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Correspondence

Response to "Histology of colorectal adenocarcinoma with double somatic mismatch-repair mutations is indistinguishable from those caused by Lynch syndrome"

Dear Editor,

Colorectal tumors with defective mismatch repair (dMMR) may arise due to inherited or acquired mutations in the mismatch repair (MMR) genes—*MLH1*, *MSH2*, *MSH6*, and *PMS2*—or mutations in the *EPCAM* gene. Sporadic MMR mutations are another cause of dMMR. A number of studies have shown that colorectal tumors caused by Lynch syndrome (LS) and tumors caused by sporadic dMMR exhibit similar pathological and molecular characteristics, such as tumor lymphocyte infiltration and right-sided colonic presentation [1,2].

The term *Lynch-like syndrome* (LLS) refers to tumors showing dMMR without germline DNA MMR variants or somatic *MLH1* promoter hypermethylation [3,4]. LLS accounts for up to 72% of dMMR cases and has significantly lower risks of LS-related cancers compared to patients with germline MMR pathogenic variants [4]. The majority of these cases are explained by double somatic variants in the MMR genes.

In the United Kingdom, LLS patients and their first-degree relatives are eligible for 2-yearly colonoscopies as per LS guidelines [5], predicated on dMMR tumor tests alone, even without an identifiable germline MMR gene mutation. Hemminger et al [1] note that sequencing of tumor DNA can help clarify sporadic versus hereditary causes of unexplained MMR deficiency. Sporadic dMMR, caused by double somatic variants, is unlikely to have implications for the proband's family, and as such, LS screening guidelines would not be recommended.

We conducted a survey among clinicians practicing in the 21 regional clinical genetics departments within the United Kingdom and Ireland. The goal was to explore awareness of LLS and to understand current risk assessment and the management of these patients. A SurveyMonkey link was emailed to and subsequently disseminated to genetic counselors and clinical geneticists by cancer lead clinicians within each department in May 2018. Respondents provided information on their job title, length of service, region of practice, and number of LS tests requested per month. Respondents were asked to provide in their own words a "free-text" definition of LLS and complete risk assessment and screening recommendation questions for LLS patients and families.

We received 49 responses from 21 centers: 21 clinical geneticists (of which 6 were lead cancer clinical geneticists), 26 genetic counselors (of which 2 were lead genetic counselors), and 2 clinical genetics specialist registrars. Of the respondents, 46 of 49 reported they managed patients for MMR genetic testing on a monthly basis.

Twenty-one of 49 respondents knew the LLS definition as outlined above. Some clinicians noted that LLS refers to individuals fulfilling Amsterdam or Bethesda criteria with no identifiable mutation. Cancer lead clinicians were more likely to be aware of the definition, as 6 of 8 cancer leads provided a correct definition (χ^2 test, $P = .0223$).

There were variations in practice within and across departments. Cancer lead clinicians were more likely to adhere to British Society of Gastroenterology guidelines [5], as 3 of 8 (37%) would recommend 2-yearly colonoscopy surveillance for this patient group. Only 12 of the 41 (29%) non–cancer leads would follow this recommendation. Cancer leads (2/8) were more likely to suggest somatic analysis to further clarify the risks for the patient and their families compared to 2 of 41 non–cancer leads (χ^2 test, $P = .0286$).

Clinicians with more than 20 years' experience were more likely to be aware of LLS definition (5 of 10 respondents) and adhere to British Society of Gastroenterology guidelines. A third of respondents from this group suggested somatic analysis.

Intradepartmental differences in assessment and recommendations were noted; some clinicians would offer screening as per LS protocol, others would base this on family history, whereas others recommended less frequent colonoscopies, starting from a later age, such as 3-yearly colonoscopies from age 35 or 5-yearly colonoscopies from age 50. Approximately half of the respondents would rely on colleagues' opinion. Some centers referred to Multidisciplinary Team Meetings (MDT) MDTs for further discussion and agreement on screening recommendations.

We agree with Hemminger et al [1] and would suggest use of somatic analysis in routine practice. Multidisciplinary team meetings as well as national policies for the management of LLS cases are needed to ensure quality and equity of care. Use of national genetic testing policies may help address some of the above issues.

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"Histology of colorectal adenocarcinoma with double somatic mismatch-repair mutations is indistinguishable from those caused by Lynch syndrome"—reply

Dear Editor,

Thank you to Drs Demetra Georgiou, Vicki Kiesel, Angela F. Brady, and Kevin Monahan for sharing their experiences with Lynch-like syndrome in the United Kingdom in response to our article [1]. We appreciate the difficulty of knowing how to manage patients with unexplained mismatch repair deficiency (dMMR) appropriately and found the authors' data very interesting. One detail we would like to note is the difference between management recommendations in the United Kingdom and the United States. The authors say that "in the UK, [patients with unexplained dMMR] and their first degree relatives are eligible for 2 yearly colonoscopy as per LS guidelines [2]." In the United States, current management guidelines from the National Comprehensive Cancer Network's Genetic/Familial High-Risk Assessment: Colorectal version 1.2018 state that "if double somatic [MMR] mutations are identified [via tumor sequencing] or if [tumor sequencing] does not help clarify the result, *it is recommended that these patients and their close relatives be managed based on their family history and NOT as if they have Lynch syndrome.* Regardless of the results of tumor sequencing, these patients and their close relatives should be managed based on their family history and NOT as if they have Lynch syndrome unless their family history warrants it" [3]. One of the biggest factors contributing to the shift from managing dMMR patients as if they had Lynch syndrome without an identified germline mutation to managing them based on their family history was the discovery that 45%-69% of patients with unexplained dMMR actually have double somatic mutations, not a missed germline mutation [4-7].

We would also like to update that although we found no histological differences between colorectal tumors due to Lynch syndrome or double somatic MMR mutations, we have found clinical differences between the 2 patient groups. We recently published the characteristics that differentiate colorectal cancer patients with Lynch syndrome from those with double somatic MMR mutations or unexplained dMMR [8]. We found that patients with double somatic MMR mutations were more likely to have loss of MLH1/PMS2 proteins in their tumor, and patients with Lynch syndrome were more likely to have a family history of Lynch-associated cancers and/or a personal history of multiple primary cancers [8]. We hope that our new publication will help to provide further insight into a complex clinical situation.

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