumors has clinical application beyond understanding genetic risk. The WHO has determined that MMR deficient CRC is low-grade as they typically pursue a less-aggressive clinical course than stage matched MMR-proficient tumors.[19] This discovery of a difference in natural history of disease in MMR deficient tumors has resulted in a reconsideration of the appropriate treatment for different stage cancers. Chemotherapy will likely not be recommended when the tumor is MMR deficient and late-stage, and if it is given, then it is less likely to elicit a beneficial response in these patients.[23-25] A recent study looked at a total of 43 patients with CRC with MMR deficient status and found that MMR deficient CRC was resistant to chemotherapy[25], confirming results from previous studies which similarly demonstrated negative response rate to fluorouracil chemotherapy in MMR deficient CRC.[24] Pharmaceutical advances have led to the development of targeted MMR chemotherapeutic agents such as pembrolizumab (Keytruda). Pembrolizumab was approved by the FDA in 2017 for the treatment of unresectable or metastatic solid tumors that have been identified to have MSI or MMR deficiency, and is the first treatment to have been approved for a genetic marker rather than a solid tumor location.[26] A total of 15 distinct cancer types were found in 149 patients that were enrolled across 5 clinical trials.[26] The most common cancer types were Lynch associated: colorectal, endometrial, and other gastrointestinal cancers.[26] Of the 149 patients who received pembrolizumab treatment there were 39.6% who showed a response.[26] Pembrolizumab is thought to be effective against MMR deficient tumors, as these tumors have a high number of frameshift mutations.[7] These frameshifts are believed to incite an immune response through activation of PD-1.[7] Pembrolizumab works to block PD-1, which leads to the inhibition of the immune response, allowing the body to more effectively defend against cancer cells.[7]

It is well understood that there is a treatment specific advantage to the identification of MSI and MMR status, yet even though treatment may be tailored based on this information, patients are not always notified of their tumor study results.[27] The explanation of benefits for families by identification of Lynch syndrome is associated with patient follow through with genetic testing and counselling by appropriate genetics providers. In a study of 1,108 patients at the Cleveland Clinic Health System, when results of tumor studies were reported in the traditional manner as a pathology addendum, only half of patients were referred to the appropriate genetics professional.[27] The lack of appropriate referrals raises an important consideration in UTS. Appropriate care and monitoring of Lynch families requires diagnosis of a pathogenic genetic variant in a Lynch associated gene. Ensuring accurate testing and interpretation of results for unaffected family members requires access to an affected family member's genetic test result. While pathology reports from an affected family member can assist with assessment of risk and consideration of which potential Lynch genes to test, testing of unaffected members without testing of an affected member is limited in its interpretation. Likewise, while the pathology report might be available to the family in the medical record, the importance might not be fully understood if it was not discussed with the family while the patient was alive. Thus, while the traditional method of reporting is reliable for the pursuit of appropriate treatment, it has not been shown to be an adequate method for the referral of individuals for genetic testing as it does not provide complete information for families at risk for Lynch syndrome.

1.1.5 Informed Consent for Universal Tumor Screening

As with any medical procedure, informed and voluntary consent is required prior to genetic testing. Within the scope of genetic counseling there is special consideration of the importance of

providing informed consent to ensure complete understanding of potential ethical implications of genetic testing. This has been considered an important aspect of genetic testing in particular, as it has implications for knowledge about other family members outside of the individual pursuing testing. The American Society of Clinical Oncology published guidelines that indicate genetic testing should only be conducted with appropriate pre- and post- test counselling and should include a discussion of risks and benefits to the individual and their biological family members.[28] With the advent of the recommendation of UTS, there has been consideration within the healthcare community as to the requirement of explicit and informed consent for MSI and IHC tumor testing and its implications beyond cancer care.[10; 18; 29] The implications of somatic mutations in conjunction with abnormal IHC testing are not always well understood by providers, including the implications for other extra-colonic Lynch-related cancers in family members presenting a potential difficulty with the responsibility of the provider to give informed consent. [30] Bombard et al., found that only 4/29 (14%) of National Cancer Institutes offered an opt-out from reflex testing.[30] This process of opt-out testing is in line with the study of 245 individuals with MMR deficient CRC done by Ward et al., in 2013.[29] This study demonstrated that approximately half (102/245, 42%) of patients for whom informed consent was provided for tumor testing declined to consent or did not provide a sample to learn their germline results.[29]

There has been controversy surrounding the requirement of informed consent and pre- and post- test counselling for MSI and IHC testing among providers.[30] Ultimately, it has been largely decided that informed consent is not an ethical prerequisite for either MSI or IHC screening for Lynch syndrome.[30] This decision was made, largely on account of the associated knowledge that there is already informed consent gathered for the medical procedures (colonoscopies, surgeries etc.) that collect the samples for pathological evaluation.[10] Rather, it has been proposed that

patients should be prepared for the possibility of a positive screening test and further testing recommendations prior to the procedure to collect a biopsy as part of the general informed consent process.[10] The pre- and post- test counselling is considered when a positive result is returned after pathological analysis as further testing for LS is typically done through a referral to a genetic counselor, or genetics professional who can provide more information regarding the implications and informed consent for germline testing.

1.2 Genetic Counseling

As a profession, genetic counseling as defined by the National Society of Genetic Counselors (NSGC) is "the process of helping people understand and adapt to the medical, psychological, and familial implications of the genetic contribution to disease."[31] This definition underscores the patient-centered approach to personal healthcare provided by genetic counselors. Genetic counselors can work in a variety of subspecialty disciplines, including oncology, pediatrics, neurology, prenatal, or laboratory services.

1.2.1 Genetic Counseling Outcomes

As professionals in genetics and psychosocial counseling, genetic counselors are considered valuable members to medical teams to enhance patient care satisfaction and well-being as well as assist with appropriate test coordination resulting in decreased cost and liability to establishments. [32]

To demonstrate the benefits and efficacy of the profession, measurement of outcomes has become a priority for research. A seminal study by Redlinger-Grosse, et al. [33] developed a comprehensive list of outcomes based on the Reciprocal Engagement Model (REM) that examines the mutual participation of patients and genetic counselors in the process of understanding and applying new information. Through their research they identified four main themes that arose:

1. Patient Knowledge
2. Decision-Making
3. Patient Satisfaction
4. Psychological Adaptation

While there are no universal themes examined across genetic counseling outcome research, the four main themes identified through Redlinger-Grosse, et al.[33] provide a context for further research. As one of the aims of genetic counseling is enabling patients to make informed decisions, it is imperative that patients are able to understand specific genetic information related to their health. There is an expected increase in patient satisfaction with genetic counseling, as patients are given personalized sessions and are encouraged to make individualized healthcare decisions with support from their social systems and healthcare team. Ultimately, psychological adaptation is an important aspect of genetic counseling. As the name implies, genetic counselors are trained to anticipate, discuss, and support patients through the psychological and emotional implications of genetic testing and results. [34] Thus, it would be expected that with increased psychological support, patients are able to make informed decisions and experience less anxiety as well as improved communication within families and systems of support.[33; 34]

1.2.2 Self-efficacy and Empowerment

Genetic counseling has been shown to result in an increased observance of medical management plans amongst patients[34; 35] A study of 143 patients at a psychiatric genetic counseling clinic demonstrated a statistically significant increase in self-efficacy and empowerment after genetic counseling.[36] These changes were not dependent on the results of genetic testing as the clinic does not provide genetic testing to these patients. A similar 2016 study found that genetic counseling led to improved levels of patient knowledge of genetic components of their health condition, and improved accuracy of risk perception when compared to patients receiving only an educational booklet.[37] The 2004 meta-analysis by Braitwaite et al.[38] indicated a statistically significant increase in knowledge and intervention in oncology based genetic counseling as compared to those with no genetic counseling. Brain et al. found that there was a statistically significant greater improvement in knowledge about breast cancer after receiving specialist genetic services. [39]

1.2.3 Genetic Counseling Compliance with UTS and LS

A 2012 study by Cragun et al.[40] found that genetic counseling and further germline genetic testing was supported by 67-72% individuals with abnormal colorectal IHC results, but that cost was a large aspect of consideration for these individuals. Irons et al.[41] found that of uptake of genetic counseling at MD Anderson in individuals with an identified abnormal IHC results was 35.7% overall, and 85.7% in patients with a family history of LS-related cancers, potentially identifying a system of self-selection for genetic counseling uptake.[41] In a study of 1,108 colorectal cancers by Heald et al.[27] it was found that more patients attended genetic counseling appointments

when the referral was facilitated by the genetic counselor rather than through the surgeon, and referral by a genetic counselor resulted in more patients who were correctly identified and tested positive for LS.[27] Hunter et al. found that cost was a common barrier to the uptake of genetic testing (54%), and that overall, the distress associated with UTS was low.[42] This demonstrates that patients are supportive of UTS, but the study failed to assess patient understanding of the implications of the results of further genetic testing. Alternatively, Manne et al.[43] were able to incorporate educational material about genetic testing prior to UTS and found that 91% of individuals with a prior educational program about genetic counseling and testing chose to pursue genetic counseling after abnormal IHC results were returned.[43] They also demonstrated that increased education prior to UTS did not increase levels of anxiety in participants.[43] The findings of these studies suggest that individuals may have a variety of reasons for not pursuing follow up genetic testing after UTS. While genetic counseling has generally shown to increase patient uptake, there seem to be a number of barriers to accessing genetic counseling and testing services.

1.2.4 Impact of Genetic Test Results

Genetic counseling addresses concerns that can be stressful and emotional for many individuals. Unlike most other conditions, inherited cancer syndromes typically have a known pattern of inheritance that can impact individuals' self-concept and self-esteem.[44; 45] It has been shown that women experience significantly different levels of psychological distress following *BRCA1* mutation testing depending on the results of their testing.[45] Significantly, positive results may present a difficult burden for individuals with a family history of inherited cancers that are often diagnosed at relatively-young ages.[44] Bereavement and grief are common in familial cancer clinics as young adults may have lost parents to cancer at young ages.[44] Patients' beliefs of genetic

testing and results have been shown to change with increased knowledge through genetic counseling; while 76% of patients surveyed expressed interest in genetic testing at baseline, following genetic counseling 71% of women were still interested.[46]

There is limited literature in regard to impact of tumor screening results on patient affect. Lindor et al.[47], ascertained that of 414 CRC patients provided with education material about their MSI/IHC results, 307 participants (74%) decided to learn the results of their testing with the understanding of the ambiguity or inherent complexity of the information. Participants were interested in receiving their MSI results to help understand future family risk, help make an informed choice, and contribute to relevant research.[47] Women with abnormal MSI results demonstrated a slight decrease in reported quality of life, whereas women with normal MSI reported no change in their self-rating of quality of life; alternatively, men with abnormal results showed a slight improvement in QOL whereas those men with normal results showed a slight decrease in self-reported QOL. None of the reported changes in QOL were statistically significant.[47] The reported disparity between perceptions of QOL between men and women based on their CRC MSI results presents an open avenue of further research to better understand the impact of these results on psychological distress in patients. It is important to make the distinction that the impact of genetic testing is not considered an outcome of genetic counseling.[33] The positive values of genetic counseling such as empowerment and self-efficacy have been shown to persist regardless of the genetic testing result. [36] Although there is a potential impact of genetic test results on an individual or family, the impact of genetic counseling on patient care should not be conflated with the impact of results and may assist with mitigating negative impacts from genetic test results.

1.3 Patient Distress

1.3.1 Distress in Cancer

As there has been a discernable impact documented from genetic test results on individuals psychological distress, the literature has also identified four attributes in relation to the concept of cancer-related psychological distress: depression, anxiety, fear, and feeling discouraged.[48] Adults with a diagnosis of cancer who have undergone surgical treatment have demonstrated relevant levels of chronic stress which has implications for biologic effects.[49] Data investigating 116 patients having recently undergone surgical treatment for breast cancer had blood drawn prior to adjuvant therapy and demonstrated that the physiologic effects of stress inhibit cellular immune responses.[49] Understanding the extent of psychological distress in cancer may have further implications as to the appropriate treatment required to combat various physiologic effects.[49] Albrecht & Rosenzweig estimated that at least 48.7% of patients with a hematologic malignancy experienced cancer-related distress.[50] Patient cancer-related distress is not only associated with poor[51] psychological outcomes for patients, but also for clinicians and family members providing care.[50; 52] A cross-sectional survey of 354 cancer patients and 336 care-providers demonstrated that 53.4% of patients and 45.2% of caregivers experienced significant levels of anxiety or depression through assessment of both clinical diagnosis and symptoms.[53] Cancer status (stable disease, remission, metastatic, recurrent) was not found to be a significant predictor of psychosocial outcomes for these patients. They identified age, gender, marital status, treatment, work status, education and income as significant bivariate correlates for psychological distress predictors, representing important variables in consideration of further research.[53]

1.3.2 Distress in Cancer Genetic Testing

Genetic risk information provides personalized assessments of risks for patients. As medicine moves toward an increasingly personalized approach, the consideration of the psychological impact of genetic test results is warranted. A 1996 study found that after controlling for level of education, women with breast cancer who had genetic counseling exhibited a statistically significant decrease in breast-cancer-specific distress at a 3-month follow up as compared with women who received generalized health education, and failed to demonstrate any statistically significant increase or decrease in generalized anxiety.[54] More recent studies have demonstrated similar results, with statistically significant decline in levels of cancer-related distress during follow-up in breast cancer patients following genetic counseling.[55] A study of 181 female participants who accessed a cancer genetic counseling clinic confirmed that genetic counseling distinct from genetic testing was not a source of psychological distress.[56] Further research in Spain has identified that cancer worry prior to genetic testing is predictive of genetic testing specific distress after results.[57] Of individuals with a known familial mutation, 10–20 % of counselees demonstrated psychological problems after testing positive, after measurement at three time points.[58] 165 counselees with a 50% risk of testing positive for *BRCA1/2* or Lynch syndrome were assessed for levels of emotional distress prior to genetic counseling.[58] These measurements were taken at 2-3 days after receiving their test result, and again 4-6 weeks later.[58] Those counselees with a positive result did not exhibit statistically significant increased levels of emotional distress, but did exhibit more cancer worries after learning of their test result.[58]Much of the research conducted thus far has focused on women pursuing testing for Hereditary Breast and Ovarian Cancer (HBOC). Little other research has been conducted as to the perception of patient distress in relation to Lynch testing and therefore, this topic is worthy of further investigation.

1.4 Distress Measures

1.4.1 PHQ-8

Depression is one indication of an individual's level of psychological distress. The Patient Health Questionnaire depression scale (PHQ-8) is a validated diagnostic measure for depressive disorders. The PHQ-8 has been assessed in epidemiological population-based studies as well as large clinical studies. A 2008 survey of 198,678 random-digit-dialed telephone participants found that the prevalence of current depression disorder was similar between diagnostic algorithms or through use of PHQ-8 score ≥10.[59] The PHQ-8 consists of eight questions based on the DSM-IV diagnostic criteria for depressive disorders, and a final question based on assessing risk for suicide or self-harm. The scores may range from 0-24. The questionnaire asks respondents to rate the frequency of their emotions corresponding to different scenarios over the past two weeks on a Likert scale of 0-3, where 0 is "Not at all", 1 is "several days", 2 is "more than half the day", and 3 is "nearly every day." The two original validation studies of the PHQ-8 totaled 6000 patients which demonstrated that the ninth question can be omitted without effect on the validity of the questionnaire.[59; 60] Of the 198,678 surveyed participants, 17,040 were identified to have a score of ≥10 indicating a current depressive status.[59] Current depression by the PHQ-8 can be defined as either as a respondent answering at least 5 of the 8 symptoms to be present "more than half the days" (value of 2), or a PHQ-8 score of ≥10 which has an 88% sensitivity and specificity for major depression. [60] The PHQ-8 has also been validated for use in cancer cohorts[61; 62] to diagnose current depressive disorders. Depression is a significant concern in individuals with cancer[48] and therefore, it is an important measurement to collect so that health care providers may assess and differentiate

the depression associated with a diagnosis of cancer and any other situation that may be affecting depression levels.

1.4.2 GAD-7

Another measurable feature of psychological distress is anxiety. Anxiety disorders are the most prevalent class of mental disorders in the general population.[63] Although anxiety disorders are widely present in the general population, prior to the establishment of the 7-item Generalized Anxiety Disorder Scale (GAD-7), there was a dearth of valid screening tools for the diagnosis of generalized anxiety disorder.[63] Validation of the GAD-7 was performed on more than 5000 subjects in the general population, affirming validity and internal consistency across age and gender.[63] It has also been validated in the primary care setting,[64] and has been used as a measurement for levels of anxiety in patients with cancer.[65] The recommended interpretation of GAD-7 in clinical settings is of scores of ≥10 as "yellow flags" and GAD-7 scores of ≥15 as "red flags" for the presence of anxiety disorders.[63] A yellow flag score is associated with a positive likelihood ratio for the presence of generalized anxiety disorder of 5.1, whereas a red flag is associated with a positive likelihood ratio of 8.7.[63] Elevated GAD-7 scores can also be indicative of panic disorder, social anxiety disorder, and posttraumatic stress disorder.[63] The GAD-7 has a range of scores from 0-21, with the 7 questions having response ranges on a Likert scale of 0-3. The questionnaire asks respondents to rate the frequency of their emotions corresponding to different scenarios over the past two weeks on a Likert scale of 0-3, where 0 is "Not at all", 1 is "several days", 2 is "more than half the days", and 3 is "nearly every day." The GAD-7 has 89% sensitivity and 82% specificity for generalized anxiety disorder and can also be used to screen for other anxiety disorders: panic disorder (sensitivity 74%, specificity 81%), social anxiety disorder

(sensitivity 72%, specificity 80%) and post-traumatic stress disorder (sensitivity 66%, specificity 81%).[66] Anxiety is another main concern in individuals with cancer [48]through measurement of anxiety over time such instruments as the GAD-7 allow for the differentiation of anxiety from cancer diagnosis and other situations under investigation.

1.4.3 IES-R

The Impact of Event Scale- Revised (IES-R) is a measurement of common symptoms of post-traumatic stress disorder (PTSD) and the impact of stressful life events within the previous seven-days.[67] The IES-R is a 22-item scale with three subscales to measure: avoidance behavior, intrusive thinking related to the event, and emotional arousal.[67] These three subscales represent the DSM criteria for PTSD.[51] The questionnaire can be adjusted to include reference to a specific traumatic event. The subject is asked to indicate frequency of the event on a five point scale (0 "not at all" to 4 "extremely") over the past 7 days.[68; 69] Total scores of the IES-R above 25 represent high risk of PTSD.[69] The IES-R yields a total score ranging from 0-88 and subscale scores calculated for intrusion, avoidance, and hyperarousal. The avoidance subscale looks at instances of individuals experiencing denial or inhibition of conscious awareness of traumatic emotions.[68] Intrusion symptoms report on persistently experienced memories, nightmare, flashbacks, distress or reactivity to reminds of the trauma. Hyperarousal report on trauma-related arousal or reactivity that either began or worsened after the trauma through irritability, changes in behavior, heightened reactions, or difficulty sleeping or concentrating.[70] In general, the IES-R is not used to diagnose PTSD, but rather has been shown to provide a preliminary diagnosis. This scale provides a self-reported measurement of patient perception of trauma resulting from their diagnosis of cancer. As an instrument, the IES-R encompasses the remaining two common features of psychological

distress in cancer: fear and discouragement. The impact from the diagnosis of cancer can be compared over time and monitored against genetic counseling and genetic testing.

1.4.4 MICRA

The Multidimensional Impact of Cancer Risk Assessment (MICRA) is a validated questionnaire used to measure the impact of result disclosure following genetic testing within the past week.[71] The MICRA questionnaire is a 25-item scale which supports 3 subscales: Distress (6 items), Uncertainty (9 items), and Positive Experiences (4 items). In MICRA the scores are allotted values of 0 (never), 1 (rarely), 3 (sometimes), and 5 (often). The Positive Experiences subscale is scored in reverse value order to account for positive interactions. In a study of 159 female participants with various positive or negative genetic testing results,[71] all 3 MICRA subscales were found to identify subgroups of vulnerable testing participants. Reponses following genetic testing were significant for the identification of risk status, decision making, and personal thoughts of self-empowerment.[72] This questionnaire elicits concerns specifically regarding the genetic testing process, results obtained, and patients' understanding of further management. It is unique in its ability to compare those who test positive for cancer-related gene mutations, to those who test negative as its responses are directly related to genetic testing outcomes.[73] MICRA provides the opportunity to compare differences in psychosocial experiences of the different clinical subgroups.[73] A limitation of MICRA is that it has been validated in women in respect to hereditary breast and ovarian cancer, but has yet to be largely used in other hereditary cancer types and that it cannot be compared to outside distress testing measurements.[73]

In a 2015 study of psychological distress based solely on women with ovarian cancer, 4 groups were selected to represent a continuum of cancer risk from demonstrated *BRCA* carriers to

women without a family history of breast or ovarian cancer.[74] Bjørnslett et al. was the first to define a high general MICRA score, identifying it as +1 standard deviation above the mean.[74] The study also implemented the IES questionnaire demonstrating internal consistency between the two measurements.[74] Of interest, the study identified that there was no statistical significance between mean group scores or total MICRA scores when compared across multiple variables including: time from diagnosis, receiving the test result, or duration from taking the result to the disclosure of test result to time of the survey. Thus, results supported the view that genetic test results and the testing process are of specific and long-term concern for individuals.[74]

The utilization of the MICRA questionnaire allows for further differentiation of psychological distress based on genetic test result. While genetic testing results are not an indicator of genetic counseling efficacy, they do represent a source of potential distress.[44; 45] UTS is not a diagnostic test method, thus it is important that research work include potential distress associated with the testing process and final results. Individuals with positive abnormal screening results may be referred to genetic counseling for germline testing without any family history of cancer. It is important to measure the uptake of management recommendations that have been made based on genetic test results whether positive or negative, especially in these individuals where prior to referral to genetic counseling, it is largely possible that LS was a previously unknown condition. MICRA supports scales of uncertainty, distress, and positive experiences which are all important factors in the continued utilization of genetic counseling and testing following abnormal UTS results.

2.0 Introduction

Current practices in oncology involve collection of tumor tissue in an effort to better understand the disease process for appropriate targeted treatment methods. One aspect of these pathological analyses involves the identification of tumor specific markers such as the presence of microsatellite instability, or DNA mismatch repair (MMR) protein deficiency.[7; 9] Inherited pathogenic variants in the DNA mismatch repair genes are associated with Lynch Syndrome (LS).[7; 9] The loss of these proteins in solid tumor testing may be indicative of a corresponding germline pathogenic variant. The use of tumor studies in colorectal cancer (CRC) has been found to detect >90% of LS patients.[7; 9] Universal tumor screening (UTS) and the recent shift in availability of next-generation sequencing has resulted in a significant number of patients being identified as having LS whose personal and family histories may lack the traditional clinical features of Lynch syndrome.[7; 8] In 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group made the recommendation of universal testing for all patients newly diagnosed with CRC, through microsatellite instability (MSI) and immunohistochemistry (IHC) staining for MMR protein expression.[10] This method has been acknowledged as cost-effective and beneficial to patients, resulting in a reduction of morbidity and mortality.[10]

LS predisposes individuals to increased risks of several types of cancer, the highest of which is CRC.[5] The lifetime-risk for colorectal cancer in individuals with LS may be as high as 70%.[5] Due to the quantification of these cancer risks, prevention and management guidelines have been established to reduce the mortality rate of those with LS. LS is known to be caused by mutations in one of five genes related to MMR: *MLH1, PMS2, MSH2, MSH6,* and *EPCAM*. Research has demonstrated that Lynch-related cancers display a specific histologic pathology that

has allowed the development of therapeutics that are most effective against these pathologies.[6; 19-21] Specifically, finding a somatic loss of MLH1, PMS2, MSH2, or MSH6 proteins through tumor screening provides a method to subsequently identify individuals at risk for a corresponding germline variant in these genes.[7; 9] The identification of LS has implications beyond therapeutic care; it can also initiate cascade screening of related family members, prompting early intervention services and decreasing Lynch-related cancer mortality.

Although there are individual and familial implications related to the identification of a LS associated pathogenic variant, there is limited research regarding patient perspectives of universal tumor screening in Lynch Syndrome.[22; 34-37] Of the literature that is currently available for LS, it has thus far concluded an overall positive attitude toward tumor screening for CRC patients, but has provided limited perspective on the impact of this testing on patient mental health and anxiety.[36] This is an important area of research as psychological distress has been associated with genetic testing results[58] and is already a concern in patients diagnosed with any type of cancer. However, the majority of research regarding patient perspectives of genetic testing has been completed in the realm of Hereditary Breast and Ovarian Cancer syndromes[38; 39]Voorwinden et al. identified that as much as 10-20% of patients with a positive diagnosis of BRCA1/2 mutation had negative psychological impacts following the result.[58] In general, patients with a diagnosis of cancer are at risk for the development of multiple psychological concerns including: depression, anxiety, fear, and feeling discouraged.[48] Psychological distress may be further complicated by the receipt of UTS results.

As a screen, the results of the UTS are not diagnostic. Moreover, germline testing may not identify an underlying pathogenic variant and leave patients with ambiguity in the interpretation of their genetic test results. Research has yet to elucidate whether there is any incongruence

between patient understanding of the implications of somatic variation versus germline variants. Given the recent surge in CRC tumor testing, it is important that patient perspectives and anxiety levels related to germline testing be considered in their management and treatment plan, including in the genetic counseling and testing process.

In a study of 414 individuals who received UTS, three-quarters (74%) wanted to receive their preliminary UTS results, while 26% did not wish to learn these results.[47] The disinterest in a quarter of the participants in learning their UTS result offers insight into UTS as a potentially distressing concept for some individuals. Within this same cohort, upon offering germline testing for the participants who received an abnormal UTS result, only 25-33% were interested in undergoing germline testing.[47] The rationale for the disinterest in receiving genetic results was proposed to be related to the stigma associated with genetic testing, while the UTS was considered more of a triage test and not a genetic test result since it still required follow-up diagnostic testing.[47] This same study similarly demonstrated that through the utilization of genetic counseling there was a reduction in patient distress (levels of depression and anxiety) in patients before and after counseling.[42] This suggests that genetic counseling may be associated with changes in patient distress related to UTS.

In summary, as a pilot study, this project has two specific aims:

(a) To investigate the role of genetic counseling in the variation of patient distress levels over time.

(b) To compare distress levels in patients with CRC and abnormal tumor study results to patients without abnormal tumor study results.

A case-control model was used to measure levels of patient distress over time, with the aim to assess the impact of UTS on patients' levels of distress, and the potential impact of genetic counseling and germline testing on these levels of distress.

3.0 Methods

3.1 Participants

In an attempt to better understand the impact of both abnormal UTS results and genetic counseling, we recruited three separate cancer patient groups. The first group included patients who were referred to the UPMC Hereditary Gastrointestinal (GI) Tumor Program for hereditary cancer risk assessment based on MMR deficiency identified in CRC on pathologic analysis. The second group was comprised of patients referred to the Hereditary GI Tumor program at UPMC who received genetic counseling for a personal history of CRC diagnosed prior to the age of 50 and who had normal UTS results (MSS tumor or intact MMR protein expression). The final group of patients, recruited through the UPMC Surgical Oncology department, was diagnosed with CRC after age 50 and had normal UTS results. Approval for the study was provided by the University of Pittsburgh Institutional Review Board (PRO18040719) (Appendix A.7).

3.2 Eligibility Criteria

Different eligibility criteria were defined for each patient group. Participants were eligible for the first group (hereafter referred to as the case group) if they had abnormal tumor testing results indicating a loss of any of MSH2, MSH6, MLH1, or PMS2, regardless of age. For those identified to have a MLH1 or PMS2 protein loss, participants were excluded if BRAF V600E or MLH1 promoter hypermethylation was identified on pathology prior to the appointment.

Participants in the second group (hereafter referred to as the genetics control group) were identified upon referral to the UPMC GI Hereditary Tumor Program as eligible for participation if they had been diagnosed with MSS CRC prior to the age of 50. The third group (hereafter referred to as cancer control group) was eligible for participation if they had MSS CRC diagnosed after age 50. Potential cancer control group participants were excluded if they had previously received genetic counseling for hereditary cancers.

3.3 Recruitment

Participants in the case group and the genetics control group were approached about the study at the beginning of their genetics appointment. Participants in the cancer control group were approached directly before their appointments with their surgical oncologist. For those participants who expressed an interest in enrolling in the research study, informed consent was obtained, any questions were answered, and the investigator then administered the questionnaires.

3.4 Instruments

In this study, multiple instruments were used in effort to obtain an accurate assessment of the overall level of patient distress. The Patient Health Questionaire-8 (PHQ-8), Generalized Anxiety Disorder-7 (GAD-7), and Impact of Event Scale-Revised (IES-R) were used to measure patients' level of depression, anxiety, and cancer-related distress respectively. The MICRA questionnaire was also used to measure patient perceptions of distress associated with their

germline genetic test results in the participants for the case group and the genetics control group. All four of these instruments are validated questionnaires. Questionnaires were administered orally at all time points.

3.4.1 PHQ-8

3.4.1.1 Instrument

The eight-item Patient Health Questionnaire (PHQ-8) depression scale is used as a validated diagnostic measure for depressive disorders and has clinical utility in comparing levels of depression overtime. The PHQ-8 was created as a tool for screening individuals to better assess their current psychological state.[55; 56] The PHQ-8 consists of eight questions based on DSM-IV depressive disorder criteria. The PHQ-8 may also contain a final question assessing risk of suicide or self-harm. For the purpose of this study, this question was omitted as it has not been found to impact the validity of the questionnaire and was not required for the aims of the study.[53; 54]

3.4.1.2 Scoring

Participants are asked to provide answers to the 8 questions based on their experiences within the last two weeks, and answers are ranked using a Likert scale of "Not at all" to "nearly every day". The answers were scored with "Not at all" being zero points, "several days" as one point, "more than half the days" as two points, and "Nearly every day" as three points. The points from each of the eight answers were then tallied for a total score, with a highest possible score of 24 points. Any score equal to or above 10 points is considered a diagnosis of depressive disorder.[54] The PHQ-8 scores were measured at all time points for all groups, and the differences were used in paired analysis.

3.4.2 GAD-7

3.4.2.1 Instrument

The seven-item Generalized Anxiety Disorder (GAD-7) tool was utilized to measure generalized anxiety disorder as well as utility in comparing anxiety levels over time, in the participant cohorts. This questionnaire may indicate diagnoses of generalized anxiety disorder, panic disorder, social anxiety disorder, and posttraumatic stress disorder.[57] It has been validated in multiple large-scale reviews, including populations of individuals with cancer.[59] For the purpose of this study, the GAD-7 was used as a measurement of generalized anxiety disorder.

3.4.2.2 Scoring

Total scores for the GAD-7 range from 0-21. A Likert scale is used in this questionnaire and participants are asked to assess their corresponding value for how often they have been bothered over the past two weeks. The scale employs the same range as is seen in the PHQ-8 using a scale from 0-3 with zero corresponding to "Not at all" and three corresponding to "nearly every day." Totals were tallied across the seven possible questions with a score ≥15 representing a clinical diagnosis of anxiety. The GAD-7 was provided to participants at all three time points and was compared across all time points to determine differences in generalized anxiety levels over time.

3.4.3 IES-R

3.4.3.1 Instrument

The Impact of Event Scale-Revised (IES-R) was used to measure the impact of trauma specifically pertaining to the participant's cancer diagnosis within the past week.[61] This 22-item scale contains three subdomains: avoidance behavior, intrusive thinking related to the event, and emotional/hyper-arousal. The three subdomains are representative of the clinical DSM criteria in the diagnosis of post-traumatic stress disorder (PTSD).[45] The IES-R is not a diagnostic tool for PTSD but acts as a preliminary screen for those at risk for PTSD from a traumatic event. The questionnaire was adjusted to ask for their responses over the past week as related to their "most recent cancer diagnosis." The date of the diagnosis was not always included as exact dates were not always available.

3.4.3.2 Scoring

The total score for the IES-R can range from 0-88. Subdomain scores can be calculated separately. The totals for avoidance and intrusion can range from 0-32 (based on eight questions being included in each), while the total for hyperarousal can range from 0-24 (based on the inclusion of six questions regarding hyperarousal). As with the PHQ-8 and GAD-7, the IES-R was measured at all three time points and both the subdomain and total scores were compared across participants over time. Cut-points for the IES-R have been widely discussed, for this study, we have utilized a cut-point of ≥25 as has been presented in various other studies to demonstrate a "high-risk" of an individual with PTSD.[75; 76]

3.4.4 MICRA

3.4.4.1 Instrument

The Multidimensional Impact of Cancer Risk Assessment (MICRA) is a more recently developed, validated questionnaire that can be used as a method to measure the impact of result disclosure following genetic testing.[65] The MICRA questionnaire is comprised of three subdomains: distress, uncertainty, and positive experiences. This questionnaire was developed to assess concerns regarding: the genetic testing process, the results obtained (positive, negative, variant of uncertain significance), and patients' understanding of any available management guidelines. The use of the MICRA questionnaires allows for comparison between groups and individuals who have received genetic testing based on the results of their testing.

3.4.4.2 Scoring

MICRA consists of 25 questions that participants are asked to answer based on their feelings within the past week. There are four responses for each question: never, rarely, sometimes, or often. The answers are allotted values of zero, one, three, and five respectively. The potential total of each subdomain varies. For the distress domain, there are 6 items included, so the highest possible score is 30 points. The uncertainty domain consists of 9 items, with highest possible score being 45 points. Conversely, the positive experiences domain consists of 4 items, but is reverse scored. As such, for positive experience, an answer of "never" corresponds with a value of 5, whereas an answer of "often" would be given a value of 0. The total possible value for positive experiences would be 20, with a higher total value corresponding with a lower positive experience. A high MICRA score is identified as being over one standard deviation above the mean.[68] The MICRA questionnaire was given only at the final time point, two weeks following the receipt of

genetic test results from genetic counselors, and thus was provided only to the case group and the genetics control group.

3.5 Study Protocol

The research investigators involved in this study included genetic counselors, a gastroenterologist, a surgical oncologist, and two genetic counseling students who facilitated the study enrollment and administration of follow-up questionnaires (Figure 1).

During the first study time point (Figure 1), patients provided informed consent, three questionnaires (PHQ, GAD-7, and IES-R) were orally administered to the patient, and the results were collected by the research investigator. The questionnaire was given in the presence of any other individuals attending the appointment with the participant. During the appointment, the participant received individualized genetic counseling by a certified, licensed genetic counselor, and was then seen by a physician for a complete consult.

The genetic counseling appointment consisted of a one-hour session. During this session, participants in the case and genetics control groups received genetic education and information pertaining to their risk of Lynch syndrome. They were provided with personalized risk assessment based on medical and family history and they received psychosocial counseling when appropriate. Visual aids were used throughout the session to support patient understanding.

Consented participants were contacted via telephone two weeks after their enrollment, before notification of their genetic test results. At this second time point, they were asked to complete the PHQ-8, GAD-7, and IES-R questionnaires again. If patients were not reached on the two-week mark, they were called until they were reached. If they could not be reached prior to the

availability of their test results, then they were excluded from the second time point, and were attempted to be reached for the third point.

Genetic test results were disclosed by the genetic counselors over the telephone. The participants were then contacted two-weeks after their results were disclosed. In instances where further genetic testing was required after the original test was completed, participants were not contacted until two weeks after the final testing results had been disclosed. All individuals in the case group and the genetics control group decided to undergo genetic testing. Patients were subsequently sent a letter outlining their results and management recommendations for themselves and their family. When patients were contacted over the telephone at the third time point, they were again asked to complete the PHQ-8, GAD-7, and IES-R, with the addition of the MICRA questionnaire for the case and genetics control groups. At that point participants were told they had reached the end of the study.

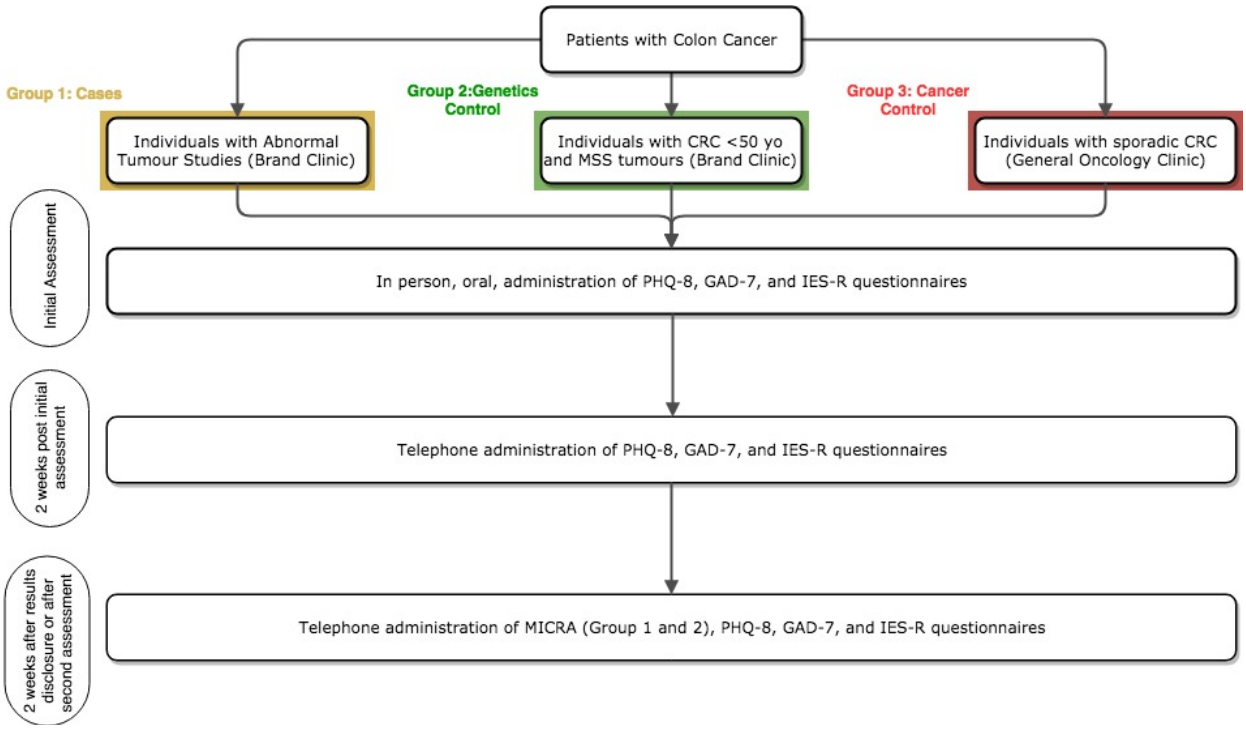

Figure 1 Protocol Flowsheet

3.6 Data Analysis

The data from each of the questionnaires were assessed for normality of distribution in total. For the measures which included multiple subscales, all domains were assessed for normality. Both, paired t-tests and non-parametric Wilcoxon ranked sign tests, were performed to determine mean differences in scores across all three time points (Appendix B). The statistical program STATA (Stata Corp 2015) was used to perform relevant analyses. The threshold for significance was set at $p<0.05$ at a 95% Confidence Interval. Given the small sample size (n=23) observed qualitative trends were also reported.

4.0 Results

Participants were recruited between July 2018 and January 2019 and a total of 23 participants were enrolled. Each participant was followed for at least four weeks following recruitment. One of the case participants was lost-to-follow up, but this participant's baseline data was still incorporated in data analysis. Two of the genetics control participants did not have a measurement at the second time point as the results were returned before the participants were reached for their second measurements. For these individuals the second time point was skipped, and the third time was administered two weeks post results disclosure. A total of 10 participants were recruited in the case group, and a total of 9 participants were recruited in the genetics control group. Due to constraints related to patient recruitment, a total of 4 patients were identified in the sporadic control group. One participant in the sporadic control group did not have a third time point collected as he was lost to follow up before the submission of this thesis. All participants had a diagnosis of either colon or rectal cancer. Additionally, while adherence to time point scheduling of two weeks between administration was attempted, given various testing methods and laboratory use for genetic testing, there was variability in the length of time between the test measurements.

4.1 Demographics

A total of 23 participants were enrolled in this pilot study. Of those enrolled, 30.4% were female, and all of the participants identified as white. Participant ages ranged from 22-89 years within the groups with a total mean age of diagnosis between the groups of 51.1 years. The

sporadic control group consisted entirely of male participants with age at diagnosis ranging between 52-59 years old, and an average time since diagnosis of 17.75 months. Of the genetics control group, the mean age at diagnosis was 39.1 years (range 22-49) and the average time in months since diagnosis was 73.6 months (approximately 6 years, range 1-297 months). The case group had a mean age of diagnosis of 60.5 years (range 39-86) and an average time since diagnosis of 5.8 months (range 0-12 months) (Table 1). All participants (100%) in the genetics control and the case groups met NCCN 2018 guideline criteria for genetic testing; none of the sporadic control participants met NCCN based on personal history alone or tumor testing as all were MSS.

Table 1 Demographics

Group	Case	Genetics Control	Sporadic Control	Total
	n=10	**n=9**	**n=4**	**n=23**
Age (years)				
Mean	60.9	45.2	56.5	**54.2**
Range	39-87	26-57	53-59	**26-87**
Sex				
Female (n)	40% (4)	33.3% (3)	0% (0)	**30.4% (7)**
Male (n)	60% (6)	66.7% (6)	100% (4)	**69.6% (16)**
Ethnicity				
White	10	9	4	**23**
Other	0	0	0	**0**
Age at Diagnosis (years)				
Mean	60.5	39.1	54.5	**51.1**
Range	39-86	22-49	52-59	**22-86**
Time Since Diagnosis (months)				
Mean	5.8	73.6	17.75	**34.4**
Range	0-12	1-297*	7-31	**0-297**

*297 months = 24.75 years

4.2 Baseline Distress Measurements Across All Participants

Baseline measurements (PHQ8, GAD-7, IES-R) demonstrated distress across groups (Table 2). Although no statistically significant differences between case and control scores were identified, the mean values for all three measurements trended higher in the case group as compared to the controls. Clinical significance for the measurements was identified in 3/10 (30%) participants in the case group for depression while only one individual in each control groups (11% in the genetics control and 25% in the sporadic control) reported a significant level of depression at the baseline measurement (Fisher's Exact p-value=0.582) (Table 4). For all other measurements, there was no difference in the number of clinically affected case versus control participants (Fisher's Exact p-values=1.000). The largest difference in mean scores between the case and genetics control groups was seen for the IES-R (p-value = 0.3864 95%CI [5.0,17.2]). The values for PTSD risk trended higher in the case group with a departure in the median value (11.5 in cases, 2 and 4 in controls).

Further investigation into the subscales of the IES-R Measurement between the genetics control and case groups found that the largest difference in mean was observed in the intrusion subscale (p=0.639 95%CI [2.3,7.2]). The scores for hyperactive thoughts were very similar across the two groups and was the lowest values of the IES-R subscales. The case group had a median value of 3.5 for the avoidance subscale, while the control group had a median value of 0. The ranges were similar across both groups. The highest values for all subscales within the control group were from the same individual.

Table 2 Baseline Distress Values

Group	Case	Genetics Control	Sporadic Control	Total	p-values
	n=10	**n=9**	**n=4**	**n=23**	
PHQ8					
Mean ± SD	6.9 ± 8.3	3.9 ± 4.8	4.8 ± 1.9	**5.4 ± 6.2**	0.587
Median	3	3	5.5	**3**	
Range	0-22	0-15	2-6	**0-22**	
Score >10	30% (3)	11.1% (1)	0% (0)	**4**	
Range >10	14-22	15	-	**14-22**	
GAD-7					
Mean	4.4 ± 5.7	4.3 ± 5.3	3.8 ± 3.3	**4.3 ± 5.0**	0.9771
Median	1.5	2	4	**2**	
Range	0-15	0-16	0-7	**0-16**	
Score >15	10% (1)	11.1% (1)	0% (0)	**2**	
Range >15	16	16	-	**16**	
IES-R					
Mean	14.5 ± 16.9	8.7 ± 12.8	8 ± 9.4	**11.1 ± 14.0**	0.6195
Median	11.5	2	4	**3**	
Range	0-55	0-36	22-Feb	**0-55**	
Score >25	10% (1)	11.1% (1)	0% (0)	**2**	
Range >25	55	39	-	**39-55**	

Table 3 IES-R Subscale Baseline Measurements

Group	Case	Genetics Control	Total	p-values
	n=10	**n=9**	**n=19**	
INT				
Mean ± SD	6.2 ± 6.3	3.9 ± 5.2	**5.1 ± 5.8**	0.639
Median	4.5	1	**2**	
Range	0-11	0-13	**0-13**	
AVD				
Mean ± SD	5.5 ± 6.5	2.6 ± 3.7	**4.1 ± 5.4**	0.65
Median	3.5	0	**2**	
Range	0-21	0-10	**0-21**	
HYP				
Mean ± SD	2.8 ± 4.8	2.3 ± 4.3	**2.6 ± 4.5**	0.091
Median	0	0	**0**	
Range	0-15	0-13	**0-15**	

Table 4 PHQ8 Clinical Depression at Baseline by Fisher's Exact

	Clinical Depression Screen		
Group	**Negative**	**Positive**	**Total**
Case	7	3	10
Genetics Control	8	1	9
Total	15	4	19
	0.2	0.8	1

Fisher's exact = 0.582

4.3 Mean Score Trends over Time

Participant scores for PHQ8, GAD7, and IESR are represented by heat maps (Tables 5,6,7). The three time points are represented in the columns. Red cells indicate clinically significant scores. Yellow-orange colors represent moderate scores (at least half the score required for clinical significance). Green cells indicate low scores, from zero up to moderate scores.

For the PHQ8 a clinical diagnosis of depression is designated by a score of >10 points. As such, the heat map distributes colors from green at 0 points to red >10 points. Some case participants demonstrated higher scores for PHQ across time points, including an increase in score from the second to the final time point (Table 5). The lowest mean levels of depression-associated distress over time is seen across the genetics control group, while sporadic control participants demonstrate moderate levels of depression. Most participants tended to approximately maintain levels of distress across the three time points.

The GAD7 scores indicate clinical concern when >15 points. The distribution of GAD7 scores across case participants demonstrate comparable mean scores when compared to the

genetics control group, but the case group did have more participants with levels indicative of clinical anxiety (Table 6). This trend is observed qualitatively though the distribution of color but can be seen in the value of means between and across groups and time points. While there were changes in scores for several participants, similarly, to the PHQ8, overall, individual participants tended to generally maintain similar levels of distress across time points.

For the IES-R, scores are clinically significant when >25. It appeared that overall scores tended to decrease between the first and second time points, with the exception of two individuals who demonstrated increased scores at the second time point (Table 7). For individuals in the genetics control group who began with clinically significant levels of PTSD, those levels persisted overtime. There are three genetics control participants with increased IES-R scores while all other participants demonstrate low levels (green) for IES-R scores. No sporadic control participants had overall increased IES-R score between the first and third time point.

Table 5 Participant PHQ8 Score Heat Map

Participant ID	Timepoint		
	Pre GC	Post GC	Post results
Cases			
ATS#1	0	0	0
ATS#3	6	0	1
ATS#6	22		
ATS#8	0	0	0
ATS#9	19	9	20
ATS#12	2	6	8
ATS#16	0	0	0
ATS#19	3	3	3
ATS#21	14	17	16
ATS#22	3	4	1
Mean	**6.9**	**4.3**	**5.4**
Controls			
ATS#2	15	12	9
ATS#5	0	0	0
ATS#10	0	0	0
ATS#11	0	-	0
ATS#13	3	-	2
ATS#14	6	5	0
ATS#15	3	4	4
ATS#17	2	1	1
ATS#18	6	2	14
Mean	**3.9**	**3.4**	**3.3**
ATS#23	2	9	1
ATS#26	5	5	5
ATS#27	6	4	5
ATS#28	6	7	7
Mean	**4.7**	**6.3**	**4.5**

Table 5. Scores are based on a gradient with low scores (0-4) range from green to orange and moderate scores (5-9) from orange to red with clinically relevant scores of ≥10 indicated in red.

Table 6 Participant GAD7 Score Heat Map

	Timepoint		
Participant ID	**Pre GC**	**Post GC**	**Post Results**
Cases			
ATS#1	0	0	0
ATS#3	0	4	1
ATS#6	9		
ATS#8	0	0	0
ATS#9	11	7	18
ATS#12	2	2	4
ATS#16	0	0	0
ATS#19	5	3	2
ATS#21	16	15	15
ATS#22	1	0	2
Mean	**4.4**	**3.4**	**4.7**
Controls			
ATS#2	16	11	14
ATS#5	0	0	0
ATS#10	0	0	0
ATS#11	0	-	1
ATS#13	2	-	3
ATS#14	1	0	3
ATS#15	7	15	12
ATS#17	6	1	1
ATS#18	7	5	12
Mean	**4.3**	**4.6**	**5.1**
ATS#23	2	11	2
ATS#26	6	3	3
ATS#27	7	1	4
ATS#28	0	0	0
Mean	**3.8**	**3.8**	**2.3**

Table 6. Scores are based on a gradient with low scores (0-10) range from green to orange and moderate scores (10-14) from orange to red with clinically relevant scores of ≥15 indicated in red.

Table 7 Participant IES-R Score Heat Map

	Timepoint		
Participant ID	**Pre GC**	**Post GC**	**Post Results**
Cases			
ATS#1	1	0	0
ATS#3	0	0	0
ATS#6	24		
ATS#8	0	0	0
ATS#9	55	56	32
ATS#12	8	7	5
ATS#16	3	1	0
ATS#19	15	7	3
ATS#21	18	43	37
ATS#22	21	5	4
Mean	**14.5**	**13.2**	**9**
Controls			
ATS#2	36	18	33
ATS#5	1	0	1
ATS#10	0	0	0
ATS#11	0	-	0
ATS#13	3	-	7
ATS#14	0	0	0
ATS#15	18	30	29
ATS#17	2	0	0
ATS#18	19	38	59
Mean	**8.8**	**12.3**	**14.3**
ATS#23	3	5	2
ATS#26	22	18	13
ATS#27	5	0	0
ATS#28	2	0	0
Mean	**8**	**5.8**	**3.8**

Table 7. Scores are based on a gradient with low scores (0-13) range from green to orange and moderate scores (13-24) from orange to red with clinically relevant scores of ≥25 indicated in red.

4.4 Individual Score Changes Across Genetic Counseling Groups

A summary of participant score changes are reported in Table 8. These changes are based on whether the clinical significance of the values reported for each individual changed between any given time points. Further interpretation is provided for each assessment for each participant. Genetic test results were also listed beside each participant identification. Within the case group a total of 4 clinically significant changes were identified, all in different individuals.

One participant was identified to have a clinically significant change in depression. ATS#12 reported no clinical depression at the first two time points with levels indicative of clinical depression reported at the final time point after disclosure of a negative genetic test result.

Two changes were noted in levels of anxiety. For participant ATS#9, their level of anxiety was reduced following genetic counseling, and subsequently increased two weeks post result disclosure where they received a positive genetic testing result. Alternatively, ATS#19 showed a decrease from mild anxiety before GC to levels not clinically significant both after GC and following results disclosure.

One participant had a change in IES-R values that was indicative of an increased risk for PTSD. They reported low-risk PTSD results prior to genetic counseling while their score subsequently increased to high risk both after genetic counseling and decreased while maintaining high-risk status two-weeks post disclosure of a positive genetic testing result.

The genetics controls similarly exhibited changes in their clinical levels of distress. For the control group there were eight clinical changes reported for four individuals. One participant, ATS#18 reported clinically significant changes across all three instruments. They were the only genetics control to report a clinically significant change in depression with their score increasing from not clinically significant to significant post result disclosure of a negative test result.

Interestingly, all clinical changes for this participant were increases at the point of assessment after result disclosure. Their anxiety level was recorded as mild until results disclosure at which point it increased to moderate. Whereas their PTSD risk increased from low to high after genetic counseling and increased in score while maintaining high risk after results disclosure.

Of the four genetics control individuals (4/9, 44.4%) that had clinically significant changes in distress scores, all four individuals demonstrated changes in anxiety. Three of the four participants demonstrated changes in both anxiety and PTSD. Of the two participants remaining that showed changes in both anxiety and PTSD (the third is discussed above), one participant (ATS#2) reported an anxiety reduction from severe before GC to moderate both after genetic counseling and post results disclosure. While this participants' risk of PTSD did drop from high risk before genetic counseling to low risk after genetic counseling, it increased to high risk again following disclosure of negative genetic test results. For the other participant (ATS#15) that demonstrated a change in both anxiety and PTSD risk the participant had an increase in anxiety from mild before genetic counseling to severe post genetic counseling, with a reduction to moderate after disclosure of results. The participant's PTSD risk scores increased for both time points following genetic counseling. The final participant that had a change in anxiety (ATS#17) reported mild anxiety before genetic counseling with a decrease to not clinically significant levels at both time points following genetic counseling.

Table 8 Summary of Changes in Clinical Significance

	Pathogenic Variant Identified	PHQ8		GAD7		IES-R	
Participant ID	Y/N	Change or No Change	Interpretation	Change or No Change	Interpretation	Change or No Change	Interpretation
Cases							
ATS#1	Y	No change	Consistent score of 0, no depression	No change	Consistent score of 0, no anxiety	No change	Score of 1 before GC, reduced to 0 for subsequent time points, low risk PTSD
ATS#3	N	No change	Score of 6 before GC, reduced to 0 and 1 for subsequent time points, no depression	No change	Score increased from 0 to 4 following GC, reduced to 1 post results, no clinical anxiety	No change	Consistent score of 0, low risk PTSD
ATS#6	N	No change	Lost to follow up, clinical depression score before GC	No change	Lost to follow up, intermediate levels of anxiety reported before GC	No change	Lost to follow up, high risk PTSD indicated before GC
ATS#8	Y	No change	Consistent score of 0, no depression	No change	Consistent score of 0, no anxiety	No change	Consistent score of 0, low risk PTSD
ATS#9	Y	No change	Consistent score above 8 indiciating clinical depression, score changed from 19 to 9 following GC, increased to 20 post results	**Change**	Change from moderate (11) anxiety before GC, reduced to mild (7) following GC, and increased to severe (15) anxiety post results	No change	Scores decreased from 56 after GC to 32 post results, still all three scores consistent with high risk for PTSD
ATS#12	N	**Change**	Score increased from no depression in first two time points, to clinical depression in final time point post results	No change	Score increased from 2 at first two time points to 4 post results, no clinical anxiety	No change	Score reduced from 8 before GC to 7 after GC, to 5 post results, all results indicate low risk PTSD
ATS#16	N	No change	Consistent score of 0, no depression	No change	Consistent score of 0, no anxiety	No change	Scores decreased from 3 before GC to 1 following GC to 0 post results, low risk PTSD
ATS#19	N	No change	Consistent score of 3, no depression	**Change**	Score decreased from mild (5) anxiety before GC to no clinical anxiety after GC (3) and post results (2)	No change	Score decreased from 15 before GC to 7 after GC, and further to 5 post results, all scores indicate low risk for PTSD
ATS#21	Y	No change	Consistent scores above 8 indicating clinical depression	No change	Consistently moderate levels of anxiety across time	**Change**	Low risk score of 18 before GC increased to high risk scores of 43 and 37 at respective subsequent time points
ATS#22	Y	No change	Score of 3 at first time point increased to 4 after GC, reduced to 1 post results, no clinical depression levels	No change	Score decreased from 1 before GC to 0 following GC and increased to 2 post results, no clinical anxiety	No change	Score decreased from 21 before GC to 5 following GC and 4 post results, all indicate low risk for PTSD
Controls							
ATS#2	N	No change	Score decreased from 15 before GC to 12 following GC, and to 9 post results, but all results still indicate clinical depression	**Change**	Severe anxiety score of 14 seen before GC, reduced to moderate score of 11 following GC and 14 post results	**Change**	High risk PTSD before GC score of 36, reduced to low risk score of 18 following GC and increased to high risk score of 33 post results
ATS#5	N	No change	Consistent score of 0, no depression	No change	Consistent score of 0, no anxiety	No change	Score reduced from 1 to 0 following GC back to 1 post results, low risk of PTSD at all time points
ATS#10	N	No change	Consistent score of 0, no depression	No change	Consistent score of 0, no anxiety	No change	Consistent score of 0, low risk PTSD
ATS#11	N	No change	Consistent score of 0, no depression	No change	Score reduced from 1 before GC to 0 post results, no anxiety	No change	Consistent score of 0, low risk PTSD
ATS#13	N	No change	Score reduced from 3 before GC to 2 post results, no depression	No change	Score increased from 2 before GC to 3 post results, no anxiety	No change	Score increased from 2 before GC to 7 post results, low risk of PTSD
ATS#14	N	No change	Score decreased from 6 before GC to 5 following GC to 0 post results, no depression	No change	Score decreased from 1 before GC to 0 following GC and increased to 3 post results, no clinical anxiety	No change	Consistent score of 0, low risk PTSD
ATS#15	N	No change	Score increased from 3 before GC to 4 both after GC and post results, no depression	**Change**	Score increased from mild anxiety (5) before GC, to severe anxiety (15) following GC, to moderate anxiety (12) post results	**Change**	Low risk score of 18 before GC increased to high risk scores of 30 and 29 at respective subsequent time points
ATS#17	N	No change	Score decreased from 2 before GC to 1 at both subsequent time points, no depression	**Change**	Score decreased from mild (6) anxiety before GC to no anxiety score of 1 at subsequent time points	No change	Consistent score of 0, low risk PTSD
ATS#18	N	**Change**	Score decreased from 6 to 2 following GC, increased to clinical depression score of 14 post results	**Change**	Score decreased from mild (7) anxiety before GC, to mild (5) anxiety after GC, and increased to moderate (12) anxiety post	**Change**	Low risk score of 19 before GC, increased to high risk scores of 38 and 59 at respective subsequent time points

4.5 MICRA Results

MICRA scores were collected for the case group and the genetics control group at the final time point (approximately 2 weeks after receiving genetic testing results). The MICRA questionnaire contains three subscales: distress, uncertainty, and positive experience. Participant subscale scores are outlined in Table 9 along with their genetic test result. For genetic test results, any VUS results or somatic testing results were labelled as negative (-) whereas pathogenic, or likely pathogenic germline results were indicated with a positive (+) result. All positive results provided patients with a diagnosis of Lynch syndrome.

In the case group, 50% of participants had a positive genetic test result, and were given a diagnosis of Lynch syndrome, whereas none of the genetics control participants had a positive germline mutation identified. Between the two groups, MICRA distress scores were similar (p-value=0.604 95%CI [0.1-1.7]) as were positive experience scores (p-value=0.535 95%CI [1.8-8.6]). The score for uncertainty was higher in the case group as compared to the control group but was not statistically significant (p-value=0.757 95%CI [2.9-9.9]).

When MICRA scores were divided by result type (positive or negative) there were no statistically significant differences observed (Distress p-value=0.575, Uncertainty p-value=0.727, Positive Experience p-value=0.591), and no consistent trends were observed between or across participants based on their result type.

Table 9 Participant MICRA Scores

Participant ID	Subscale			Genetic Test Result
	Distress	Uncertainty	Positive Experience	
Cases				
ATS#1	0	3	0	+
ATS#3	0	0	0	-
ATS#8	1	12	6	+
ATS#9	3	21	3	+
ATS#12	0	8	0	-
ATS#16	1	5	0	-
ATS#19	5	22	5	-
ATS#21	0	4	10	+
ATS#22	1	8	20	+
Mean	**1.2**	**9.2**	**4.9**	
Controls				
ATS#2	1	6	0	-
ATS#5	0	0	8	-
ATS#10	0	0	20	-
ATS#11	1	0	2	-
ATS#13	0	2	5	-
ATS#14	0	1	10	-
ATS#15	0	7	0	-
ATS#17	0	6	0	-
ATS#18	3	9	0	-
Mean	**0.6**	**3.4**	**5**	

5.0 Discussion

In this pilot-study, genetic counseling was not associated with any specific change in psychological distress over time. Previous research in genetic counseling has resulted in increased psychological adaptation and patient empowerment, but limited research has been conducted on the effect of genetic counseling in situations with abnormal UTS results. [36; 37] In this study, it was seen that participants who received genetic counseling for abnormal UTS demonstrated an average decrease in psychological distress scores at the second time point for all measurements. When looking at clinically significant changes to scores in the group which received genetic counseling, there seemed to be fluctuations in the changes depending on the individual at different time points. No one trend was identified to account for these fluctuations in clinical significance.

The majority (77.8%, 7/9) of patients in the genetics control group demonstrated a decrease in distress measurements between the first and second time points. One participant in the genetic control group indicated that his increased level of distress at the second time point was related to waiting for the results from a recent scan, separate from the genetic testing. Of note, the mean distress levels in case participants were lower at the second time point when compared to genetics controls but did increase at the third time point.

When looking at clinically significant changes in the genetics control population, 44.4% of patients (4/9) demonstrated some sort of clinically significant change in their scores. Three of these four (3/4) individuals reported increased clinical levels of the measurements between the time point before genetic counseling and the time point post results disclosure. Only one genetics control participant (1/9, 11.1%) reported a decrease in anxiety between the first time point before genetic counseling and the final time point following results disclosure. The genetics control

participants also had a larger time since diagnosis as compared to the case group. These fluctuations in clinical significance may be due to the resurgence of thought surrounding their previous cancer diagnoses and the increased awareness of potential future diagnoses. Whereas the case patients were all recently diagnosed within the last year, and their maintained clinical levels of distress may be consistent with an ongoing, active diagnosis of cancer.

The two case patients (20%, 2/10) that reported clinical changes to anxiety exhibited a decreased level of anxiety following genetic counseling. The participant that tested positive for a pathogenic variant indicated an increased level of anxiety following that result, which is consistent with the literature which suggest positive genetic test results may increase anxiety in some individuals. For the participant (ATS#21) that exhibited a change in risk of PTSD, they reported higher risk of PTSD following genetic counseling. Yet, genetic counseling did not seem to have an effect on the case participant that had a clinical change in depression score. Participant ATS#12 exhibited an increase to clinically significant levels of depression following disclosure of a negative genetic test result. The fluctuations and inconsistency between the reported clinical changes in the case patients would have been better supported if it had been possible to recruit a larger number of sporadic case controls. This would have allowed for comparison between the fluctuation of distress levels in participants with more recent cancer diagnoses to better discern the impact of genetic testing from that of active cancer treatment and management. The interpretation of these results is greatly limited by the sample size, yet the data does present data suggesting that further investigation is warranted to better understand any patterns between genetic counseling and abnormal UTS results.

The MICRA questionnaire was employed for the case and genetics control groups and the results were recorded in Table 9. No differences in means across the samples were statistically

significant. Given the small sample size present in this pilot study the lack of statistical significance is not surprising, yet it did appear that there did not seem to be distress associated with the genetic test results as more than half (10/19, 52.6%) of participants reported a score of 0 for distress. However, when looking at the scores for uncertainty (Table 9) following the report of genetic test results, only 1/10 (1%) of the case participants reported a score of 0, while 3/9 (33.3%) of genetics controls reported a score of 0. Again, no statistical significance was identified between these case and control groups for uncertainty (p-value=0.757), however the mean of the case group was reportedly higher for uncertainty than the control group (9.2 as compared to 3.4 respectively). Across both groups there was no statistical significance associated with a positive versus a negative result and the score of uncertainty (p-value=0.727). Similarly, no qualitative trend is identified across uncertainty scores depending on result type as both positive and negative cases each report increased and lower scores of uncertainty. Although these results are not statistically significant, they do merit further investigation in larger populations.

A potential explanation for the uncertainty in individuals who tested positive for pathogenic variants is that there is an increased concern for other family members' similarly having a hereditary predisposition, and the uncertainty associated with family members testing outcomes as well as their own future cancer risks. A potential hypothesis for the change in individuals who tested negative may be related to the uncertainty in the interpretation of the residual risk following a negative germline result with an abnormal UTS. This is particularly possible considering the results of the MICRA demonstrated increased levels of uncertainty in the case group regardless of germline testing result. Ultimately, this presents a potential area of further research into the reasons for which individuals might have increased levels of perceived psychological distress after receiving results of genetic testing following abnormal UTS. Changes in scores across all

participants were not statistically significant, yet, given the small number of participants included in this study, observed trends may still suggest meaningful impact from genetic counseling on psychological distress, adding to the existing work suggesting value in the impact of genetic counseling.[36-38; 44; 56; 73]

Contrary to previous research indicating the impact of results on individuals' quality of life,[34 47] the genetic testing result did not appear to impact distress levels of individuals at the final time point. Interestingly, there were no participants in the genetics control group that were identified to have a positive germline mutation which is not consistent with the current thought that approximately 8% of individuals with MSS CRC diagnosed before age 50 have an actionable pathogenic variant identified through multigene panel testing.[5] Regardless of result type (positive or negative) case participants seemed to express increased levels of uncertainty as compared to the genetics control group, which is again inconsistent with previous research.[74] This identifies a potential area of increased concern with UTS, although acknowledges that further investigation in large cohort sizes is required.

Although this study was unable to identify a significant difference in distress associated with result type, there was an increased level of uncertainty which while not statistically significant may be of interest for further research. MICRA questions which indicate uncertainty include questions surrounding the patient's interpretation of risk associated with the genetic test results, as well as the understanding of individual management guidelines and risk for family members (Appendix B). This same uncertainty and ambiguity associated with follow-up germline testing was noted in Lindor et al.[47] as a difficulty of UTS, and as a potential barrier to further access. The level of uncertainty similarly represents a potential area for investigation in future research with larger patient cohorts.

When considering the variation in uncertainty, one consideration that can be made is whether there is a more appropriate testing approach for these patients, such as paired tumor-germline testing. As this test type includes somatic as well as germline results it may provide more information for patients with the possibility of a somatic answer when a germline is not available. Two participants in the case groups underwent paired tumor testing (ATS#6 and ATS#16). Unfortunately, ATS#6 was lost to follow up and ATS#16 had two somatic mutations associated with their tumor loss as well as a VUS in an unrelated Lynch gene. Participant ATS#16 is currently waiting for results associated with the VUS through functional RNA testing, but as an explanation for the abnormal UTS result was identified the third timepoint was evaluated 2 weeks after return of the paired-testing results. All other participants in the case group received either single gene testing (followed by hypermethylation if PMS2 or MLH1 associated) or gene panels. All participants in the genetics control group received testing via gene panels. With further research, governing bodies such as the NCCN may be able to establish standardizes stepwise testing guidelines for these patients. Paired testing represents an important area of further research that may contribute knowledge to developing guidelines that target these patients. As studies have identified that a major concern of patients following UTS is the cost of genetic testing [41;42], changes in guidelines may lead to an increase in insurance coverage for paired genetic testing, or any other relevant testing methodology, ultimately providing more information to patients in the interpretation of results with hopes of decreasing patient uncertainty.

In addition to the consideration of further research to identify a more systematic testing approach, this research also illuminates an area of further genetic counseling research. This study showed that when presenting for genetic counseling, individuals with abnormal tumor screening results may have higher levels of psychological distress (including depression) as compared to

patients referred for a personal history of an early-onset cancer, or a family history of cancer, although in this study differences were not to a statistically significant level. An important consideration in the interpretation of psychological distress between case and controls groups within this study is the time since diagnosis. As many individuals in the genetics control group had been diagnosed more than one year prior, the diagnosis of cancer was more recent for case participants. Several participants in the control group indicated anecdotally that had the study been conducted at the time of their diagnoses they would have had increased psychological distress levels. Considering that there was a large discrepancy between the cases and the genetics control in their time since diagnosis, it is a considerable limitation in this study as we are unable to disentangle differences in score based on time since diagnosis, or UTS results.

Genetic counseling research may be helpful in developing targeted counseling for this patient sample. This could include investigation of different counseling styles such as increased focus on somatic tumor loss in the pre-counseling session, or an in-person result disclosure rather than over the phone to better explain the nuances with the interpretation of germline testing with somatic results. As reported in this study, no consistent pattern of distress change was identified following genetic counseling. Further research could possibly uncover whether these or any other approaches assist in improving the understanding of genetic test results and the impact of genetic counseling on psychological distress.

5.1 Study Limitations and Future Research

The preliminary results outlined in this pilot study merit additional research. Further investigation using large sample sizes may provide more robust evidence regarding the impact of

UTS and genetic testing on patient distress levels. Larger sample sizes would also allow for risk stratification based on additional confounding variables.

As a pilot study, the conclusions are greatly limited by the number of participants in this study cohort. Original study design had intended to match case participants to sporadic cancer controls. The matching was to be based on: cancer type, stage, sex, age (±5 years), and time since diagnosis (>1 year or <1 year). Due to the limited patient sample in the available enrollment clinics at UPMC, it was not possible to match participants based on these criteria. Even with less restriction on matching criteria, only six sporadic control patients were identified. Of those six, two candidates refused enrolment, leaving four available for analysis.

Another limitation is that the data collection at time point one was done in the presence of any other individual in the room. There is some evidence to suggest that participants may report socially desirable traits rather than true traits. As such, further research may wish to conduct interviews in private with participants to control for this bias.

Some participants had trouble interpreting what the questionnaire was asking or misinterpreted the scoring system. One case participant answered "never" on the MICRA questionnaire for positive experiences because it was "never a concern," but that relayed a score that was actually negatively associated with positive experiences. Another consideration was that there was some difficulty with the administration of the IES-R as the time since diagnosis of participants largely varied. Some individuals had many years since their original diagnosis of cancer and expressed that had the questions been asked closer to diagnosis they would have responded differently. While the ability to measure psychological distress is important, the measurement tools utilized were limited. All measurements utilized in this study were previously

externally validated but are largely self-administered by participants. Ultimately, the pilot study did not have enough participants to confirm these conclusions given the lack of power.

All analysis was conducted with non-parametric testing analysis given the non-normal distribution of data. Due to the small sample size, the use of non-parametric analyses reduces the power of the results. The interpretation in the lack of statistically significant results is therefore limited as it is difficult to conclude if any differences represent meaningful patterns that could be extrapolated to larger populations.

Participants whose results came back before they could be re-contacted for follow-up at the second time point represented a limitation of this study. Given the importance of receiving genetic testing results, participants were contacted when results came in, as appropriate in any other genetic counseling scenario. As such, this limited the ability to collect time point two data. Some participants' genetic testing required reflexing to other testing options, and therefore did not have a consistent time between points two and three.

Further investigation into patient understanding of UTS and implications after negative genetic testing may also be an avenue of potential research. Given the uncertainty levels present in the individuals who received germline genetic testing after abnormal UTS, the identification of educational resources or development of counseling guidelines for these patients may be warranted. Similarly, it may be relevant to assess the process of testing in these individuals to observe any differences in uncertainty for those who received paired-tumor and germline testing, versus patients receiving only germline testing as follow-up for UTS. Research may also be conducted as to the identification of potential interventions that may decrease patient distress throughout the diagnosis and testing processes.

Finally, an area of further interest may be in the assessment of distress at baseline depending on the level of education given at the time of referral. This may include providing a script or educational guidelines for doctors who are reviewing abnormal UTS with patients prior to referral to genetic counseling, or promoting initial referral contact to be made through the genetic counseling office rather than the surgical provider. It may be relevant to assess whether increased patient distress at baseline is solely related to a recent diagnosis of cancer, or the uncertainty of their genetic counseling appointment relative to their health. It would also be prudent for providers to ensure that counseling and psychological assistance is available after diagnosis. These patients have demonstrated clinically significant levels of distress that are important to address within their overall care management potentially inviting the incorporation of psychological counseling as a first-line treatment for cancer patients.

6.0 Conclusion

This pilot study is the first report that presents preliminary support of psychological distress in patients undergoing genetic counseling and testing for abnormal UTS results. No significant change in distress was reported from patients who underwent genetic counseling. Given the significant constraint of sample size, no observations were statistically significant. The qualitative differences seen in levels of distress suggest that UTS may be associated with increased psychological distress, and uncertainty after genetic testing, regardless of results. Further investigation of larger participant cohorts is warranted to provide more insight as to the full effect of UTS on patient distress levels and the impact of genetic counseling.

7.0 Relevance to Genetic Counseling and Public Health

The aim of this pilot study was to investigate the impact of abnormal UTS results on patient distress levels and to determine if genetic counseling influenced distress levels. This research is of importance to the fields of both public health and genetic counseling. Specifically, this study can be contextualized within the three core functions of public health: assessment, policy development, and assurance.

A core function of public health is the assessment of a community's needs. Research on the impact of genetic counseling on distress levels for patients who are receiving genetic counseling for UTS is limited. As such, the needs of this community have not been adequately assessed. Some previous research has demonstrated that genetic counseling can increase patient satisfaction and understanding.[36-38; 44; 56; 73] Further research on patient distress levels over time after receiving genetic counseling can contribute to the understanding of the role of genetic counselors in overall quality of care for these patients. Continuing this type of research can contribute to the assessment of the needs of this patient population including an increased understanding of the outcomes and impact of genetic counseling on patient health and satisfaction.

The second core function of public health is policy development. UTS is a public health measure that was historically controversial as it was considered by some to be a form of genetic testing yet, does not require informed consent by patients. It has been largely established that informed consent is not an ethical obligation for UTS as it is considered one part of routine pathological analysis for which consent is provided though the surgical consent process. However, as a public health initiative it is imperative that both the benefits and potential risks or adverse effects of screening tests are examined during the development of public health policies. Thus far,

there has been inadequate information as to the perception of patient distress levels in the population receiving UTS and thus we cannot accurately assess whether the developed policies are addressing the priority health needs in this patient population. For UTS to continue and to be implemented in more healthcare organizations as a public health policy, it is important that the potential effects of these tests on patients' mental health is better understood.

Finally, public health interventions should function to provide a level of assurance to the community. This includes the evaluation of resources, the implementation of programs, and educating the public. Levels of anxiety, depression, and stress have long been associated with cancer diagnoses and are currently considered a comorbidity of many types of cancer.[48] In an effort to improve overall patient health, it is important to evaluate whether UTS is contributing to or exacerbating the level of distress in these patients and whether there is potential to manage resources that are currently available, or to implement new programs through which to improve the wellbeing of these individuals. As depression is the most common psychological symptom of individuals diagnosed with cancer, it has been found to be associated with poorer survival rates and decreased immune response. [69] Various studies have determined that psychotherapeutic interventions can be effective in the mitigation of the effects of depression on cancer outcomes.[69] Therefore, should it be determined that patients who are receiving UTS have increased levels of psychological distress, then it may be within the best interest of patients and providers to initiate appropriate screening protocols and begin psychotherapeutic intervention as early as possible. Similarly, if one is able to identify that these patients are at an increased risk for psychological distress, then it may be appropriate to focus on psychosocial aspects of genetic counseling within any subsequent genetic counseling sessions.

As established, this study is not only well positioned within the discipline of public health but also demonstrates relevance to the field of genetic counseling. As a profession genetic counseling has strived for patient-centered care and uptake of counseling information.[31] This study presents novel data in the assessment of genetic counseling utility in the context of patient distress associated with abnormal UTS results, cancer diagnoses at young ages, and genetic test results. One of the aims of this study was to determine the impact of genetic counseling on distress levels in patients. As previously mentioned, the study size was not large enough to find statistically significant changes in distress related to genetic counseling, but trends in the data did demonstrate some interesting patterns associated with the groups who underwent genetic counseling. One such trend was that patients in the case group demonstrated a decreased mean distress level at the second time point, but that their values subsequently increased at the third time point. Comparably, the participants who underwent germline genetic testing after genetic counseling for abnormal UTS demonstrated higher levels of uncertainty following results disclosure as compared to those individuals who had received genetic counseling and testing based on diagnosis of CRC before the age of 50. This finding is relevant to genetic counseling as it appears that genetic counseling did provide a decrease in patient distress levels, but that potential uncertainty regarding the results was contributing to increased distress at the final time point. It provides a starting point for future genetic counseling research to assess the reasons behind individuals' uncertainty post result disclosure. It may lead to identification of a more systematic testing strategy, or the development of a specific educational framework for discussion of UTS results in the context of germline testing.

This study identified trends associated with increased levels of depression at the baseline in participants who received abnormal UTS results. While this study is limited by the number of

participants included, it outlines a potential concern for public health services within the three core functions of public health: assessment, policy development, and assurance. It represents and encourages assessment of patients receiving UTS and advocates for the continued evaluation of the UTS policy as it is currently development. Furthermore, continued study in this area may be able to provide assurance through the implementation and management of resources available to these individuals including but not limited to the potential consideration for increased intervention for psychological wellbeing in these individuals receiving abnormal UTS results. Similarly, this study contributes relevant data to the field of genetic counseling in hopes of encouraging continued assessment of patient distress levels in this patient population. As scores for psychological distress for those who had abnormal UTS results decreased directly after genetic counseling, further studies may lead to recommendations for providers and genetic counselors including increased upfront discussion and education as to the results and risks of their UTS results. In conclusion, this study represents an important facet of public health and encourages continued research in the definition of the impact of psychological distress in these patients within the realm of public health.

Appendix A Documentation for Methodology

This appendix includes all instruments used for measurements, participant data documents, the applicable consent form, and the IRB study approval letter.

A.1 PHQ-8 Measure

Personal Health Questionnaire Depression Scale (PHQ-8)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?
*(circle **one** number on each line)*

How often during the past 2 weeks were you bothered by...	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

Scoring

If two consecutive numbers are circled, score the higher (more distress) number. If the numbers are not consecutive, do not score the item. Score is the sum of the 8 items. If more than 1 item missing, set the value of the scale to missing. A score of 10 or greater is considered major depression, 20 or more is severe major depression.

Characteristics

Tested on 1165 subjects with chronic conditions.

No. of items	Observed Range	Mean	Standard Deviation	Internal Consistency Reliability	Test-Retest Reliability
8	0-24	6.63	5.52	.86	NA

Source of Psychometric Data

U.S. National Chronic Disease Self-Management Study. Study described in Ory MG, Ahn S, Jiang L, et al. National study of chronic disease self-management: six month outcome findings. Journal of Aging and Health. 2013 [in press].

Comments

This is an adaptation of the PHQ-9 scale. Since this scale is self-administered in our studies, question #9, "How often during the past 2 weeks were you bothered by thoughts that you would be better off dead, or of hurting yourself in some way?", was deleted. This scale available in Spanish.

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This scale is free to use without permission

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A.2 GAD-7 Measure

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

A.3 IES-R Measure

IMPACT OF EVENTS SCALE-Revised (IES-R)

INSTRUCTIONS: Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you DURING THE PAST SEVEN DAYS with respect to _____ _____(event) that occurred on _____(date). How much have you been distressed or bothered by these difficulties?

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Any reminder brought back feelings about it	0	1	2	3	4
2. I had trouble staying asleep	0	1	2	3	4
3. Other things kept making me think about it.	0	1	2	3	4
4. I felt irritable and angry	0	1	2	3	4
5. I avoided letting myself get upset when I thought about it or was reminded of it	0	1	2	3	4
6. I thought about it when I didn't mean to	0	1	2	3	4
7. I felt as if it hadn't happened or wasn't real.	0	1	2	3	4
8. I stayed away from reminders of it.	0	1	2	3	4
9. Pictures about it popped into my mind.	0	1	2	3	4
10. I was jumpy and easily startled.	0	1	2	3	4
11. I tried not to think about it.	0	1	2	3	4
12. I was aware that I still had a lot of feelings about it, but I didn't deal with them.	0	1	2	3	4
13. My feelings about it were kind of numb.	0	1	2	3	4
14. I found myself acting or feeling like I was back at that time.	0	1	2	3	4
15. I had trouble falling asleep.	0	1	2	3	4
16. I had waves of strong feelings about it.	0	1	2	3	4
17. I tried to remove it from my memory.	0	1	2	3	4
18. I had trouble concentrating.	0	1	2	3	4
19. Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart.	0	1	2	3	4
20. I had dreams about it.	0	1	2	3	4
21. I felt watchful and on-guard.	0	1	2	3	4
22. I tried not to talk about it.	0	1	2	3	4

Total IES-R Score:_____

INT: 1, 2, 3, 6, 9, 14, 16, 20
AVD: 5, 7, 8, 11, 12, 13, 17, 22
HYP: 4, 10, 15, 18, 19, 21

Weiss, D.S. (2007). The Impact of Event Scale-Revised. In J.P. Wilson, & T.M. Keane (Eds.) *Assessing psychological trauma and PTSD: a practitioner's handbook* (2nd ed., pp. 168-189). New York: Guilford Press.

AETR2N 22 1/13/2012

A.4 MICRA Measure

Appendix

The Multidimensional Impact of Cancer Risk Assessment (MICRA) Questionnaire

The questions below are about some specific responses you may have had after receiving your genetic test results. Please answer every question in Section 1, regardless of whether you were given a positive or negative test result. Please indicate whether you have experienced each statement *never, rarely, sometimes*, or *often* in the past week, by circling the corresponding number.

Section 1	Never	Rarely	Sometimes	Often
1. Feeling upset about my test result	0	1	3	5
2. Feeling sad about my test result	0	1	3	5
3. Feeling anxious or nervous about my test result	0	1	3	5
4. Feeling guilty about my test result	0	1	3	5
5. Feeling relieved about my test result	0	1	3	5
6. Feeling happy about my test result	0	1	3	5
7. Feeling a loss of control	0	1	3	5
8. Having problems enjoying life because of my test result	0	1	3	5
9. Worrying about my risk of getting cancer [or getting cancer again if you have ever been diagnosed with cancer]	0	1	3	5
10. Being uncertain about what my test result means about my cancer risk	0	1	3	5
11. Being uncertain about what my test result means for my child(ren) and/or family's cancer risk	0	1	3	5
12. Having difficulty making decisions about cancer screening or prevention (e.g., having preventive surgery or getting medical tests done)	0	1	3	5
13. Understanding clearly my choices for cancer prevention or early detection	0	1	3	5
14. Feeling frustrated that there are no definite cancer prevention guidelines for me	0	1	3	5
15. Thinking about my test results has affected my work or family life	0	1	3	5
16. Feeling concerned about how my test results will affect my insurance status	0	1	3	5
17. Having difficulty talking about my test results with family members	0	1	3	5
18. Feeling that my family has been supportive during the genetic counseling and testing process	0	1	3	5
19. Feeling satisfied with family communication about my genetic test result	0	1	3	5
20. Worrying that the genetic counseling and testing process has brought about conflict within my family	0	1	3	5
21. Feeling regret about getting my test results	0	1	3	5

Section 2. *If you have children, regardless of your test result, please answer Questions 22 and 23. Otherwise, please go to Section 3.*

	Never	Rarely	Sometimes	Often
22. Worrying about the possibility of my children getting cancer	0	1	3	5
23. Feeling guilty about possibly passing on the disease risk to my child(ren)	0	1	3	5

Section 3. *If you currently have cancer, or have had it in the past, please answer Questions 24 and 25. Otherwise, please check this box* ☐. *You are finished with this questionnaire.*

	Never	Rarely	Sometimes	Often
24. Feeling that the genetic test result has made it harder to cope with my cancer	0	1	3	5
25. Feeling that the genetic test result has made it easier to cope with my cancer	0	1	3	5

Note. Distress subscale = Items 1–4, 7, and 8; Uncertainty subscale = Items 9–12, 14–17, and 20; Positive Experiences subscale (reverse scored) = Items 5, 6, 18, and 19. Subscales are scored by summing circled numbers.

A.5 Participant Data Documents

Participant ID	Case/ Control Group #	Age	Sex	Cancer Dx	Age at Dx	Date of cancer dx	Months since Dx	Stage of Cancer	Previous cancer diagnoses?	Meets NCCN guidelines?	GT Results	BMI	Smoking Status (Never, Past, Current)	Alcohol Use (Yes, No)
ATS#1	1	51	M	Rectal; loss MSH2 & MSH6	50	2017-07-24	11	pT2N0	No	Yes	MSH2 Positive (Lynch)	50.2	Past	No
ATS#3	1	82	F	Colon; PMS2 loss	82	2018-04-04	3	pT3(m)N0	Yes	Yes	MLH1 hypermethylation	20.3	Past	No
ATS#6	1	61	F	Colon; MLH1 & PMS2 loss	60	2017-11-03	9	pT2N0	No	Yes	Negative panel	34.7	Past	Yes
ATS#8	1	87	M	Colon; MSH6 loss	86	2017-09-05	12	pT2N0	No	Yes	MSH6 positive (Lynch)	22	Never	Yes
ATS#9	1	47	M	Colon; MSH6 loss	46	2017-11-03	10	T3N1	No	Yes	MSH6 Positive (Lynch)	27.3	Past	Yes
ATS#12	1	75	F	Colon; Loss MLH1 and PMS2	75	2018-04-18	5	T2N0	No	Yes	Negative panel, negative MLH1 hypermethylation	28.1	Never	No
ATS#16	1	56	M	Colon; Loss MLH1 and PMS2	56	2018-08-21	2	pT3N0	No	Yes	Negative panel, negative MLH1 hypermathylation, 2 somatic MLH1 muations, germline MSH6 VUS	29.3	Past	No
ATS#19	1	39	F	Colon; Loss MLH1 and PMS2 BRAF V600E neg	39	2018-09-14	2	pT3N0	No	Yes	MLH1 VUS, Negative hypermethylation	29.5	Never	Yes
ATS#21	1	57	M	Colon; Loss MSH2 and MSH6	57	2018-11-29	0	pT1	Yes	Yes	MSH2 Positive (Lynch)	36.3	Never	No
ATS#22	1	54	M	Colon: Loss PMS2	54	2018-08-27	4	PT1N0	No	Yes	PMS2 Positive (lynch)	28.3	Never	Yes
ATS#2	2	44	M	Rectal	44	2018-03-22	4	uT3N0M0	No	Yes	MSH6 VUS	31.8	Never	No
ATS#5	2	49	M	Colon	49	2018-04-08	4	pT3N1	No	Yes	Negative panel	32.1	Past	Yes
ATS#10	2	48	F	Rectal	38	2008-08-22	120	uT2N0	Yes	Yes	Negative panel	38.4	Past	Yes
ATS#11	2	57	M	rectal	48	2010-05-10	100	T1N0	No	Yes	Negative panel	25.9	Never	Yes
ATS#13	2	53	M	Rectal	43	2007-12-06	129	T1N0	No	Yes	Negative panel	32.7	Never	Yes
ATS#14	2	49	M	Colon	48	2018-05-04	5	T3N0	No	Yes	POLE VUS	38.7	Current	Yes
ATS#15	2	35	M	Colon	35	2018-09-13	1	pT1Nx	No	Yes	POLD1 VUS, PMS2 VUS	27.3	Past	Yes
ATS#17	2	46	F	Colon	22	1994-01-01	297	TisN0	No	Yes	Negative panel	26.2	Never	No
ATS#18	2	26	F	Colon	25	2018-08-30	2	pT3N0	No	Yes	Negative	37.9	Never	Yes
ATS#23	3	59	M	colon	59	2018-05-16	7	pT3N1	No	No	-	26.9	Past	No
ATS#26	3	53	M	Rectal	52	2016-06-15	31	pT2N1a	No	No	-	34.6	Never	Yes
ATS#27	3	55	M	Rectal	54	2017-06-22	7	T3N1	No	No	-	38.2	Past	Yes
ATS#28	3	59	M	Colon	53	2015-11-18	26	T4N2bM1b	No	No	-	27.9	Never	No

A.6 Consent Form

UPMC LIFE CHANGING MEDICINE

CONSENT TO USE MEDICAL RECORDS AND/OR QUESTIONNAIRES FOR RESEARCH IN THE **UPMC Shadyside Division of Gastroenterology**

PRINCIPAL INVESTIGATOR:

Randall Brand, MD. University of Pittsburgh.
Shadyside Medical Office Building 5200 Centre Avenue, Suite 409 Pittsburgh PA 15232 (412) 623-3105

ABOUT THE STUDY:

We are interested in patient perceptions regarding colorectal tumor screening and genetic testing. In order to learn more, we would like to invite you to participate in a research study. The goal of this study is to collect information that will help doctors and genetic counselors to better understand patients' well-being throughout the process of colorectal tumor screening and genetic testing.
Participation in the study would involve the following three components:

1. Your completion of surveys
2. Permission to re-contact you over the phone at later dates
3. Permission to review your medical records

YOUR PARTICIPATION:

If you choose to participate you will be verbally asked questions during your office visit. These questions should take about **10** minutes to complete and will involve your assessment of your current emotional state. You will also be contacted again over the phone in 2 weeks and asked these questions again. If you undergo genetic testing at your appointment, you will be contacted over the phone 2 weeks after disclosure of those test results and asked questions about your emotional state and your perceptions of the genetic testing process. If you do not undergo genetic testing, you will be contacted 4 weeks after our initial meeting and asked questions about your emotional state.

We are also requesting your permission to review your medical records for information about your medical history, cancer diagnosis and treatment, and family history of cancers to determine in which study group you should be placed. Information may be obtained from your medical records and used by this research team for an indefinite period of time. This authorization is valid for an indefinite period of time. However, you can always withdraw your authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing. If you do so, you will no longer be permitted to participate in this study. Any information obtained from you up to that point will continue to be used by the research team. If you undergo genetic testing as part of this research study, the results from this testing will become part of your clinical medical record at UPMC.

Participation is completely voluntary and will not affect your care or management with UPMC or any affiliated organizations. Your doctor may be involved as an investigator in this research study, but you are not under any obligation to participate in any research study offered by your doctor. Before agreeing to participate in this research study, or at any time thereafter, you may wish to discuss participation in this study with another health professional, to obtain a 'second opinion' about study participation. You are free to withdraw from the study at any time, for any reason, without any penalty or change of care. However, any identifiable information obtained

from you before you withdraw from this study will continue to be used by the investigators, as described above. You are also free to withdraw authorization for the research team to access your medical records, while still participating in the study. To formally withdraw your consent for participation in the study you should provide a written and dated notice to the primary investigator at the address above.

CONFIDENTIALITY:

If you choose to participate in the study, your confidentiality will be protected and your personal identifying information will be coded with limited access. Your information will only be available to the research team, and possibly to auditors from the University of Pittsburgh Research Conduct and Compliance Office. There is always the small chance of a breach in confidentiality, but strong precautions and the federal confidentiality guidelines are followed to protect your information to the best of our abilities. If the researchers learn that you or someone with whom you are involved is in serious danger of harm, they will need to inform the appropriate agencies as required by Pennsylvania law. The research data collected may also be used for future unspecified research and shared in a de-identified manner with investigators both inside and outside of the University.

RISKS AND BENEFITS

There are no direct benefits to you involved in this study. The only risk associated with this study is the possibility of breach of confidentiality. There is no cost associated with this study, and neither you nor your insurance will be billed for study-related matters if you choose to participate. However, you will be responsible for standard clinical charges regardless of your participation in the study.

VOLUNTARY CONSENT:

This study has been explained to me, and all of my questions have been answered. Additional questions will be answered by the study team. The Human Research Subject Advocate of the University Institutional Review Board (1.866.212.2668) can answer any questions about my rights as a research subject. By signing this form, I give my authorization to share my medical records with the research team and answer their questions.

_____ _____

Patient/Subject Signature Date

_____

Printed Name of Patient/Subject
(*or* Patient Identification Sticker)

****

I certify that I have explained the nature and purpose of this research study to the above-named individual, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual has about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Signature of individual obtaining consent Date

A.7 IRB Approval Letter

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Randall Brand, MD

From: IRB Office

Date: 7/5/2018

IRB#: PRO18040719

Subject: Universal Tumor Screening for Lynch Syndrome: A Prospective Study of Patient Distress Levels

---

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(5)
45 CFR 46.110.(7)

The IRB has approved the waiver for the requirement to obtain informed consent to use protected health information to identify potential research subjects.

The risk level designation is Minimal Risk.

Approval Date: 7/5/2018
Expiration Date: 7/4/2019

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

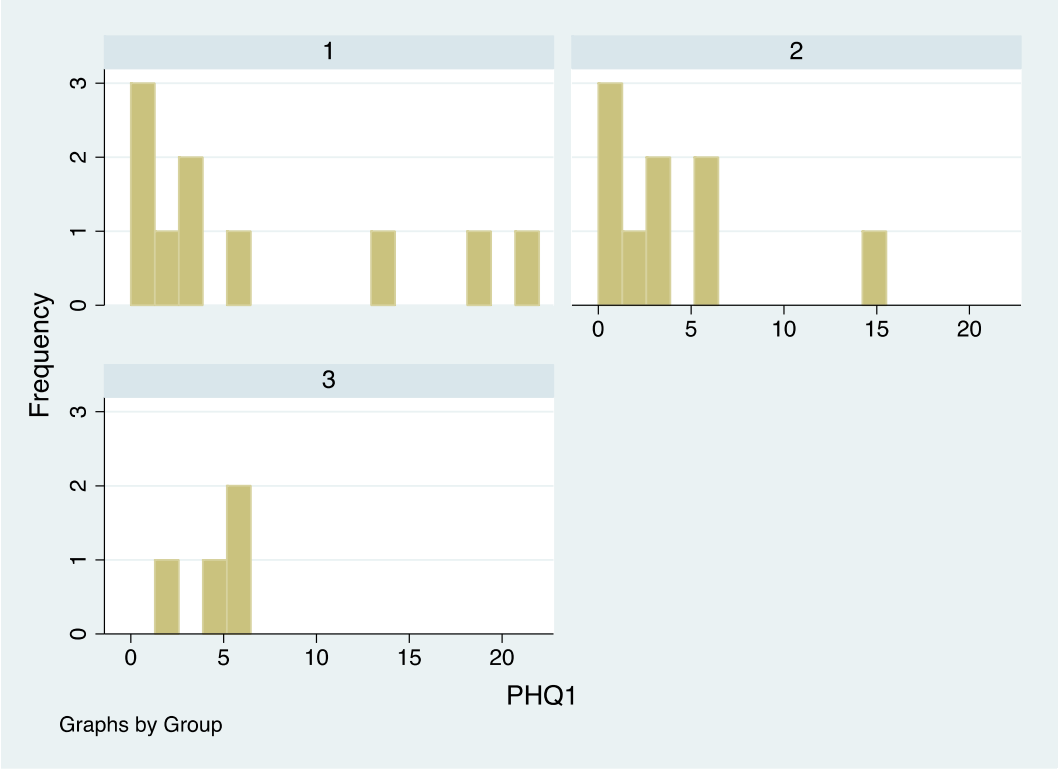
The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Appendix B Data Distribution and STATA Output

This appendix includes STATA output of histograms and applicable statistical tests.

B.1 PHQ8 Distribution Graphs and Output

PHQ8 BASELINE DISTRIBUTION BY GROUP



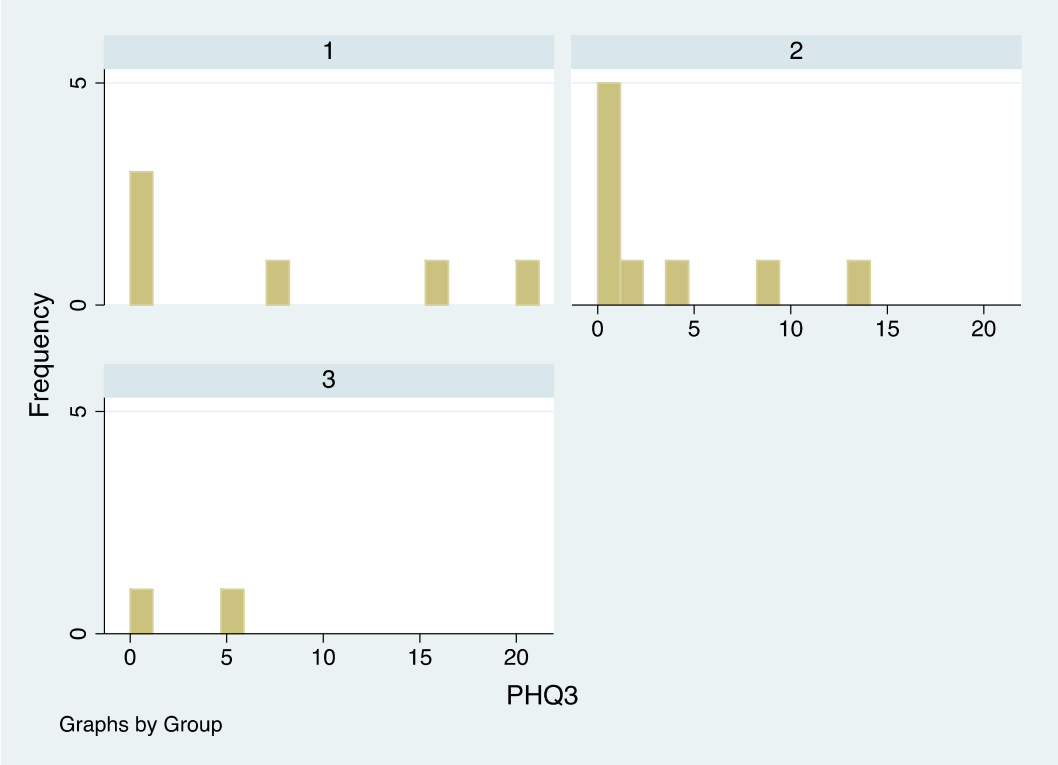
Group 1= Case participants

Group 2= Genetics Control Participants

Group 3= Sporadic Control Participants

PHQ8 TIMEPOINT 2 DISTRIBUTION BY GROUP

PHQ8 TIMEPOINT 3 DISTRIBUTION BY GROUP



PHQ8 ONEWAY ANOVA OUTPUT

```
. oneway PHQ1 Group, tabulate
```

Group	Summary of PHQ1 Mean	Std. Dev.	Freq.
1	6.9	8.3193216	10
2	3.8888889	4.7813294	9
3	4.75	1.8929694	4
Total	5.3478261	6.256696	23

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	44.6785024	2	22.3392512	0.55	0.5870
Within groups	816.538889	20	40.8269444		
Total	861.217391	22	39.1462451		

Bartlett's test for equal variances: chi2(2) = 6.6153 Prob>chi2 = 0.037

PHQ8 RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIME POINT 1 & 2

```
. . ranksum TPQ12, by(Group) porder
```

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

Group	obs	rank sum	expected
1	9	67.5	76.5
2	7	68.5	59.5
combined	16	136	136

unadjusted variance 89.25
adjustment for ties -4.86

adjusted variance 84.39

Ho: TPQ12(Group==1) = TPQ12(Group==2)
z = -0.980
Prob > |z| = 0.3272

P{TPQ12(Group==1) > TPQ12(Group==2)} = 0.357

PHQ8 RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIME POINT 1 & 3

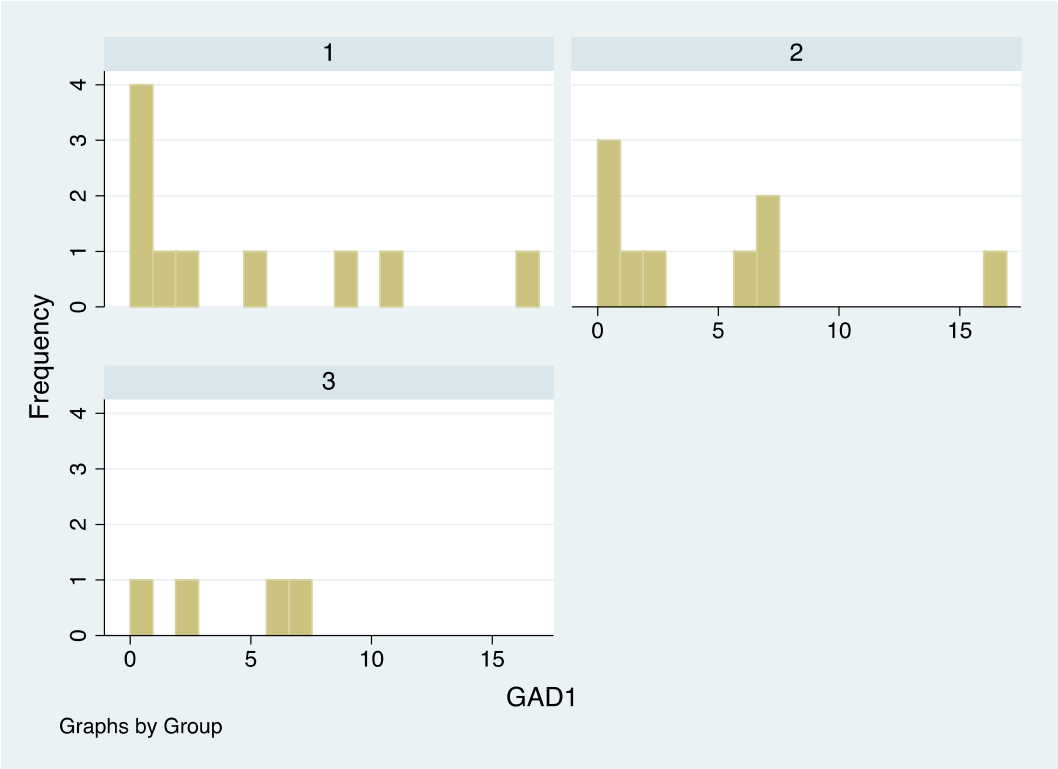
```
. ranksum TPQ13, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |      obs    rank sum    expected
-------------+---------------------------------
           1 |        7        52.5        59.5
           2 |        9        83.5        76.5
-------------+---------------------------------
    combined |       16         136         136

unadjusted variance       89.25
adjustment for ties       -3.02
                     ------------
adjusted variance         86.23

Ho: TPQ13(Group==1) = TPQ13(Group==2)
             z =  -0.754
    Prob > |z| =   0.4510

P{TPQ13(Group==1) > TPQ13(Group==2)} = 0.389
```

PHQ8 RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIME POINT 2 & 3

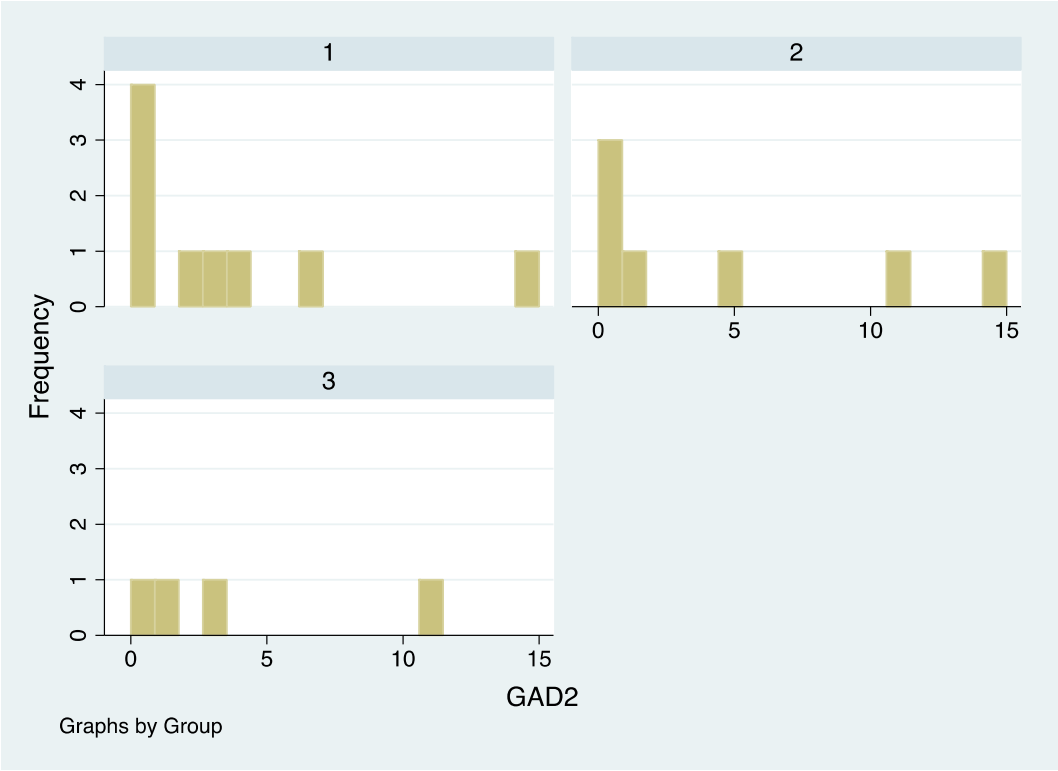
```
. ranksum TPQ23, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |      obs    rank sum    expected
-------------+---------------------------------
           1 |        7          48        52.5
           2 |        7          57        52.5
-------------+---------------------------------
    combined |       14         105         105

unadjusted variance       61.25
adjustment for ties       -4.71
                     ------------
adjusted variance         56.54

Ho: TPQ23(Group==1) = TPQ23(Group==2)
             z =  -0.598
    Prob > |z| =   0.5495

P{TPQ23(Group==1) > TPQ23(Group==2)} = 0.408
```

B.2 GAD7 Distribution Graphs and Output

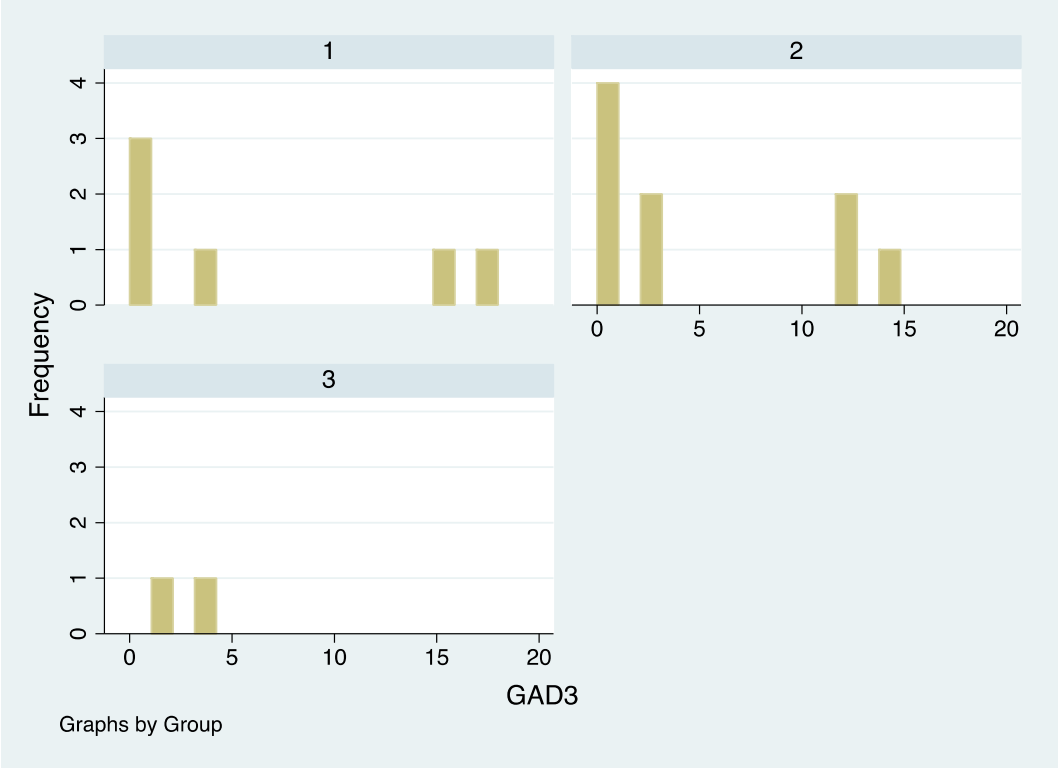
GAD7 BASELINE DISTRIBUTION BY GROUP



GAD7 TIMEPOINT 2 DISTRIBUTION BY GROUP



GAD7 TIMEPOINT 3 DISTRIBUTION BY GROUP



GAD7 ONEWAY ANOVA OUTPUT

```
. oneway GAD1 Group, tabulate
```

Group	Summary of GAD1 Mean	Std. Dev.	Freq.
1	**4.4**	**5.7193628**	**10**
2	**4.3333333**	**5.3150729**	**9**
3	**3.75**	**3.3040379**	**4**
Total	**4.2608696**	**5.0201176**	**23**

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	**1.28478261**	**2**	**.642391304**	**0.02**	**0.9771**
Within groups	**553.15**	**20**	**27.6575**		
Total	**554.434783**	**22**	**25.201581**		

Bartlett's test for equal variances: chi2(**2**) = **1.0205** Prob>chi2 = **0.600**

GAD7 RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIMEPOINT 1 & 2

```
. ranksum TPG12, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test
```

Group	obs	rank sum	expected
1	**9**	**70.5**	**76.5**
2	**7**	**65.5**	**59.5**
combined	**16**	**136**	**136**

```
unadjusted variance       89.25
adjustment for ties       -5.38
                     ----------
adjusted variance         83.87

Ho: TPG12(Group==1) = TPG12(Group==2)
            z =  -0.655
    Prob > |z| =   0.5124

P{TPG12(Group==1) > TPG12(Group==2)} = 0.405
```

GAD7 RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIME POINT 1 & 3

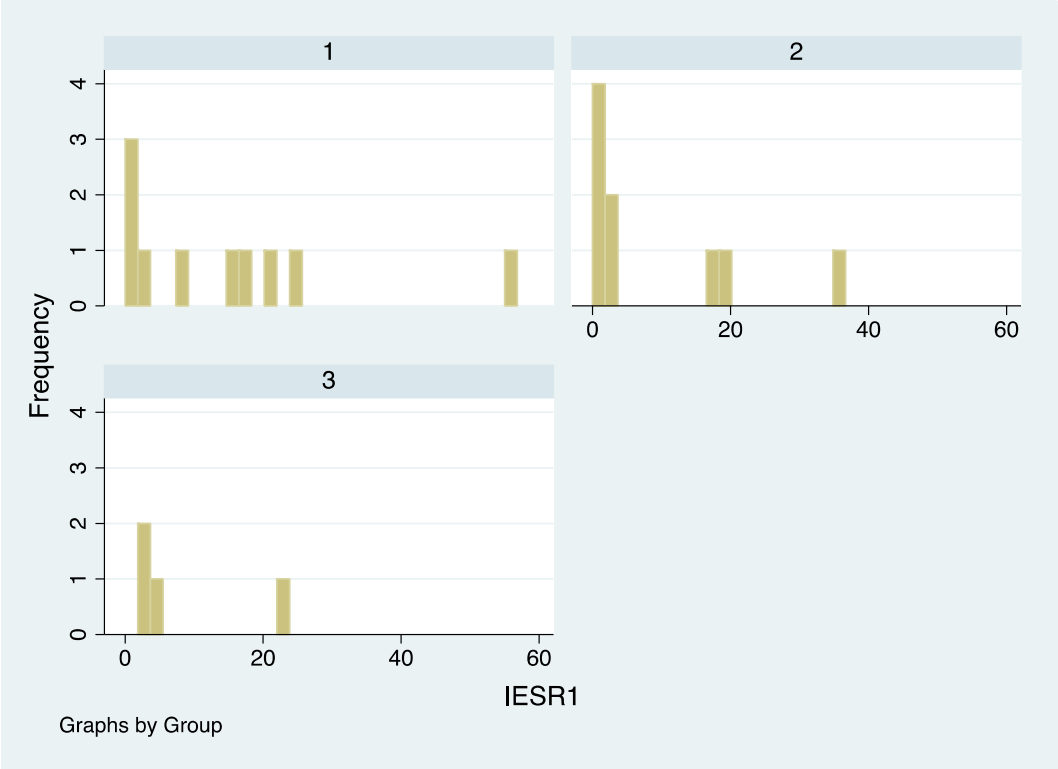
```
. ranksum TPG13, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |      obs    rank sum    expected
-------------+---------------------------------
           1 |        6        46.5          48
           2 |        9        73.5          72
-------------+---------------------------------
    combined |       15         120         120

unadjusted variance       72.00
adjustment for ties       -2.06
                        --------
adjusted variance         69.94

Ho: TPG13(Group==1) = TPG13(Group==2)
             z =  -0.179
    Prob > |z| =   0.8577

P{TPG13(Group==1) > TPG13(Group==2)} = 0.472
```

GAD7 RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIME POINT 2 & 3

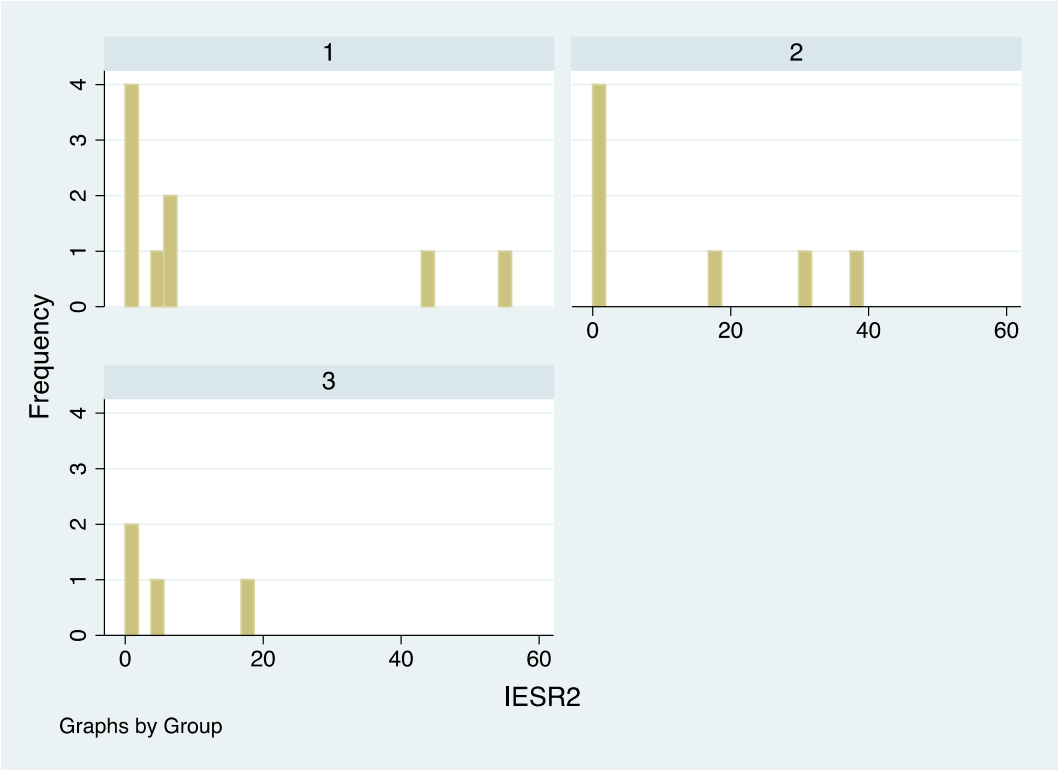
```
. . ranksum TPG23, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |      obs    rank sum    expected
-------------+---------------------------------
           1 |        6          44          42
           2 |        7          47          49
-------------+---------------------------------
    combined |       13          91          91

unadjusted variance       49.00
adjustment for ties       -4.98
                        --------
adjusted variance         44.02

Ho: TPG23(Group==1) = TPG23(Group==2)
             z =   0.301
    Prob > |z| =   0.7631

P{TPG23(Group==1) > TPG23(Group==2)} = 0.548
```

B.3 IES-R Distribution Graphs and Output

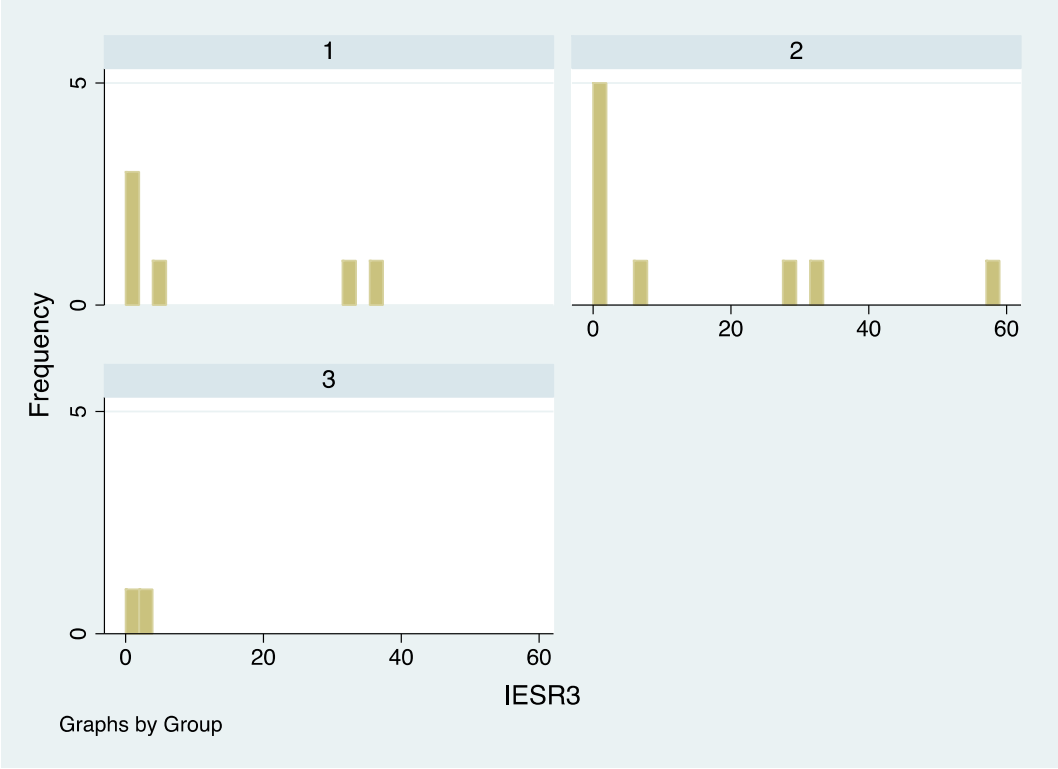
IES-R BASELINE DISTRIBUTION BY GROUP



IES-R TIMEPOINT 2 DISTRIBUTION BY GROUP



IES-R TIMEPOINT 3 DISTRIBUTION BY GROUP



IES-R ONEWAY ANOVA OUTPUT

```
. oneway IESR1 Group, tabulate
```

Group	Summary of IESR1 Mean	Std. Dev.	Freq.
1	**14.5**	**16.873714**	**10**
2	**8.7777778**	**12.755173**	**9**
3	**8**	**9.4162979**	**4**
Total	**11.130435**	**14.033416**	**23**

Analysis of Variance					
Source	SS	df	MS	F	Prob > F
Between groups	**202.55314**	**2**	**101.27657**	**0.49**	**0.6195**
Within groups	**4130.05556**	**20**	**206.502778**		
Total	**4332.6087**	**22**	**196.936759**		

Bartlett's test for equal variances: chi2(**2**) = **1.4293** Prob>chi2 = **0.489**

IES-R RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIME POINT 1 & 2

```
. ranksum TPI12, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test
```

Group	obs	rank sum	expected
1	**9**	**79.5**	**76.5**
2	**7**	**56.5**	**59.5**
combined	**16**	**136**	**136**

```
unadjusted variance      89.25
adjustment for ties      -1.97
                        ------
adjusted variance        87.28

Ho: TPI12(Group==1) = TPI12(Group==2)
            z =   0.321
    Prob > |z| =   0.7481

P{TPI12(Group==1) > TPI12(Group==2)} = 0.548
```

IES-R RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIME POINT 1 & 3

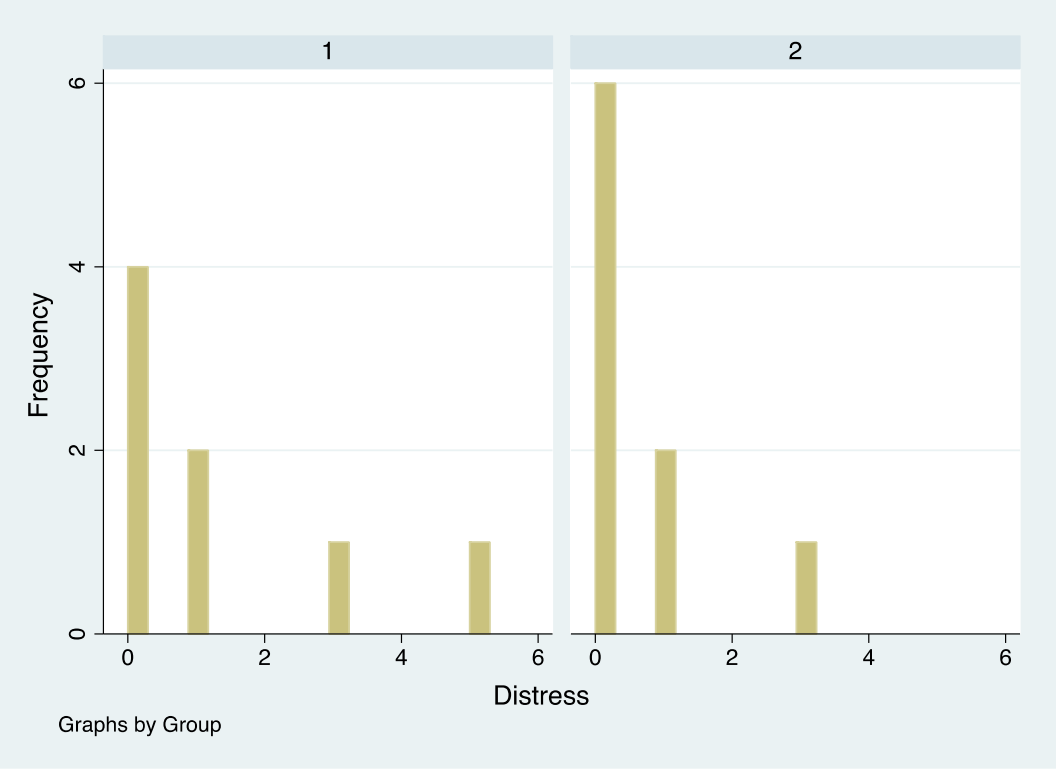
```
. ranksum TPI13, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |       obs    rank sum    expected
-------------+---------------------------------
           1 |         6        56.5          48
           2 |         9        63.5          72
-------------+---------------------------------
    combined |        15         120         120

unadjusted variance       72.00
adjustment for ties       -4.63
                     ------------
adjusted variance         67.37

Ho: TPI13(Group==1) = TPI13(Group==2)
             z =   1.036
    Prob > |z| =   0.3004

P{TPI13(Group==1) > TPI13(Group==2)} = 0.657
```

IES-R RANK-SUM OUTPUT (GROUP 1 & 2) BETWEEN TIME POINT 2 & 3

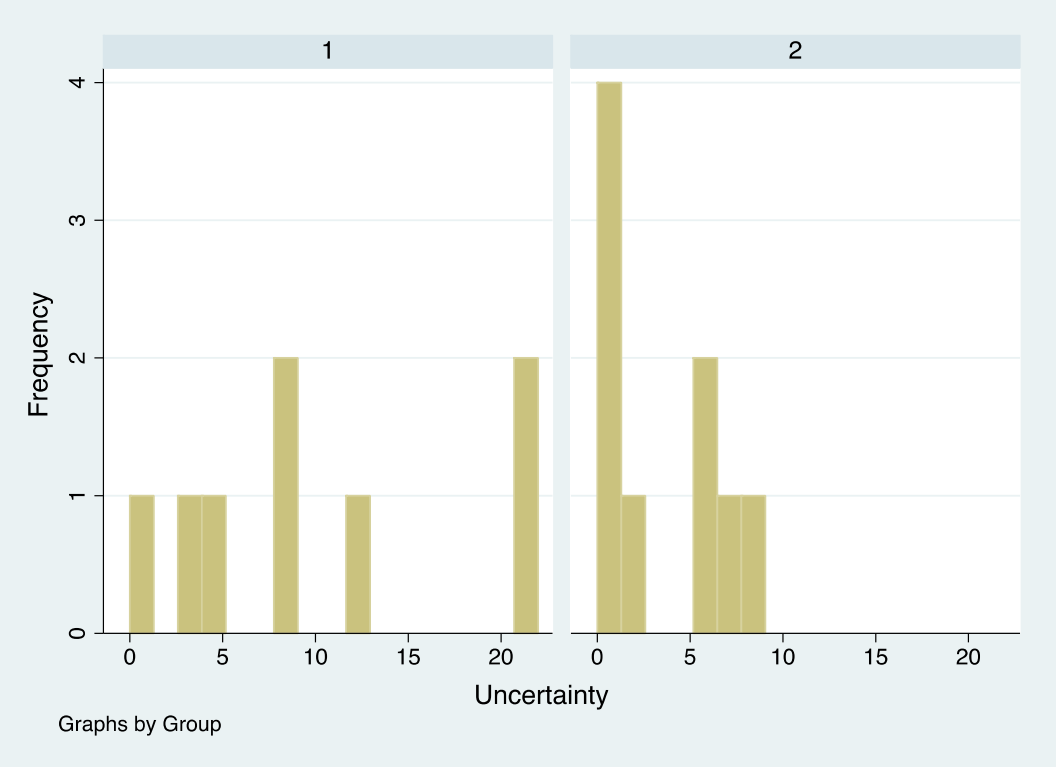
```
. ranksum TPI23, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |       obs    rank sum    expected
-------------+---------------------------------
           1 |         6        55.5          42
           2 |         7        35.5          49
-------------+---------------------------------
    combined |        13          91          91

unadjusted variance       49.00
adjustment for ties       -4.71
                     ------------
adjusted variance         44.29

Ho: TPI23(Group==1) = TPI23(Group==2)
             z =   2.029
    Prob > |z| =   0.0425

P{TPI23(Group==1) > TPI23(Group==2)} = 0.821
```

B.4 MICRA Output

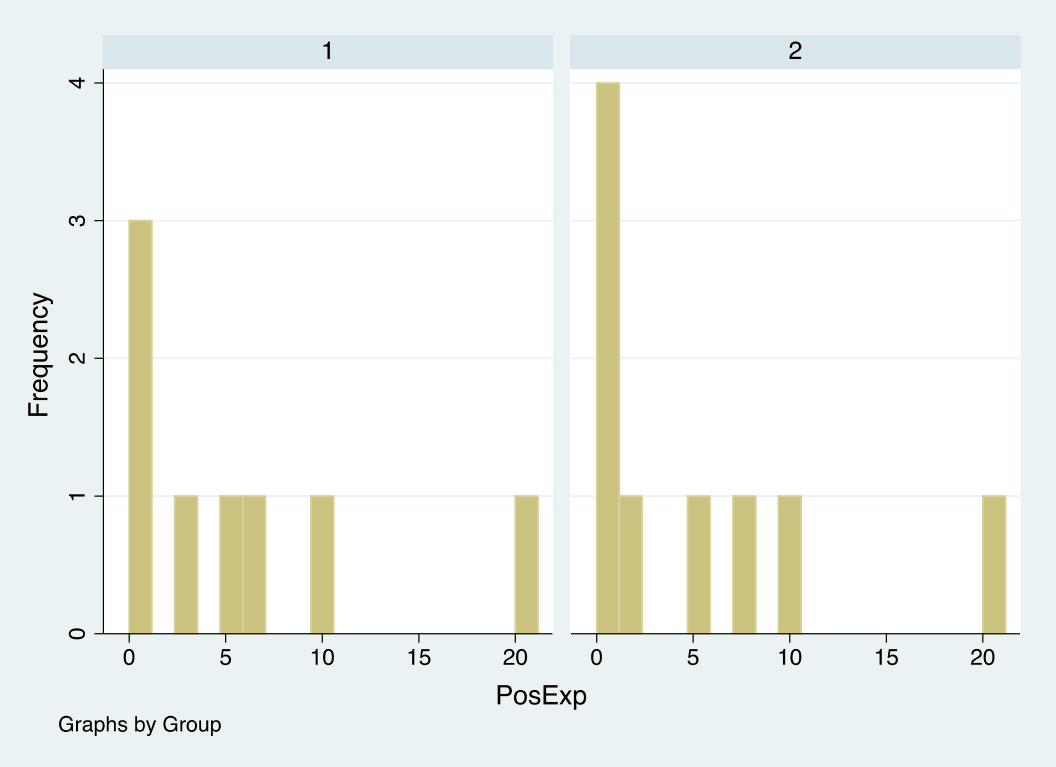
MICRA DISTRESS DISTRIBUTION BY GROUP



MICRA UNCERTAINTY BY GROUP



MICRA POSITIVE EXPERIENCES DISTRIBUTION BY GROUP



MICRA DISTRESS SCORES BY GROUP (1 & 2)

```
. ranksum Distress, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |       obs    rank sum    expected
-------------+---------------------------------
           1 |         8        79.5          72
           2 |         9        73.5          81
-------------+---------------------------------
    combined |        17         153         153

unadjusted variance      108.00
adjustment for ties      -23.29
                         ------
adjusted variance         84.71

Ho: Distress(Group==1) = Distress(Group==2)
             z =   0.815
    Prob > |z| =   0.4151

P{Distress(Group==1) > Distress(Group==2)} = 0.604
```

MICRA UNCERTAINTY SCORES BY GROUP (1 & 2)

```
. ranksum Uncertainty, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |       obs    rank sum    expected
-------------+---------------------------------
           1 |         8        90.5          72
           2 |         9        62.5          81
-------------+---------------------------------
    combined |        17         153         153

unadjusted variance      108.00
adjustment for ties       -1.59
                         ------
adjusted variance        106.41

Ho: Uncert~y(Group==1) = Uncert~y(Group==2)
             z =   1.793
    Prob > |z| =   0.0729

P{Uncert~y(Group==1) > Uncert~y(Group==2)} = 0.757
```

MICRA POSITIVE EXPERIENCE SCORES BY GROUP (1 & 2)

```
. ranksum PosExp, by(Group) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

       Group |      obs    rank sum    expected
-------------+---------------------------------
           1 |        8        74.5          72
           2 |        9        78.5          81
-------------+---------------------------------
    combined |       17         153         153

unadjusted variance      108.00
adjustment for ties       -7.81
                     ------------
adjusted variance        100.19

Ho: PosExp(Group==1) = PosExp(Group==2)
             z =   0.250
    Prob > |z| =   0.8028

P{PosExp(Group==1) > PosExp(Group==2)} = 0.535
```

MICRA DISTRESS SCORES BY RESULT TYPE (Positive (1) & Negative (0))

```
. ranksum Distress, by(Result) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

      Result |      obs    rank sum    expected
-------------+---------------------------------
           0 |       12       101.5         108
           1 |        5        51.5          45
-------------+---------------------------------
    combined |       17         153         153

unadjusted variance       90.00
adjustment for ties      -19.41
                     ------------
adjusted variance         70.59

Ho: Distress(Result==0) = Distress(Result==1)
             z =  -0.774
    Prob > |z| =   0.4391

P{Distress(Result==0) > Distress(Result==1)} = 0.392
```

MICRA UNCERTAINTY SCORES BY RESULT TYPE (Positive (1) & Negative (0))

```
. ranksum Uncertainty, by(Result) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

      Result |       obs    rank sum    expected
-------------+---------------------------------
           0 |        12        94.5         108
           1 |         5        58.5          45
-------------+---------------------------------
    combined |        17         153         153

unadjusted variance       90.00
adjustment for ties       -1.32
                         -------
adjusted variance         88.68

Ho: Uncert~y(Result==0) = Uncert~y(Result==1)
             z =  -1.434
    Prob > |z| =   0.1517

P{Uncert~y(Result==0) > Uncert~y(Result==1)} = 0.275
```

MICRA POSITIVE EXPERIENCE SCORES BY RESULT TYPE (Positive (1) & Negative (0))

```
. ranksum PosExp, by(Result) porder

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

      Result |       obs    rank sum    expected
-------------+---------------------------------
           0 |        12          97         108
           1 |         5          56          45
-------------+---------------------------------
    combined |        17         153         153

unadjusted variance       90.00
adjustment for ties       -6.51
                         -------
adjusted variance         83.49

Ho: PosExp(Result==0) = PosExp(Result==1)
             z =  -1.204
    Prob > |z| =   0.2287

P{PosExp(Result==0) > PosExp(Result==1)} = 0.317
```

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