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Uptake of Genetic Testing Among Cancer Patients at Risk for Lynch Syndrome in the National Health Interview Survey

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Abstract

Lynch syndrome (LS) is the most common inherited cancer syndrome that increases the risk of developing colorectal (CRC) and endometrial cancer (EC). Universal screening guidelines were first recommended by the Centers for Disease Control and Prevention in 2009 and are updated annually by multiple societies. Therefore, one would expect genetic testing rates to increase over time. But testing remains underutilized among those with CRC or EC, even though early detection can improve prognosis and survival rates. In this study, we aimed to understand differences in genetic testing uptake among those with CRC or EC from 2005, 2010, 2015, using data from the National Health Interview Survey. We examined genetic testing uptake across cancer type, age (<50 or ≥51), sex, race, insurance, and education using a chi-square statistical analysis. Despite an upward genetic testing trend in 2010, we found no significant differences in genetic testing uptake over time. In 2010, non-White individuals experienced the highest increase from 2005 in comparison to White individuals. However, genetic testing rates declined for both groups by 2015. Our findings show that genetic testing for CRC and EC did not increase over a 10-year period in spite of guidelines that recommend testing.

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Keywords
Lynch syndrome; colorectal cancer; endometrial cancer; genetic testing uptake; national health interview survey

Introduction
Lynch syndrome (LS) is an autosomal dominant hereditary cancer syndrome caused by variants in DNA mismatch repair (MMR) genes and deletions in the EPCAM gene (1). Depending on the gene, the lifetime risk of colorectal cancer (CRC) and endometrial cancer (EC) drastically increases, respectively, by up to 80% and 60% for individuals with LS (2). Surveillance and early detection are essential for a good prognosis, which requires screening through a combination of genetic testing, routine colonoscopies, and gynecological visits (2,3). However, genetic testing uptake remains low among individuals who meet LS criteria based on 2019 National Comprehensive Cancer Network (NCCN) guidelines and less is known about the rate of testing for cancer patients most at risk (4).

Historically, many patients with LS failed to meet the strict family history requirements of the Amsterdam II criteria and the revised Bethesda criteria (1). As a result, both criteria have performed poorly at identifying patients with LS, and have led to low diagnostic and genetic testing rates (1,5). In 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) group from the Centers for Disease Control and Prevention (CDC) first recommended universal screening guidelines for CRC. These guidelines state that all newly diagnosed patients should undergo tumor-based microsatellite instability (MSI) testing or immunohistochemistry (IHC) testing of MMR proteins, which has a higher sensitivity for LS than traditional screening methods (5). Since 2010, many societies annually update their guidelines with a strong recommendation for tumor screening across CRC patients (3,5–7), and the Society of Gynecologic Oncology also endorses screening guidelines for EC (8). For example, NCCN guidelines recommend germline testing for individuals with abnormal tumor testing as well as for those with a family history of any LS-associated cancer (1).

MMR deficiency in solid tumors has a prevalence of 14% in the United States (9), but studies have reported a prevalence as high as 19.7% for CRC and up to 40.2% for EC (10). This variation across studies could be explained by the challenges of germline testing in the event of Lynch-like phenotypes, variants of unknown significance, poor implementation of universal screening programs, and genetic counseling barriers (8,10,11).

Tumor screening is important as it can inform cancer treatment and indicate a need for follow-up genetic testing for LS, where tumors can grow faster and develop at a younger age. Thus, with the development of new testing methods (10), one might expect that as tumor screening rises, so will follow-up germline genetic testing, which has drastically improved the detection rate of LS in patients with CRC and EC (12). However, this has not been the case, despite individuals meeting universal screening guidelines (4,13). Therefore, in this study, we aimed to understand genetic testing uptake before and after the introduction of universal screening guidelines among National Health Interview Survey (NHIS) CRC and EC patients, which account for the highest proportion of LS cases (1,2).
This evaluation focused on facilitation of these guidelines over time to aid in tailoring future testing procedures for these cancers.

**Materials and Methods**

**Data source**

We used publicly available national survey data from the NHIS, an annual in-person, cross-sectional household survey conducted by the CDC since 1957 ([https://www.cdc.gov/nchs/nhis/index.htm](https://www.cdc.gov/nchs/nhis/index.htm)). The NHIS captures self-reported health data from a civilian noninstitutionalized U.S. population that is interviewed throughout the year. These data are de-identified and based on a stratified, multistage, cluster sample design. The NHIS is approved by the National Center for Health Statistics Research Ethics Review Board.

**Study population**

Cancer control supplements are released every five years and contain information on individual genetic testing behaviors. We identified individuals who had CRC and/or EC based on responding yes to having colon, rectal, or uterine neoplasms across 2005, 2010, and 2015 Sample Adult files. Individuals who did not have CRC and/or EC cancer were excluded. We then identified which of these participants received genetic testing based on responding yes to ever “had genetic test for cancer risk” in the cancer supplements. Genetic testing was defined as “testing your blood to see if you carry genes which may predict a greater chance of developing cancer at some point in your life”. Participants who refused, were not ascertained, or answered don’t know were removed. We compared the proportion of cancer patients who reported receiving genetic testing across this 10-year period. In addition, we reported differences in cancer type, sex, race, age, education level, and insurance status by year. Participants were separated by age (≤ 50 or ≥ 51) based on guidelines set by the NCCN strategies for the evaluation of LS ([1](https://www.nccn.org/聖pubs/聖guidebook/聖cancer-prevention/聖cancer-risk-evaluation/聖lung-screening/)), which recommends testing patients diagnosed with CRC or EC at age < 50 years.

**Statistical analysis**

Statistical analyses were performed using the “survey” module in STATA version 16 to account for the complex survey design of NHIS. Weighted descriptive statistics were calculated for respondents who had genetic testing uptake and respondents who did not. Differences between these two weighted groups were assessed using chi-square tests. Descriptive statistics for the underlying unweighted sample are reported in Supplementary Table S1. Genetic testing uptake rates across 2005, 2010 and 2015 was then examined by cancer type and race (Figure 1).

**Results**

Our sample included a weighted total of 3,745,344 patients with CRC (66.3%) or EC (33.7%) where the majority were female (68.8%), below the age of 50 (48.7%), and White (71.9%) (Table 1). Overall, rates of genetic testing uptake (6.1%) were low among cancer patients with no significant differences between years, cancer type, sex, or education level. The highest rate of genetic testing for both cancers was 8.1% in 2010, but uptake dropped...
to 6.5% in 2015 (Figure 1). This increase in uptake was also found separately for CRC and EC, where EC experienced the greatest decrease in genetic uptake from 11.5% in 2010 to 7.1% in 2015 compared to CRC with 8.9% in 2010 to 6.1% in 2015 (Supplementary Table S2). Non-White (28.1% vs 13.1%, \( p = < 0.0001 \)) and uninsured cancer patients (21.1% vs 5.8%, \( p = 0.04 \)) had significantly higher rates of genetic testing. Between 2005 and 2010, non-White individuals had over a 4-fold increase in genetic testing while White individuals only had about a 2-fold increase in genetic testing uptake (Supplementary Table S2). However, both groups experienced declines in 2015.

**Discussion**

In this study, our findings show that there have been no significant changes in genetic testing uptake for CRC and EC patients from 2005 to 2015. Although there was a promising upward trend in testing in 2010, rates declined in 2015, with the greatest decrease observed in EC patients. Interestingly, significantly higher proportions of testing were reported in non-White and uninsured individuals with cancer. However, this might not be generalizable to the entire population but a unique characteristic of NHIS patients.

Prior studies using NHIS have reported similar findings among non-White patients who showed an increased understanding of genetic testing perceptions and were more likely to undergo genetic testing and counseling (14-16). However, known genetic testing disparities were prevalent in other public datasets, where non-Hispanic Blacks were less aware of genetic testing and less likely to seek cancer-related information (17,18). This could be a result of the NHIS sample design, which oversamples residential areas with higher minority populations based on U.S. census data as a way to mitigate small sample sizes possibly due to urbanization and geographical regions (19,20). However, it is also possible that the cancer supplements attract respondents who are more aware of the benefits of cancer-related genetic testing and receive standard care at U.S. health centers. Not only has it been shown that CRC screening rates were higher among patients attending U.S. health centers compared to the general population, but this also contributed to an increase of CRC screening for African Americans as well (21).

The lack of significant changes over time raises concerns about screening implementation for CRC and EC even though it is becoming more cost-effective and accessible (22). EC patients with LS are more likely to be undiagnosed compared to CRC patients with LS and with numerous CRC targeted guidelines, this difference in testing among these two cancers may be further exacerbated since universal screening is not routinely performed for EC (12). Although EC had the largest increase in genetic testing uptake in 2010, due to our small sample size, it is difficult to make any causal inferences as to why this spike occurred for both cancer types, which could have been the result of our statistical weights and the sampling of our population. Nevertheless, decreased rates for both cancer types by 2015 suggests a decline in knowledge about these initiatives and/or poor implementation of screening programs in conjunction with the annual guideline updates. Not only can expanding universal screening programs for EC increase detection rates of LS, but long-term enforcement of these programs can increase genetic testing uptake for non-CRC tumors.
especially for uncommon cancers with high susceptibility for LS associated variants like sebaceous tumors (12,23).

Our study has several limitations; notably, our unweighted sample of cancer patients who received genetic testing was small. As previously shown, genetic testing uptake was low in the general NHIS survey population who met 2019 NCCN LS criteria (4). Since our study focused on genetic testing among individuals with cancer, our sample size was further reduced. It is also possible that some participants may not have categorized their germline testing as genetic testing based on the survey definition, which could have led to underreporting in our available dataset. However, participants may not have undergone germline testing if tumor screening (MSI/IHC) did not indicate a necessity for germline testing. Although we do not have information on MSI/IHC testing rates over time, MSI/IHC testing rates should be evaluated to examine if this is a reason for insignificant increases in uptake of genetic testing for LS since a decrease could occur as universal screening stringency is relaxed and cancer screening becomes more common (12). Another limitation is that we are unable to confirm if testing is clinically appropriate given the lack of genetic testing LS risk factors within the survey including somatic testing results, since somatic mutations can occur at a high frequency for EC and CRC (23). Therefore, future work should examine genetic testing among those with indicated somatic testing results to understand the uptake of appropriate germline testing over time.

Overall, we found that genetic testing has not significantly increased over time in individuals with CRC and EC despite annual recommendations of universal screening guidelines from numerous cancer societies (3,6–8). Further research is needed to understand the cause of these results, which could possibly be due to a lack of education and awareness of screening for LS, especially for those with EC (18). More education strategies should be implemented at the provider and patient level to help in identifying individuals with LS. Improving genetic testing education among physicians can help promote positive genetic testing behaviors among high-risk patients who may be unaware of its benefits for identifying hereditary cancers or who have negative perceptions and beliefs (24). Support and guidance from health care practitioners can promote autonomy, self-advocacy, and awareness about LS risk factors amongst patients (24,25). This can encourage them to participate in more screening strategies that can benefit both them and their family members.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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References


Figure 1. Genetic testing uptake in cancer patients.
This plot shows the proportion of genetic testing uptake by year and racial group for CRC and EC. Colors represent racial groups and cancer type. CRC = colorectal cancer; EC = endometrial cancer.
Table 1.
Descriptive statistics of genetic testing in cancer respondents (N=3,745,344).

<table>
<thead>
<tr>
<th></th>
<th>Received Genetic Testing (n = 229,348)</th>
<th>No Genetic Testing (n = 3,515,996)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>24,375 (10.6%)</td>
<td>776,509 (22.1%)</td>
<td>0.40</td>
</tr>
<tr>
<td>2010</td>
<td>70,290 (30.7%)</td>
<td>798,039 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>134,683 (58.7%)</td>
<td>1,941,448 (55.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer Type (%)</strong></td>
<td></td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>152,007 (66.3%)</td>
<td>2,188,692 (62.3%)</td>
<td></td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td>77,341 (33.7%)</td>
<td>1,327,304 (37.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (%)</strong></td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 50</td>
<td>33,029 (14.4%)</td>
<td>492,480 (14.0%)</td>
<td></td>
</tr>
<tr>
<td>Above 51</td>
<td>102,026 (44.5%)</td>
<td>1,657,748 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 50</td>
<td>78,645 (34.3%)</td>
<td>756,024 (21.5%)</td>
<td></td>
</tr>
<tr>
<td>Above 51</td>
<td>15,648 (6.8%)</td>
<td>590,601 (16.8%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>19,143 (0.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex (%)</strong></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Female</td>
<td>175,457 (76.5%)</td>
<td>2,384,978 (67.8%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53,891 (23.5%)</td>
<td>1,131,018 (32.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>148,462 (71.9%)</td>
<td>3,198,024 (86.86%)</td>
<td></td>
</tr>
<tr>
<td>Non-White</td>
<td>80,886 (28.1%)</td>
<td>317,972 (13.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Socioeconomic Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Less than a high school education</td>
<td>34,707 (15.1%)</td>
<td>454,659 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>High school/GED</td>
<td>41,853 (18.3%)</td>
<td>1,111,664 (31.6%)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>38,091 (16.6%)</td>
<td>804,210 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>College education</td>
<td>1,111,994 (48.8%)</td>
<td>1,132,417 (32.2%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2,703 (1.2%)</td>
<td>13,046 (0.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Health Insurance (%)</strong></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Insured</td>
<td>181,023 (78.9%)</td>
<td>3,303,345 (94.0%)</td>
<td></td>
</tr>
<tr>
<td>Non-Insured</td>
<td>48,325 (21.1%)</td>
<td>204,927 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>7,724 (0.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Chi-square tests were used for statistical analyses. p < 0.05 was considered significant.