Response to “histology of colorectal adenocarcinoma with double somatic mismatch-repair mutations is indistinguishable from those caused by lynch syndrome”

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

Dear Editor,

Colorectal tumours 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 tumours caused by Lynch Syndrome (LS) and tumours caused by sporadic dMMR exhibit similar pathological and molecular characteristics, such as tumour lymphocyte infiltration and right-sided colonic presentation [1,2].

The term “Lynch-like syndrome (LLS)” refers to tumours 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 UK, LLS patients and their first-degree relatives are eligible for 2 yearly colonoscopies as per LS guidelines [5], predicated on dMMR tumour tests alone, even without an identifiable germline MMR gene mutation. Hemminger et al [1] note that sequencing of tumour 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 amongst clinicians practising in the 21 regional clinical genetics departments within the UK 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 counsellors 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 centres: 21 clinical geneticists (of which 6 were lead cancer clinical geneticists), 26 genetic counsellors (of which 2 were lead genetic counsellors) and 2 clinical genetics specialist registrars. Of the respondents, 46 out of 49 reported they managed patients for MMR genetic testing on a monthly basis.

Twenty-one out of 49 of respondents knew the LLS definition as outlined above. Some clinicians noted 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 out of 8 cancer leads provided a correct definition ($\chi^2$ 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 (BSG) guidelines [5] as 3 out of 8 (37%) would recommend 2 yearly colonoscopy surveillance for this patient group. Only 12 out 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 out of 41 non cancer leads ($\chi^2$ test, $P = .0286$).

Clinicians with over 20 years’ experience were more likely to be aware of LLS definition (5 out of 10 respondents) and adhere to BSG 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, while 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 centres referred to 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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References


