5-2018

Attitudes Toward Updated Genetic Testing Among Patients with Unexplained Mismatch Repair Deficiency

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ATTITUDES TOWARD UPDATED GENETIC TESTING AMONG PATIENTS WITH UNEXPLAINED MISMATCH REPAIR DEFICIENCY

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A

THESIS

Presented to the Faculty of

The University of Texas

MD Anderson Cancer Center UTHealth

Graduate School of Biomedical Sciences

in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF SCIENCE

by

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Houston, Texas
May 2018

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Individuals who have colorectal cancer (CRC) or endometrial cancer (EC) displaying loss of immunohistochemical (IHC) staining of one or more mismatch repair (MMR) proteins without a causative germline mutation are said to have unexplained mismatch repair deficiency (UMMRD, also known as mutation-negative Lynch syndrome). Comprehensive genetic testing that could potentially further clarify Lynch syndrome (LS) carrier status is essential to provide tailored screening guidelines to affected individuals and their family members; however, patient understanding of the potential impact of updated genetic testing for LS is unclear. This study aimed to evaluate the interest in and perceived impact of updated genetic testing among individuals with UMMRD at a tertiary academic center. A survey evaluating interest in updated genetic testing was mailed to 98 potential participants, and an electronic health record review was completed for the 31 individuals who returned the survey. Results indicate that this population is highly interested in updated genetic testing, and their perceived impact is primarily for family members to have appropriate testing and screening options. Updated risk assessment and genetic counseling, along with a discussion of the benefits and limitations of genetic testing, is essential as the understanding of potential causes of UMMRD evolves. Updated genetic counseling may allow patients with UMMRD to better understand the interpretation of their tumor and germline testing, as well as the impact of comprehensive genetic testing for themselves and their family members.

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INTRODUCTION

Lynch syndrome (LS) is a hereditary cancer syndrome affecting 1 in 440 individuals (1), and is characterized by an increased risk to develop colorectal cancer (CRC) and endometrial cancer (EC), as well as ovarian, stomach, small intestine, pancreatic, urinary tract, and brain cancers and sebaceous neoplasms (2). LS is caused by a heterozygous pathogenic variant in one of four genes involved in the DNA mismatch repair (MMR) system: *MLH1, MSH2, MSH6,* and *PMS2.* Additionally, deletions of the *EPCAM* gene cause hypermethylation of the *MSH2* promoter region and are also associated with LS (3).

CRC and EC in individuals with LS typically display high levels of microsatellite instability (MSI-H) and/or show loss of immunohistochemical (IHC) staining of one or more MMR proteins, most frequently corresponding with the underlying germline mutation. If a CRC or EC presents with loss of function of the DNA MMR system, genetic testing is recommended to determine if there is an underlying germline mutation causing LS. In most cases when MLH1 and PMS2 proteins are absent, the loss of staining can be attributed to sporadic causes such as somatic methylation of the *MLH1* promoter (4) or *BRAF* mutations in CRC only (5). The presence of either of these molecular events is most consistent with sporadic cancer rather than LS.

In approximately 2-4% of patients with CRC, IHC staining indicates MMR protein loss, but genetic testing does not detect a germline mutation (6, 7). This situation is known as unexplained mismatch repair deficiency (UMMRD), and individuals are said to have Lynch-like syndrome or mutation-negative Lynch syndrome (8). Recent studies have shown that biallelic somatic mutations explain the loss of protein staining in 45-69% of individuals with UMMRD (6, 9). However, the etiology continues to be unknown for the remaining 31-55%

of individuals with MMR deficiency. Some of these cases of UMMRD may be caused by an underlying germline pathogenic variant that was not detected by the original genetic testing. The suspicion for a previously undetected germline mutation is especially high for patients meeting Amsterdam criteria for the detection of individuals likely to have LS (10).

Traditional genetic testing for LS, especially prior to the advent of next-generation sequencing (NGS) panel testing, was based on the pattern of protein loss on IHC staining (i.e., *MSH2* genetic testing for absence of MSH2/MSH6 protein staining). However, this strategy can fail to detect an underlying germline mutation for several reasons. First, sequencing and deletion/duplication analysis of MMR genes may not detect the causative pathogenic variant. For example, the *MSH2* inversion of exons 1-7 causes a proportion of LS cases that have MSH2/MSH6 loss of staining upon IHC analysis, but these inversions cannot be identified on traditional gene sequencing or deletion/duplication analysis alone; this was only recently identified and therefore not previously tested (11). Second, IHC analysis may indicate a pair of missing proteins. If only one of the corresponding genes is analyzed, or if a pathogenic variant is present in one of the other MMR genes, a germline mutation may be missed. Third, IHC analysis may be false-normal, indicating that staining is intact while the tumor is, in fact MMR deficient (12). For these reasons, as well as decreased cost of testing multiple genes via NGS panel testing, patients suspected to have LS based on tumor testing are now frequently offered sequencing and deletion/duplication analysis of all LS-associated genes, as well as *MSH2* inversion analysis.

Due to the high expected number of patients with UMMRD who are expected to have biallelic somatic mutations, comprehensive germline genetic testing is not expected to identify an underlying germline mutation in many cases. It is possible that future tests may

have a higher yield or be able to definitively determine if an individual with UMMRD has LS. For example, identification of biallelic somatic mutations on paired germline/tumor testing may suggest a sporadic etiology for patients who have UMMRD. However, comprehensive evaluation of individuals with UMMRD for underlying germline mutations is essential to provide appropriate risk assessment and screening recommendations. There is no difference between the median age of cancer diagnosis of an individual with LS as compared to one with UMMRD (7). However, the standardized incidence ratio for family members of individuals with UMMRD to develop CRC is 2.12 as compared to 6.04 for family members of individuals with an identified germline mutation and 0.48 for family members with sporadic CRC. This suggests that UMMRD is a heterogeneous group composed of some patients who have LS and others who have sporadic cancers. Determining which individuals have LS and which have sporadic cancers allows for appropriate screening tailored to the risk of cancer in each group, as well as appropriate testing for the identified familial variant in individuals determined to have LS (7).

There is currently no consensus as to whether individuals with UMMRD should follow surveillance recommendations based on their personal/family histories of cancer or if more stringent LS surveillance should be utilized. Decisions about surveillance for individuals with UMMRD and their family members may therefore be at the discretion of the physician (13). The lack of clarity surrounding surveillance recommendations for individuals with UMMRD highlights the importance of comprehensive genetic testing for germline MMR mutations.

The identification of underlying germline mutations in individuals who were originally classified as having UMMRD is imperative for providing tailored screening

guidelines to individuals and their family members. In addition, it is important that the affected individuals themselves understand how identifying an underlying germline mutation may change screening recommendations. If patients do not understand the potential impact of updated genetic testing for themselves or their family members, they may fail to receive updated genetic testing or to communicate these changes to relatives. Therefore, this study aims to evaluate the interest in and perceived impact of further germline genetic testing among individuals with UMMRD.

METHODS

Study Population

The study population consisted of patients from the University of Texas MD Anderson Cancer Center (UTMDACC) with a personal history of CRC or EC and UMMRD due to loss of IHC staining but no presence of germline pathogenic variant upon incomplete clinically available germline testing for LS. This included patients with variants of uncertain significance. Full clinically available germline testing was defined as sequencing and deletion/duplication analysis of *MLH1, MSH2, MSH6,* and *PMS2,* deletion/duplication analysis of *EPCAM,* and *MSH2* inversion testing. All study participants were English-speaking and 18 years or older. Individuals meeting the study population criteria were identified by querying the UTMDACC genetic counseling database. Exclusion criteria included individuals with tumors showing loss of MLH1 on IHC staining with *BRAF* mutations or *MLH1* promoter hypermethylation on tumor studies, thus indicating sporadic tumors. Eligibility criteria was confirmed by evaluating patient electronic medical records. The study was approved by the UTMDACC Institutional Review Board (PA17-0473) and the University of Texas Health Science Center at Houston Institutional Review Board (HSC-MS-17-0831).

Instrumentation

A survey containing questions about current screening behaviors, original testing considerations, interim family histories, and the perceived impact of identification of a germline mutation as opposed to the perceived impact of negative germline testing was utilized (see Supplementary Material).

Procedures

The survey and informed consent were mailed to each potential participant along with information about the availability of updated genetic testing as part of clinical care. The informed consent document provided consent for survey participation as well as review of medical records. Up to three attempts were made to contact the participants regarding study participation. Participants also had the option to complete the survey over the phone or when approached while attending scheduled clinic visits.

An electronic health record review was completed for each participant. The information obtained included basic demographic information, personal and family history of cancer, dates of genetic counseling visits, tumor pathology results, and genetic testing results.

Deidentified survey responses and data collected from the electronic health record were entered in the online survey tool RedCap. Patient data was stored on a secure server hosted by UTMDACC.

Data Analysis

A level of p=0.05 was set for significance. Descriptive statistics were used to analyze the data.

RESULTS

A total of 98 patients met the eligibility criteria, of whom 31 individuals responded to the survey (response rate of 32%). Twenty-five (81%) participants were non-Hispanic white. Twenty-seven (87%) participants had at least some college education, and 21 (68%) had an annual household income greater than $50,000. The average age of the study population was 62 years (range 33-81 years). The demographic characteristics of the respondents are summarized in Table 1.

Table 1: Participant Demographics

	N (%)
Ethnicity[a]	
Non-Hispanic White	25 (81)
Hispanic	2 (6)
Asian	1 (3)
Other	3 (10)
Education	
<High School	1 (3)
High School/GED	3 (10)
Associate/Bachelor	10 (32)
Postgraduate degree	17 (55)
Religion[b]	
Christian	29 (94)
Do not identify	1 (3)
Hinduism	1 (3)
Annual Household Income	
<$50,000	5 (16)
$50,000-100,000	8 (26)
>$100,000	13 (42)
Sex[c]	
Female	19 (61)
Male	12 (39)
Average Age	62 years (range of 33-81)

[a, b] Based on participant self-identification

[c] Participant sex was collected from the electronic health record

Cancer History

Twenty-one (68%) respondents had a personal history of CRC, and 10 (32%) of EC. Nine (29%) respondents had a personal history of another cancer including breast, prostate, skin, and stomach tumors. One of these nine respondents had a personal history of colorectal, skin, and stomach cancers, as well as a sebaceous neoplasm. IHC results of CRC or EC were abnormal in all 31 participants. On IHC analysis, 14 (45%) respondents had tumors with loss of MLH1, 8 (26%) had loss of MSH2, 14 (45%) had loss of MSH6, and 13 (42%) had loss of PMS2. Twenty (65%) respondents displayed loss of more than one protein.

Family History

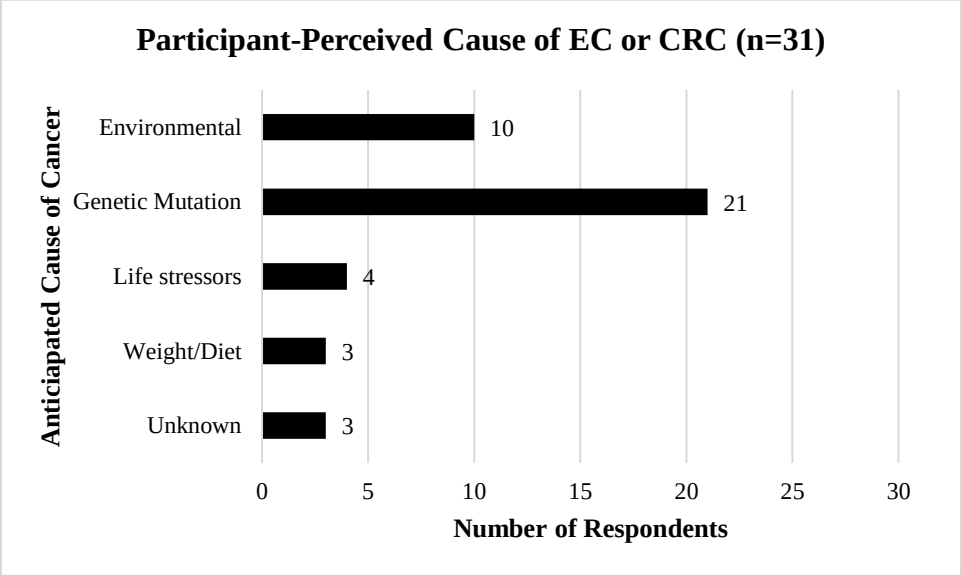
The family history information gathered from the electronic health record and the survey were compiled to determine if respondents met Amsterdam criteria for the identification of individuals likely to have LS (10). Four (13%) respondents met Amsterdam criteria.

Based on the family history collected from the electronic health record, 29 (94%) respondents had a family history of some type of cancer at the time of original genetic counseling. Of these 29 individuals, 23 (79%) had a family history of at least one Lynch-related cancer. Of the two remaining respondents without a family history of cancer, one had no family history of cancer at the time of genetic counseling, and the other respondent was adopted. In an evaluation of the reported interim family history of cancer, 10 (32%) respondents had a family history of cancer since original genetic counseling. Of these individuals, 4 (40%) respondents had an interim family history of at least one Lynch-related cancer, while 6 (60%) respondents had a family member diagnosed with non-LS-associated cancer since original genetic counseling.

Perceived Cause of EC or CRC

Respondents were asked what they believed to be the cause of their cancer (Figure 1). Eight (26%) respondents indicated they felt there was more than one cause for their cancer. Twenty-one respondents (68%) indicated they thought an underlying genetic mutation was at least one reason for the development of cancer. When asked about the level of importance of determining the cause of cancer, 27 (87%) respondents thought that it was important or extremely important.

Figure 1

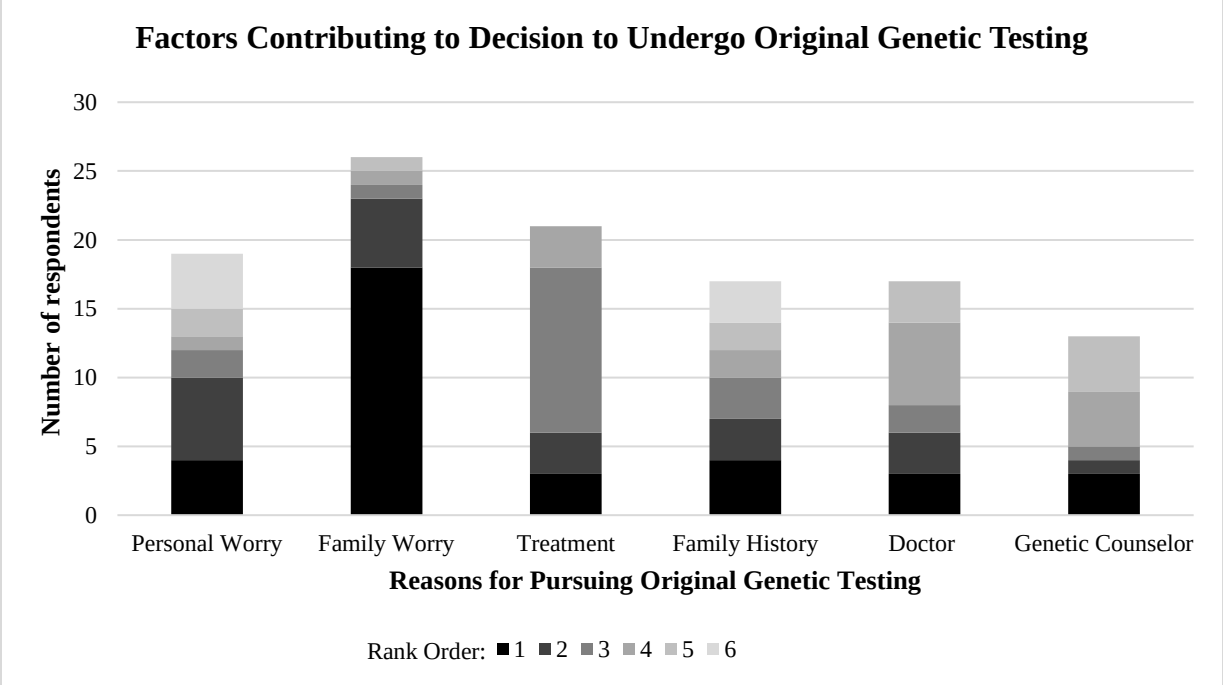


Psychosocial Issues Surrounding Original Genetic Testing

The average time since original cancer diagnosis was 9.7 years (range = 1-35 years). Fourteen (45%) respondents initially had genetic counseling within the last 5 years. Ten (32%) respondents originally had genetic counseling 6-10 years prior to completion of the survey, while 7 (23%) respondents originally had genetic counseling 11-20 years prior. Twenty-six respondents (84%) indicated the original decision to undergo genetic testing was either not stressful or only a little stressful.

Respondents were asked to rank potential reasons for undergoing original genetic testing. If participants did not feel a listed factor influenced their original genetic testing decision, it was not ranked. Eighteen (58%) respondents indicated their primary reason for pursuing genetic testing was concern that other family members may develop cancer as well (Figure 2). Overall, 26 (84%) respondents indicated that concern for family members to develop cancer factored in to their decision to undergo genetic testing, and this was the most frequently ranked factor impacting the original genetic testing decision. The most frequently ranked second answer was concern for an increased risk to develop another cancer related to a genetic mutation. This factor had a bimodal distribution, with 10 participants selecting this factor as a primary or secondary reason, and 6 participants selecting this factor as the fifth or sixth reason they originally pursued genetic testing. Associations between concern for an increased risk to develop another cancer and current age (p=0.79) or number of children (p=0.37) were not statistically significant.

Figure 2

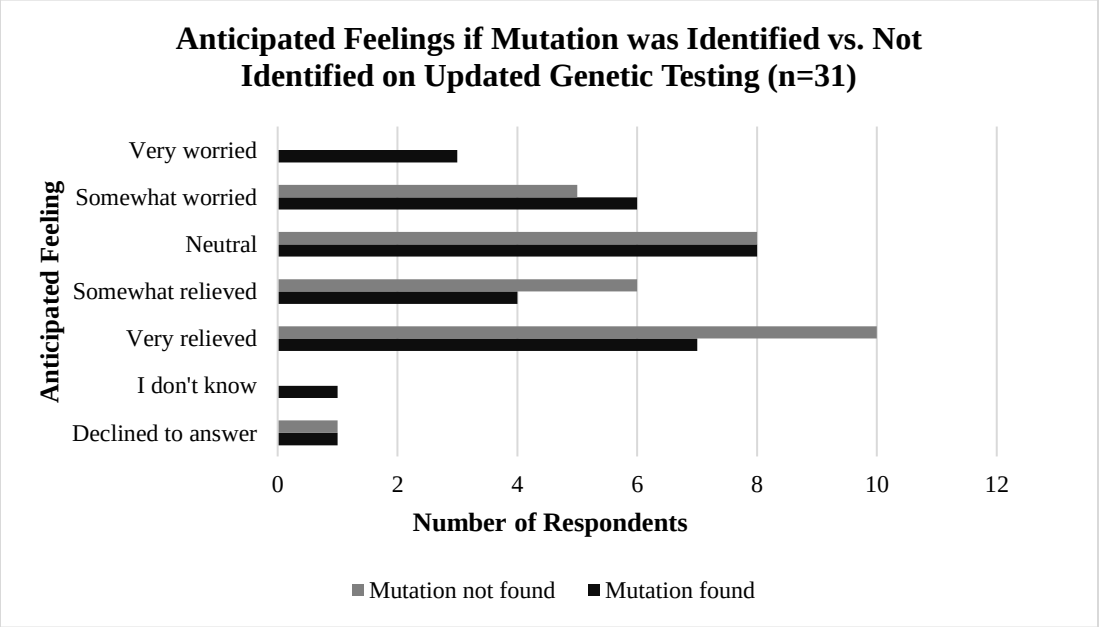


Psychosocial Issues Surrounding Updated Genetic Testing

Twenty-four (77%) respondents indicated they were either interested or extremely interested in updated genetic testing. When asked about level of concern for family members to develop cancer, 23 (74%) respondents were at least somewhat worried, with 13 (42%) respondents indicating they were very worried that family members would develop cancer.

Respondents were asked about expected feelings if a pathogenic variant were found on updated genetic testing compared to negative results. Seven (23%) respondents indicated they would feel very relieved if genetic testing results indicated a pathogenic variant consistent with LS, while 10 (32%) respondents indicated they would feel very relieved if updated genetic testing were negative (Figure 3). In comparison, 3 (10%) respondents indicated they would feel very worried if a pathogenic variant were found on updated genetic testing, whereas no respondents indicated they would feel very worried if no mutation were found. Overall, 14 (45%) respondents indicated they would feel relatively less concerned or more relieved if a pathogenic variant were not identified on updated genetic testing. The remainder of the respondents were divided between those who would be relatively more worried/less relieved if no mutation were found, or their concern would not change regardless of the result. This was not a statistically significant difference (p=0.207).

Figure 3



When asked about concerns regarding updated genetic testing, 23 (74%) respondents did not have any concerns, 2 (6%) respondents did have concerns, and 6 (19%) respondents were unsure. Cited reasons for concern included the time requirements for testing, concerns about the impacts of the results, and concerns about insurance coverage and privacy.

Genetics Knowledge

Respondents were asked questions to elicit understanding about the current genetic testing recommendations for family members. These questions included indicating whether respondents thought family members were recommended to pursue genetic testing and which specific family members, if any, were recommended. In most cases, family members of individuals with an uninformative negative result or a VUS would not be recommended to pursue genetic testing. However, 20 (65%) participants either indicated that their family members are currently recommended to pursue genetic testing or selected at least one family member for whom genetic testing would be recommended. Similarly, 21 (68%) participants

either indicated that genetic testing would be recommended or that a specific family member would be recommended to have genetic testing if a pathogenic variant were not found on updated genetic testing. There was not a statistically significant correlation between genetics knowledge and time since original genetic counseling (p=0.66).

When asked if family members would be recommended to have genetic testing if a pathogenic variant were identified on updated genetic testing, 29 (94%) respondents indicated that genetic testing would be recommended.

Screening Behaviors

Fifteen (48%) respondents indicated they undergo colonoscopies at least annually. Of the 19 female respondents, 14 (74%) have had a total hysterectomy and bilateral salpingo-oophorectomy, 3 (16%) had a hysterectomy only, and 2 (11%) had their uterus and ovaries intact. The reasons for surgeries were not elicited. Of the 10 women who had EC, 80% had colonoscopies at least every 2-3 years.

When asked about perceived frequency of colonoscopies if a pathogenic variant were identified on updated genetic testing, 18 of 31 (58%) respondents indicated that they would have colonoscopies at the same frequency, while 11 (35%) respondents thought the frequency of colonoscopies would increase.

Interpretation of Prior IHC and Germline Testing

Medical record review indicates that original genetic testing consisted of analysis of one gene for 13 (42%) of the respondents. Nine (29%) respondents had two of the genes associated with LS tested upon original genetic testing. Twenty-three (74%) participants had uninformative negative results upon original genetic testing, while 8 (26%) participants had a variant of uncertain significance (VUS).

Information last reported to the participants regarding their likelihood to have LS was gathered from the medical record. Seven (23%) participants were told they have a definitive diagnosis of LS based on IHC results. Nine (29%) participants were told they likely have LS, while 14 (45%) participants were told it is unclear whether they have LS. One participant was told that based on personal and family history evaluation, LS is an unlikely explanation for the IHC results. Of the 9 participants who were told they likely have LS, 8 (89%) perceived a genetic mutation to be an underlying cause of their EC or CRC.

DISCUSSION

Our study aimed to evaluate the interest in and perceived impact of updated genetic testing among patients with UMMRD. The results of the study emphasize that the primary reason for interest in updated genetic testing among individuals with UMMRD is concern for family members to develop cancer and desire for family members to have appropriate screening. Providing family members with accurate information was the most frequently stated reason for interest in updated genetic testing, as well as the most frequently stated reason that participants felt it was important to determine the cause of their cancer. Concern for family members to develop cancer was the most frequently selected primary reason for originally pursuing genetic testing, and it was the most frequently selected choice overall. Because 74% of respondents are at least somewhat worried about family members developing cancer, it is reasonable that concern for family members was a primary factor in originally pursuing genetic testing. This is concordant with previous studies evaluating the motivators for pursuing original genetic testing for LS (14, 15). Therefore, our findings suggest that the reasons for interest in updated genetic testing among this population are similar to those indicated in the literature for original genetic testing for LS.

Participants also indicated that concern or relief for family members may impact anticipated feelings regarding results of updated genetic testing. The effect of genetic testing results on family members was most frequently raised in the context of feeling relief after updated genetic testing, both if a pathogenic variant was or was not identified. Participants indicated they would feel relief because family members could have genetic testing if a pathogenic variant was identified, and appropriate high-risk surveillance if they were found to be positive for the familial variant. This may indicate that a primary motivating factor for

updated genetic testing is anticipated relief felt for family members, either in the context of positive or negative genetic testing results. Concern for family members was not mentioned as a possible deterrent for updated genetic testing. Instead, possible deterrents for genetic testing included lack of information about the test, concerns about insurance coverage, time considerations, and the possibility of an uncertain result. It may be that interest in updated genetic testing is fueled by what is viewed as definitive information being helpful for family members, regardless of the results.

Because participants are focused primarily on impacts of genetic testing for family members, it may be important for clinicians to emphasize the potential implications of updated genetic testing for participants themselves. Forty-eight percent of the participants had at least annual colonoscopies. This points to a greatly increased screening regimen compared to people in the general population. Women with no history of CRC who are receiving frequent colonoscopies are having more screening than would be recommended if they could be determined to have sporadic cancer rather than LS, for example, using paired somatic/germline testing for the identification of biallelic somatic mutations. Therefore, the potential impact of updated genetic testing on the personal screening recommendations for women with UMMRD should be emphasized.

The results of this study also indicate a need for updated genetic counseling among individuals with UMMRD. There was wide variation in participants' anticipated feelings if a pathogenic variant were found or not found on updated genetic testing. If updated genetic testing were negative, many respondents who indicated they expected to feel relief suggested their family members may be required to have less frequent screening, while respondents who expected to feel worried indicated they would still have no information about the cause

of the cancer. From a clinician perspective, updated negative germline testing for LS cannot rule out LS. In the context of UMMRD and uninformative negative germline genetic testing for LS, an updated review of family and personal medical histories as well as review of additional testing options, both germline and somatic, is necessary to elicit screening recommendations for family members. Therefore, updated genetic counseling with or without updated genetic testing can provide participants with the most current information regarding the evolving understanding of the clinical significance of MMR deficiency, as well as the most appropriate screening recommendations.

Updated genetic counseling may also be important for clarifying genetic testing recommendations for family members. Although most family members of individuals with an uninformative negative result or VUS would not be recommended to undergo genetic testing, exceptions exist including testing for research purposes or situations in which other family members also meet criteria for genetic testing independent of the uninformative negative genetic testing results of a family member. Ninety-four percent (29 respondents) understood family members would be able to have testing for the familial variant if updated genetic testing identified a pathogenic variant. However, participants were more likely to have confusion about recommendations for family members in the context of an uninformative negative result. This is not surprising given that the average time since original genetic counseling was 7 years, and points to the necessity of updated genetic counseling and risk assessment for individuals with UMMRD.

Upon original genetic testing, 8 participants had a VUS. Because implications of genetic testing results are especially nuanced for family members of patients with a VUS on original genetic testing, updated genetic counseling may be especially important for this

subgroup of participants. Three of these 8 individuals met Amsterdam criteria based on an analysis of the original family history reported at the time of original genetic counseling and an analysis of the interim family history reported on the patient survey. Given the strong personal and family histories of cancer in these three families, their VUS could potentially represent pathogenic mutations. Updated genetic counseling should include a reevaluation of these variants for potential updates in classification.

Perhaps the most important reason for updated genetic counseling in this population is to provide updates about clinician understanding of potential causes of MMR deficiency. Until approximately 2014, the primary cause of tumor defects in the MMR pathway (other than *MLH1* promoter hypermethylation or *BRAF* V600E mutation) was thought to be LS, and patients were often counseled that they likely had LS even in the absence of a pathogenic variant on germline testing. The changing understanding of the contribution of biallelic somatic mutations as an etiology of UMMRD and the advent of paired somatic/germline genetic testing may require re-contacting patients with UMMRD, even those who previously had comprehensive germline genetic testing. While our study does not evaluate patient interest in paired germline/tumor testing, this exploration of the interest toward germline genetic testing among patients with UMMRD allows for a better understanding of the psychosocial concerns of these patients, which is critical at a time when paired germline/tumor testing is entering the genetic testing landscape. Previous studies have shown that patients believe it is important to know about updates in available genetic testing for other cancer types, but the most effective method for notifying patients about updated genetic testing remains unclear (16). This area of study may be critical for this patient population as paired somatic/germline genetic testing is adopted.

The participants who did not meet Amsterdam criteria may have other explanations for MMR defects in their tumors. While 45-69% of patients with UMMRD are expected to have biallelic somatic mutations causing MMR deficiency (6, 9), 68% percent of respondents perceived at least one cause of their cancer to be an underlying mutation. This is higher than previous estimates of expectations of individuals with CRC to carry a mutation causing cancer (14). It is possible that this is due to differences in original counseling, as individuals with UMMRD have a higher risk of having LS compared to the general population of those with CRC. However, it is unlikely that all the participants who perceive that an underlying pathogenic mutation caused their cancer truly have LS. Therefore, updated genetic counseling and risk assessment is critical for this population to provide information about best screening practices, as well as to potentially provide reassurance that LS is not the sole explanation for UMMRD.

Study Limitations

Our population was overall highly-educated, with a non-Hispanic white background and an average age of 62-years-old. It is not clear if the results of the study can be extrapolated to individuals of a lower socioeconomic status or younger individuals who may have different perceptions of their personal cancer risks. Our population was subject to selection bias, as individuals interested in updated genetic testing may be more likely to respond to a survey on this subject. Our study is limited by a low response rate and low statistical power. Although UTMDACC is a large tertiary care center with an extensive patient database, only 98 individuals met eligibility criteria. This reflects the specificity required to meet the eligibility criteria.

Practice Implications

This patient population is extremely interested in updated genetic testing, with the primary reason being the potential impact of updated genetic testing on family members. An understanding of the psychosocial concerns of this population can help clinicians validate these concerns while also emphasizing the importance of updated genetic testing for the patients themselves. For individuals who received genetic counseling years ago, a discussion of other potential causes of MMR deficiency as well as an updated risk assessment and discussion of screening recommendations will provide patients with the most up-to-date information. While a formal updated genetic counseling session for all patients with UMMRD may not be possible in the context of a busy clinic, a counselor-based effort to reestablish contact with this population may be helpful in initiating a conversation with those who are interested in an updated risk assessment.

Research Recommendations

Because our population was primarily highly educated and non-Hispanic white, further research is necessary to elucidate if similar concerns are prevalent across other socioeconomic backgrounds. A cross-institutional study of individuals with UMMRD will also provide adequate statistical power to establish factors that contribute to interest or lack of interest in updated genetic testing. Such a study will also provide the opportunity to further investigate subgroups of interest, including those who fulfill Amsterdam criteria and those with a VUS upon original genetic testing. Additionally, a survey of patient attitudes toward somatic MMR testing is necessary as paired tumor/germline testing becomes an important component of the genetic testing landscape. Furthermore, a study regarding the uptake of

updated genetic counseling and results of updated genetic testing may provide more information about this population.

APPENDIX

Title: Patient Perceptions of Germline Mutation Findings in People with Unexplained Mismatch Repair Deficiency

Survey

You are receiving this survey because you were evaluated for Lynch syndrome based on previous testing on your colorectal or endometrial tumor. Lynch syndrome is a genetic condition that leads to an increased risk for colorectal, uterine (endometrial), and other cancers. You had genetic testing for Lynch syndrome, but results came back negative. This means we did not find a genetic change that explained why you developed cancer. You have received a letter explaining that there is now updated genetic testing available to you.

The following survey aims to evaluate your views and opinions about additional testing to determine if you have Lynch syndrome. If you decide to take part in the study, your total time commitment is estimated to be 15 minutes. You can refuse to answer any questions asked or written on any forms. Participation in this study is voluntary. A decision not to take part in this study will not change the services you receive through MD Anderson Cancer Center.

Please answer the following questions as completely as possible:

Demographics

1. With which ethnicity do you identify?
    - ☐ Black
    - ☐ Caucasian
    - ☐ Hispanic
    - ☐ Asian
    - ☐ Other (please specify):

2. What is the highest level of education that you have completed?
    - ☐ Did not finish high school
    - ☐ High school/Equivalent
    - ☐ Associate's degree (2 years of college)
    - ☐ Bachelor's degree (4 years of college)
    - ☐ Master's degree/PhD/Professional degree (MD, JD)
    - ☐ Trade school
    - ☐ Other (please specify):

3. How many biological children do you have?

4. With which religious belief system do you identify?
   - ☐ Christian
   - ☐ Muslim
   - ☐ Judaism
   - ☐ I do not identify with a religion
   - ☐ Other: (please specify)

5. Do you have health insurance from a private company (such as Cigna, BlueCross BlueShield) or from a public source (such as Medicare or Medicaid)? Please circle one option below.

PUBLIC INSURANCE PRIVATE INSURANCE I DON'T HAVE INSURANCE

6. What is your total annual **household** income before taxes?

- ☐ Less than $10,000 per year
- ☐ $10,000-$24,999 per year
- ☐ $25,000-$49,999 per year
- ☐ $50,000-$74,999 per year
- ☐ $75,000-$99,999 per year
- ☐ Greater than $100,000 per year

Family History

7. Since the time that you originally had genetic counseling and genetic testing, have any biological family members (parents, siblings, children, aunts/uncles, grandparents, cousins) been diagnosed with cancer? If so, please list them below including the relationship to you, the type of cancer, and the age of the family member when he/she was diagnosed.

Family Member	**Type of Cancer**	**Age at Diagnosis**
Example: Brother	*Colon Cancer*	*56*

If you do not have any family members who have been diagnosed with cancer since the time of your original genetic counseling, please check here: _____

Previous Genetic Testing

8. What do you think caused your cancer? Please check all that apply.

   - ☐ Environmental exposures
   - ☐ Genetic mutation
   - ☐ Life stressors
   - ☐ Smoking
   - ☐ Diet/weight
   - ☐ Other (please explain):

9. What was your original reason for pursuing genetic testing for Lynch syndrome? Please rank the following reasons, with "1" being the most important reason to you. If any of the reasons do not apply, please write "N/A."

   - ____ I was worried about getting cancer again
   - ____ I was worried about my family members getting cancer
   - ___ To determine the best treatment or screening regimen
   - ____ My family history of cancer
   - ____ My doctor told me to
   - ____ My genetic counselor told me to
   - ____ Other (please explain):

10. How stressful or worrisome was it for you to decide to have genetic testing for Lynch syndrome originally?

1	2	3	4	5
Not stressful	A little stressful	Neutral	Stressful	Extremely Stressful

Please explain:

11. How important to you is it to find out what caused your cancer?

1	2	3	4	5
Not important	A little important	Neutral	Important	Extremely Important

Please explain:

12. We have not currently found a genetic change that explains why you developed cancer. Based on your negative test results, do you think your family members would currently be recommended to pursue genetic testing?

YES NO

12a. If so, for which living family members do you think genetic testing would currently be recommended?

- ☐ Parents
- ☐ Siblings
- ☐ Children
- ☐ Aunts/Uncles
- ☐ Nieces/Nephews
- ☐ Cousins
- ☐ Grandparents
- ☐ Other:

13. Have any of your family members already undergone genetic testing for a hereditary cancer syndrome?

YES NO I DON'T KNOW

13a. If so, what is this person's relationship to you, and what were the results of the test?

14. Based on your history of cancer, do you think any of your family members currently wish to pursue genetic testing?

YES NO I DON'T KNOW

Comments:

15. How concerned are you that your family members may also get cancer?

1	2	3	4	5
Not worried	A little worried	Somewhat Worried	Moderately Worried	Very Worried

Comments:

16. How frequently do you receive colonoscopies?

- ☐ Multiple times a year
- ☐ Once a year
- ☐ Every 2-3 years
- ☐ Every 4-5 years
- ☐ Every 6-10 years
- ☐ Never

17. Do you have any other regular screening to check for cancer?
    - ☐ Mammogram/breast exam
    - ☐ Prostate cancer blood test
    - ☐ Ovarian cancer blood test
    - ☐ Upper endoscopy
    - ☐ Other:

Updated Genetic Testing

18. Updated genetic testing is available to you. Are you interested in pursuing further genetic testing that could identify a cause for your cancer?

1	2	3	4	5
Not interested	A little interested	Neutral	Interested	Extremely Interested

If interested, why? If not interested, why not?

19. How would you feel **if a genetic mutation were found** in the updated testing?

1	2	3	4	5
Very worried	Somewhat Worried	Neutral	Somewhat Relieved	Very relieved

Comments:

20. If you were found to have a mutation that explained your cancer, with whom would you share this information? Check all that apply

- ☐ Spouse/partner
- ☐ Family: parents, siblings, children, etc.
- ☐ Friends
- ☐ Healthcare provider
- ☐ A spiritual leader
- ☐ A support group
- ☐ Other (please list):

21. How do you think you would feel **if no genetic mutation were found** in the updated testing?

1	2	3	4	5
Very worried	Somewhat Worried	Neutral	Somewhat Relieved	Very relieved

Comments:

22. **If a mutation was found** that predisposed you to develop cancer, do you think your family members would be recommended to pursue genetic testing for a predisposition to develop cancer?

YES NO

22a. Based on these test results, to which family members do you think genetic testing for a predisposition to develop cancer would be recommended?

- ☐ Parents
- ☐ Siblings
- ☐ Children
- ☐ Aunts/Uncles
- ☐ Nieces/Nephews
- ☐ Cousins
- ☐ Other:
- ☐ None of my relatives

23. **If no mutation was found** that predisposed you to develop cancer, do you think your family members would be recommended to pursue genetic testing for a predisposition to develop cancer?

YES NO

23a. Based on these test results, to which family members do you think genetic testing for a predisposition to develop cancer would be recommended?

- ☐ Parents
- ☐ Siblings
- ☐ Children
- ☐ Aunts/Uncles
- ☐ Nieces/Nephews
- ☐ Cousins
- ☐ Other:
- ☐ None of my relatives

24. How do you think your colonoscopy screening would be different if we found a mutation that caused your colorectal cancer?

- ☐ More frequent colonoscopies
- ☐ Same number of colonoscopies
- ☐ Less frequent colonoscopies

25. If a mutation were found that explained why you developed cancer, what other types of screening do you think would be recommended? Check all that apply.
    - ☐ Skin exam
    - ☐ Mammogram/breast exam
    - ☐ Prostate cancer blood test
    - ☐ Ovarian cancer blood test
    - ☐ Upper endoscopy
    - ☐ Other:

26. Do you have any concerns about pursuing further genetic testing?

YES NO UNSURE

a. If so, what are they?

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