Uptake and predictors of colonoscopy use in family members not participating in cascade genetic testing for Lynch syndrome

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Cascade genetic testing provides a method to appropriately focus colonoscopy use in families with Lynch syndrome (LS). However, research suggests that up to two-thirds at risk to inherit LS don’t participate. Within the United States, no studies have assessed colonoscopy use within this elusive and high-risk subset. We set forth to (1) document colonoscopy use within those not undergoing genetic testing (NGT) and (2) identify factors associated with completing colonoscopy. Data came from a cross sectional survey of families with molecularly confirmed LS. One hundred seventy-six (176) adults participated; 47 of unknown variant status and 129 with variant status known (59 carriers/70 non-carriers). Despite a high level of awareness of LS (85%) and identical recommendations for colonoscopy, NGT reported significantly lower use of colonoscopy than carriers (47% vs. 73%; \( p = 0.003 \)). Our results show that perceived risk to develop colon cancer (AOR = 1.99, \( p < 0.05 \)) and physician recommendations (AOR = 7.64, \( p < 0.01 \)) are significant predictors of colonoscopy use across all family members controlling for carrier status. Given these findings, health care providers, should assess patients’ perceived risk to develop cancer, assist them in adjusting risk perceptions and discuss recommendations for colonoscopy with all members in families with LS.

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Lynch syndrome (LS) is an inherited cancer susceptibility syndrome caused by inactivating variants in one of four mismatch repair genes (MSH2, MLH1, MSH6, PMS2) or in the EPCAM gene. LS is the most common inherited cause of colorectal cancer (CRC) accounting for 2–4% of CRC cases. Lifetime risks for developing CRC approach 75% in men and 50% in women. Women also have lifetime risks for endometrial cancer equivalent to their risks for CRC. In addition, individuals carrying pathogenic variants in LS associated genes are at increased risk for a broad spectrum of other cancers including stomach and ovarian cancers.

It is estimated that between 1 in 100⁴ and 1 in 279⁵ persons carry a pathogenic variant for LS. Based upon the U.S. Census data for 2010, this translates into a range of people at increased risk for the early onset of cancers associated with LS between 1 and 3 million. The identification of these individuals prior to the occurrence of disease provides for targeted screening preserving resources for those at high risk of developing cancer, avoids unnecessary procedural risks while providing reassurance for those testing negative⁶. Previous research demonstrates clear medical benefits from early detection and screening for CRC associated with LS reporting a 62% reduction in the incidence of CRC⁷ and a 65–72% decrease in mortality in families with a LS-associated variant⁸. From a behavioral perspective, research reveals significant and appropriate changes in colonoscopy use following genetic counseling and testing; carriers increase colonoscopy use and non-carriers significantly.

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decrease use\textsuperscript{10,11}. While research has not shown a psychological benefit, it has shown that adaptation to genetic results seemingly occurs without lasting, harmful psychological sequela in those utilizing genetic services\textsuperscript{12-14}. If a pathogenic variant is identified in families suspected to have LS, cascade genetic testing is recommended within the family following the provision of genetic counseling. As noted, cascade genetic testing allows for the differentiation of family members at high risk of developing LS cancers (carriers) that require earlier and periodic screening from those at population risk (non-carriers). However, the medical and economic benefits of cascade genetic testing depend on maximizing uptake of genetic testing by at risk relatives while ensuring adherence to recommended cancer screening guidelines\textsuperscript{15,16}. Both parameters present challenges and would benefit from additional research to maximize uptake and improve adherence to recommendations for cancer screening in families with LS.

Uptake of genetic testing in families with pathogenic variants associated with LS. A systematic review of the literature on LS\textsuperscript{17} reports that up to 66% of first-degree relatives (parent, child or sibling) do not undergo genetic testing following the identification of a pathogenic variant in the family. Furthermore, the literature suggests that the uptake of genetic testing in more distant relatives (second and third-degree relatives) is significantly lower than in close relatives\textsuperscript{18}. Collectively, these studies indicate that a clear majority of family members are not utilizing genetic services to clarify their risk for developing a LS cancer. Not surprisingly, LS does not stand alone in this statistic as a number of studies have reported lower than expected uptake of genetic testing within families facing other dominantly inherited diseases with options available to prevent the disease or provide early detection\textsuperscript{6,15,20}.

A number of factors have been reported and associated with the uptake of genetic testing in LS\textsuperscript{18,21,22}. The list includes demographics factors, psychological wellbeing (lack of depressive symptoms), family history (number of relatives with cancer), parental adherence to regular screening, being an only child, being a sibling of a tested carrier, family communication and social networks interactions within families.

Colonoscopy use within families with pathogenic variants. Since the published literature has consistently focused on family members who receive genetic services and undergo testing, the screening behaviors of the silent majority, i.e. family members not utilizing genetic services, have been ignored. Of concern is the absence of data on their use of colonoscopy given the proven benefits of interval screening in families with LS.

Perceptions of one's risk to develop colon cancer have also been identified as a variable influencing colonoscopy use in families with LS. Research efforts are needed to assess cancer screening behaviors within this population as well as to identify modifiable variables that can be used to influence behavior within our existing health care system.
care system. Therefore, this study was designed to (1) assess colonoscopy use in family members not utilizing genetic services; (2) assess the role of perceived risk in colonoscopy use and (3) explore the role of provider recommendations in influencing colonoscopy use.

Results

Participant characteristics. The majority of the study sample was white (97%), female (61%), health insured (92%), college educated (55%), married or partnered (65%), employed (72%), and lacking a history of cancer (75%). Ages ranged from 18 to 87 years with an average age of 46 years. GT+ were more likely to have a personal history of cancer than GT− (p < 0.001).

The subset of family members who were at risk to inherit the family variant but did not receive genetic counseling nor undergo genetic testing (NGT; n = 47) was composed of:

- Seventeen family members (17/47; 36%) whose parent was identified as a carrier (Mendelian risk = 50%);
- Twenty-six family members (26/47; 55%) whose parent, at-risk to inherit the familial variant, was deceased at the time of the study (Mendelian risk = 25%). Twenty-one of the 26 deceased parents were reported to have had a LS associated cancer at less than 55 years of age and
- Four family members (4/47; 8.5%), whose living, at-risk parent also chose not to utilize variant testing (Mendelian risk = 25%). Three of five (3/5; 60%) of these parents were reported to have a personal history of cancer.

Eighty-five percent (40/47) of the NGT group reported that they were aware that family members were taking part in a study about LS; 74% (35/47) spoke directly with family members about being involved in the LS study. Seven (7/47; 15%) reported that they were neither aware of the study nor spoke to a family member about the study prior to being invited to complete the current survey.

Table 1 provides a comparison of socio-demographic and other variables of interest stratified by variant status (n = 176).

| Characteristic                        | Variant carriers GT+ (n = 59) | Non-carriers GT− (n = 70) | Unknown variant status NGT (n = 47) | p value* (GT+ vs. NGT) |
|-------------------------------------|-------------------------------|--------------------------|-----------------------------------|------------------------|
| Age                                 | Mean = 44 years S.D. = 13 years Range = 21–71 years | Mean = 47 years S.D. = 15 years Range = 23–81 years | Mean = 45 years S.D. = 17 years Range = 18–83 years | p = 0.88 |
| % Female                            | 64%                           | 61%                      | 57%                               | p = 0.30 |
| % having/had cancer                | 37%                           | 14%                      | 28%                               | p = 0.35 |
| % health insurance                 | 93%                           | 94%                      | 87%                               | p = 0.32 |
| % physician recommended colonoscopy| 90%                           | 73%                      | 79%                               | p = 0.06 |
| % College educated                 | 54%                           | 63%                      | 45%                               | p = 0.60 |
| % Employed                         | 78%                           | 69%                      | 70%                               | p = 0.36 |
| Perceived risk of colon cancer     | Mean = 4.66 S.D. = 0.73 Range = 1–5 | Mean = 3.24 S.D. = 0.79 Range = 1–5 | Mean = 3.77 S.D. = 1.40 Range = 1–5 | p = 0.001 |
| CESD score                          | Mean = 3.78 S.D. = 4.03 Range = 0–15 | Mean = 4.56 S.D. = 5.13 Range = 0–26 | Mean = 6.88 S.D. = 5.10 Range = 0–24 | p < 0.001 |
| Colonoscopy use                    | 73%                           | 36%                      | 47%                               | p = 0.003 |

Table 1. Demographic characteristics, physician recommended colonoscopy, perceived risk, wellbeing, and colonoscopy screening by variant status (n = 176).

Colonoscopy use. Overall, 73% of GT+ underwent colonoscopy within the 2 years prior to completing the survey, compared to 47% of NGT and 36% of GT− (Fig. 1). Controlling for demographic characteristics, personal cancer history, and psychological wellbeing, GT+ were nearly 4 times more likely (Adjusted Odds Ratio [AOR] = 4.02, p = 0.006) to have had a colonoscopy than not during the specified time compared to NGT. However, NGT did not significantly differ from GT− in their use of colonoscopy (AOR = 1.83, p = 0.15). Consistent with the reported literature, GT+ were 6 times more likely than GT− to have had a colonoscopy than not within the 2 years prior to the assessment (AOR = 6.36, p < 0.001). Age was the only significant covariate; age was positively associated with colonoscopy use (AOR = 1.04, p = 0.008).

Provider recommendation for colonoscopy. There is a marginal association in provider recommendation for colonoscopy by testing status, with 90% of GT+, 70% of GT−, and 73% of NGT reporting receiving such recommendations (p = 0.06). Controlling for covariates, GT+ are significantly more likely to report provider rec-
Recommendations for colonoscopy than NGT (AOR = 6.56, \( p = 0.03 \)), with no difference in referrals between NGT and GT− (AOR = 1.30, \( p = 0.70 \)). Age was the only significant covariate (AOR = 1.08, \( p < 0.001 \)).

**Perceived risks to develop colon cancer.** NGT had significantly lower perceived risk of developing colon cancer (\( p = 0.001 \)) than GT+. Results remain consistent when controlling for covariates. Those with health insurance reported significantly lower risk perceptions (\( p = 0.027 \)) as well.

**Multivariate analysis.** As stated, NGT perceived themselves to be at lower risk of developing colon cancer compared to GT+. Mediation analysis was conducted to explore whether these lower risk perceptions explain NGT’s lower rates of colonoscopy screening compared to GT+. Provider recommendation partially mediates the association between testing status and colon cancer screening (Model 2a: AOR = 10.65, \( p < 0.001 \)) and is a strong, consistent predictor of colonoscopy use when perceived risk is added to the model (Model 2b: AOR = 7.64, \( p < 0.001 \)). Perceived risk for developing colon cancer was a significant predictor (AOR = 2.05, \( p = 0.004 \)) of colonoscopy use suggesting that risk perception may play a role in how knowledge (or lack of knowledge) regarding one’s variant status may impact screening behavior. Inclusion of both physician referral and perceived risk appears to fully explain observed differences in colonoscopy use between NGT and GT+ (Table 2).

**Discussion**

The existing literature indicates that less than half (23–45%) of first degree relatives at risk for inheriting Mendelian (monogenic) diseases with risk reducing or preventive strategies, utilize genetic services to guide their medical management; these data include families with Lynch syndrome[17,19]. However, published research has focused on family members who receive intensive genetic education, counseling and undergo testing, and as such, neglect the behavioral and psychological outcomes of the ‘silent majority’ of family members who don’t seek genetic services. To our knowledge, the present report is the first US study to document colonoscopy use by family members at risk for inheriting Lynch syndrome but not utilizing genetic services.

Our data show that less than half (47%) of family members not participating in genetic testing complete colonoscopy within the 2 years prior to their participation in this study compared to 73% of relatives known to carry the pathogenic familial variant. This is a significant difference in colonoscopy use and occurs despite identical recommendations for colon cancer screening. Ideally, improving the uptake of genetic testing within families would allow for more targeted and efficient use of cancer screening resources. However, in the current climate of low uptake of genetic testing and significantly reduced levels of colonoscopy by at risk family members, professional societies are promoting a ‘better safe than sorry approach’ to colon cancer screening while acknowledging the inefficiencies and associated medical risks of undergoing a potentially unnecessary colonoscopy. Ultimately,
and encouragement by health care providers has been shown to improve cancer screening25,38. Match the objective risk (either molecularly determined or Mendelian risk), both education about cancer risk of developing cancer may provide opportunities to assess and clarify misperceptions potentially arising from underwent testing and know their carrier status, reviewing cancer risks associated with LS and cancer screening broadly (primary health care providers as well as specialists). In both situations, health care providers have the encounter individuals pursuing genetics services and health care providers encountering family members more colonoscopy use within families with LS will best be addressed through enlisting both genetics providers who communication among patients and providers related to their family history of LS. Therefore, efforts to improve discussing both Mendelian risks to inherit LS and the associated cancer risks. As part of that process, health care providers can assess the patient’s perception of their risks to develop colon cancer as well as other potential barriers. Patients may provide insights useful in aligning subjective risks with objective risks with the ultimate goal of improving compliance with recommendations for colonoscopy even in the absence of genetic testing. Previous research has shown that preventive messages tailored to persons with a family history of colorectal cancer have been shown to be effective at increasing disease risk perceptions among those who underestimate their risk for colon cancer45. It is plausible that a proportion of patients come to the clinical encounter with limited understanding of their family history of LS and the associated risks. Likewise, it is also possible that family members who don't utilize genetic services aren't sharing the family history and/or genetic test results of family members with their provider. As such, providers may not be aware of their patients' potentially increased risk for developing cancer. Furthermore, in the absence of a genetic test result, providers may not know what the recommendations are for colonoscopy. All of these scenarios point to additional need to promote effective family communication about genetic risks and facilitate open communication among families, patients and providers.

In regards to the potential of utilizing health care providers to motivate screening, there appears to be an underlying assumption that health care providers understand the hereditary and lifetime cancer risks associated with Lynch syndrome, know the cancer screening guidelines recommended for individuals within families with LS and accept a role in identifying and managing patients in families with LS. Unfortunately, existing literature within and outside of the United States raises doubt about those assumptions. A study conducted in Australia assessing clinicians’ knowledge, attitudes and referral patterns of patients with suspected Lynch syndrome40 reported that 30% of physicians did not feel that their role is to identify patients for genetic referral. A second study by a group from Denmark41 investigated knowledge about key features of LS in at risk individuals and

### Table 2. Multivariate logistic regression, predicting colonoscopy use within 2-years of assessment (n = 176).

| Covariates                        | Colonoscopy use (Model 1) | Colonoscopy use (Model 2a) | Colonoscopy use (Model 2b) |
|-----------------------------------|---------------------------|---------------------------|---------------------------|
|                                  | OR (95% CI)               | OR (95% CI)               | OR (95% CI)               |
| Age                               | 1.05** (1.02; 1.08)       | 1.04* (1.00; 1.07)        | 1.05* (1.00; 1.09)        |
| Male                              | 1.08 (0.51; 2.27)         | 1.22 (0.54; 2.76)         | 1.41 (0.66; 3.04)         |
| Has health insurance              | 1.01 (0.31; 3.33)         | 0.92 (0.15; 5.56)         | 1.09 (0.17; 6.99)         |
| College educated                  | 1.58 (0.79; 3.15)         | 1.58 (0.76; 3.27)         | 1.52 (0.72; 3.22)         |
| Employed                          | 1.00 (0.43; 2.32)         | 1.06 (0.44; 2.56)         | 0.96 (0.35; 2.61)         |
| Depressive symptoms               | 1.03 (0.98; 1.08)         | 1.01 (0.95; 1.08)         | 1.00 (0.94; 1.07)         |
| Cancer history                    | 1.49 (0.55; 4.02)         | 1.38 (0.52; 3.64)         | 1.32 (0.48; 3.60)         |

**Genetic testing**

| GT+ (carrier) | Referent | Referent | Referent |
|---------------|----------|----------|----------|
| GT– (non-carrier) | 0.15*** (0.08; 0.30) | 0.18*** (0.09; 0.34) | 0.40* (0.17; 0.96) |
| NGT (status unknown) | 0.24** (0.08; 0.69) | 0.34* (0.12; 0.99) | 0.53 (0.20; 1.37) |
| Physician colonoscopy referral | 10.65*** (3.08; 36.76) | 7.64** (1.85; 31.59) | 1.99* (1.14; 3.47) |
| Perceived risk | Referent | Referent | Referent |

* p < 0.05; ** p < 0.01; *** p < 0.001.
numbers of self-reported depressive symptoms compared to family members identified as variant carriers within the subset of family members not undergoing genetic testing (NGT), we identified significantly higher increased risk to develop cancer. 

While the actual scores did not consistently reach a level of clinical significance, this finding is worrisome and could potentially contribute to the lower uptake of genetic services (education, counseling and testing) within families with LS and potentially families confronting other inherited diseases/disorders. 

While further research is needed, this data provides additional support for implementation of the 2016 recommendations put forth by the United States Preventive Services Task Force (USPSTF) on screening adults for depression especially in families with inherited diseases/disorders.

While we are enthusiastic about the importance of our findings, we acknowledge that there are limitations within the current study. First and of significant concern, is the fact that our cohort does not adequately represent the racial, ethnic or socioeconomic diversity of families with LS or the general population within the United States. Future studies addressing this issue should focus on recruiting a more diverse and representative sample to broaden the usefulness of results. Second, while our sample size of family members at risk to inherit a LS variant but not utilizing genetic services (NGT) is admittedly small, the population is difficult to recruit and engage as evidenced by the lack of published research on this topic. In addition, our method of recruiting NGT through participating family members is likely to have biased the sample completing surveys, possibly recruiting family members more engaged in family communication, less resistant to genetic risk information, generally less distressed and possibly more engaged in cancer screening. Given this likely recruitment bias, outcomes from a larger, more inclusive sample would possibly result in more worrisome outcomes.

In closing, we hope this research serves to engage not only genetic health care providers in the care of this seemingly ignored subset of family members at risk for LS but also recruits health care providers encountering them in other health care settings. Reservations about and initial decisions to not pursue genetic services may change as situations within the family evolve; e.g. new cancer diagnoses within the family, successful outcomes due to the early diagnosis of cancer, change in employment/insurance status, parenthood, etc. At these times, revisiting family experiences, personal feelings, risk perceptions, knowledge of LS, options for testing, and cancer screening, may increase the uptake of cascade genetic testing and focus cancer screening on those truly at increased risk to develop cancer.

**Patients and methods**

**Sample.** Study participants were drawn from a cohort of 52 families from 34 of the continental United States with clinically confirmed, pathogenic variants associated with LS. Family members at 50% risk to inherit a pathogenic variant were offered participation in a prospective study investigating the psychological, social and behavioral outcomes of genetic counseling and the option of variant testing45. In situations where the ‘at risk’ connecting relative was deceased or declined genetic services, invitations were extended to second degree relatives of known variant carriers (25% Mendelian risk). Within this cohort, 259 family members at risk to inherit their family’s variant participated in genetic counseling, underwent genetic testing, received test results (carrier [GT+] or non-carrier [GT−]) and completed the initial study surveys between 1997 and 2008. Nearly half (49%) of first-degree relatives at risk to inherit the family variant did not participate46, suggesting even higher numbers of more distant relatives also at risk for LS but not utilizing genetic services44. The sample considered within the current report includes (1) family members receiving genetic counseling and undergoing genetic testing [GT] who completed all questions pertaining to the variables of interest within the long-term follow-up assessment (59 GT+ and 70 GT−) as well as (2) family members at risk to inherit the family variant but not receiving genetic counseling nor undergoing genetic testing [NGT] (n = 47). Recruitment and data collection of NGT occurred simultaneous with the long-term prospective follow-up of cohort participants who underwent genetic testing (Fig. 2).

**Procedures.** The Institutional Review Board at the National Human Genome Research Institute of the National Institutes of Health in Bethesda, Maryland approved these investigations; NIH protocol 95-HG-0165, Outcomes of Education and Counseling for HNPPC/Lynch Syndrome Testing (https://clinicaltrials.gov/ct2/show/NCT0004210?term=lynch+syndrome+and+benhesda&rank=2; 01/27/2003). All research was performed in accordance with all guidelines and regulations required by the National Human Genome Research Institute at the National Institutes of Health. Detailed descriptions of the recruitment, genetic education, counseling and offer of variant testing have been previously reported45. In brief, family members opting to receive genetic services provided written consent for their longitudinal participation. Participants who elected to receive genetic
counseling and consider genetic testing completed surveys at baseline (prior to receiving genetic education and counseling), at 6 months and 1 year after receiving their variant results. A final 'long term' follow-up survey was mailed to family members undergoing genetic testing (GT) yielding information from 137 participants 3 to 8 years after their receipt of variant results (Fig. 2).
One hundred forty-eight (148) potential NGT participants were identified and provided a paper questionnaire and postage paid return envelope through GT family members who completed a long-term follow-up survey. For NGT choosing to take part in the study, data were collected simultaneous to that of GT who completed the final long-term follow-up survey. Consent for NGT was implied by the completion and return of the questionnaire. A $50 gift card was provided for the completion and return of the GT long-term follow up and NGT survey. Sixty-four (64) surveys were completed and returned (43% response rate) by NGT at risk for inheriting the identified family variant. Thirteen (13) of these surveys were excluded due to the participants’ reported receipt of genetic services elsewhere and knowledge of their variant status; this left fifty-one (51) NGT whose variant status was not known for the final analyses. Responses to the GT long-term follow up and the NGT survey are the focus to the current report; 12 participants were missing data on key variables, resulting in a total sample size \( n = 176 \) (59 GT+, 70 GT−, 47 NGT).

**Variables.**  The primary outcome in the current report is colonoscopy use in the 2 years prior to assessment. Participants’ self-reported use of colonoscopy was elicited from their response to a single question asking when they had last undergone colonoscopy. Responses included: (1) within the last year; (2) within the last 2 years; (3) more than 2 years ago, or (4) never. Responses to colonoscopy use were dichotomized into (1) within the last 2 years (responses 1 and 2) or (2) more than 2 years/never (responses 3 and 4).

The primary predictor variable of interest is whether the participant underwent genetic testing (GT or NGT). For those receiving genetic services, categorization of variant status (GT+ or GT−) was based on test results conducted within a laboratory approved by the Clinical Laboratory Improvement Amendment (CLIA).

Perceived risk of developing colon cancer was considered a cognitive factor mediating the association between receipt of genetic services and resulting variant status with the main outcome, colonoscopy screening. Participants' perceived risk of developing colon cancer was assessed through response to a single question eliciting what they believe their chance of developing colon cancer was relative to other people their age. Responses were collected on a 5-point scale that ranged from 1 (Much less) to 5 (Much more) with 3 (About the same) being the neutral response.

Provider recommendation for colonoscopy was also considered as a potential mediator between receipt of genetic services and resulting variant status with the main outcome, colonoscopy screening. Provider recommendation for colonoscopy was assessed through a single ‘Yes/No’ question eliciting whether any of their doctors recommended that they undergo a colonoscopy.

Covariates considered in the reported analyses included demographic characteristics, personal cancer history and psychological wellbeing. Demographic variables included age, gender, employment status, health insurance coverage and education level. Personal history of cancer (affected or not affected and type of cancer) was determined by review of medical records for GT family members and self-reported for NGT family members. Psychological wellbeing was assessed through participants’ completion of a short form of the Center for Epidemiology Studies—Depression (CESD) scale. Total CESD scores reflect the summed response across items. Four participants were missing at most a single response on the CESD item set; mean imputation was used to infer these missing responses prior to constructing the total CESD score.

**Statistical analysis.**  To account for possible clustering of individuals within families, generalized estimating equations (GEE) with an exchangeable covariance structure were used. All multivariate analyses included the aforementioned covariates and used robust standard errors in the computation of significance tests. Three models were fitted. In the final, we test whether NGT participants are less likely to uptake colonoscopy screening than GT+ (Model 1). We then investigate whether inclusion of provider referral to colonoscopy and perceived risk account for observed differences in testing status. In Model 2a, we add provider referral, and in Model 2b, we add perceive cancer risk.
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Author contributions

D.W.H. conceived the design of the study, was responsible for the acquisition of data, drafting of the manuscript, approval of the final version and agreed to be accountable for all aspects of the work. D.E. was responsible for the initial analysis and interpretation of the data and review/edits of the manuscript. Y.A. contributed to the acquisition of the data, data entry and review/edits of the manuscript. A.G. contributed to the acquisition of the data, data entry and review/edits of the manuscript. S.A. contributed to the data analysis and interpretation of the data and review/edits of the manuscript drafts. L.K. contributed by providing substantial contributions to the analysis of the data, data analysis, critical revisions to the manuscript and agreed to be accountable for all
aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of Health and Human Services, nor the U.S. Government.

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**Competing interests**
The authors declare no competing interests.

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