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Implementing recommendations for routine mismatch repair (MMR) immunohistochemistry (IHC) testing of endometrial cancer and subsequent patient management

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ABSTRACT

Lynch syndrome is associated with an increased risk of cancer, including endometrial cancer. We audited the introduction of a nurse-led testing and management pathway for Lynch syndrome. All 191 patients diagnosed with endometrial cancer at Somerset NHS Foundation Trust between January 2022 and December 2023 were tested for mis-match repair (MMR) protein immunohistochemistry; germline testing was offered to all 13 who were eligible. Seven patients were diagnosed with Lynch syndrome; all were referred for bowel screening and Helicobacter pylori testing. Information about prophylactic aspirin recommendations was missing for 3/7 patients. We established an effective, nurse-led Lynch syndrome testing pathway, in line with national guidelines.

BACKGROUND

Lynch syndrome is an autosomal dominant inherited cancer syndrome, associated with an increased risk of cancer, including endometrial cancer, with a population incidence of 1/278.[1] Lynch syndrome is caused by pathogenic variants of the mismatch repair (MMR) system genes *MLH1*, *MSH2*, *MSH6* and *PMS2*, which prevent the correction of acquired errors during DNA synthesis and is associated with an increased risk of endometrial, bowel, ovarian, gastric and prostate cancer, among others (as reviewed in Georgiou *et al*[2]). Only about 5% of those with Lynch syndrome are aware of their diagnosis, so 95% of those with Lynch syndrome in the community are unaware, preventing opportunities for cascade testing of relatives, prevention, screening and early diagnosis.[3]

Routine testing of endometrial cancers for abnormal MMR immunohistochemistry (IHC) and genome testing in those at risk was recommended by the National Institute for Health and Care Improvement (NICE) in 2020 and introduced in 2021, following the British Association of Gynaecological Pathology (BAGP) recommendations and inclusion in the most recent update of the British Society of Gynaecological Cancer uterine cancer guidelines.[4 5]

METHODS

Setting

Somerset NHS Foundation Trust gynaecological cancer centre, taking referrals from the local population and that of our referral unit, covering a population of around 550 000 people, with double the national average of over 65s and over 80s.[6] The service had a nominated 'Lynch Champion' and Clinical Nurse Specialist (CNS) team training to perform 'mainstream' genetic testing for BRCA and Lynch testing. Those found to have a germline mutation were referred to the regional clinical genetics service for further advice and discussion of cascade testing.

Data

We designed a Microsoft Excel database[7] to prospectively monitor MMR testing, genetic counselling, results and preventative management of all patients diagnosed with endometrial cancer to facilitate implementation of NICE and BAGP guidance. Data included basic demographic data, MMR test results (including MLH-1 methylation) and genetic counselling referral. For those diagnosed with Lynch syndrome, we checked for bowel cancer surveillance programme referral, *Helicobacter pylori* testing and recommendations for aspirin prophylaxis. Data were analysed using Microsoft Excel and GraphPad Prism software.[8]

Intervention

With the introduction of NICE and BAGP guidance, we collected details for those diagnosed with endometrial cancer through our gynaecological oncology multidisciplinary

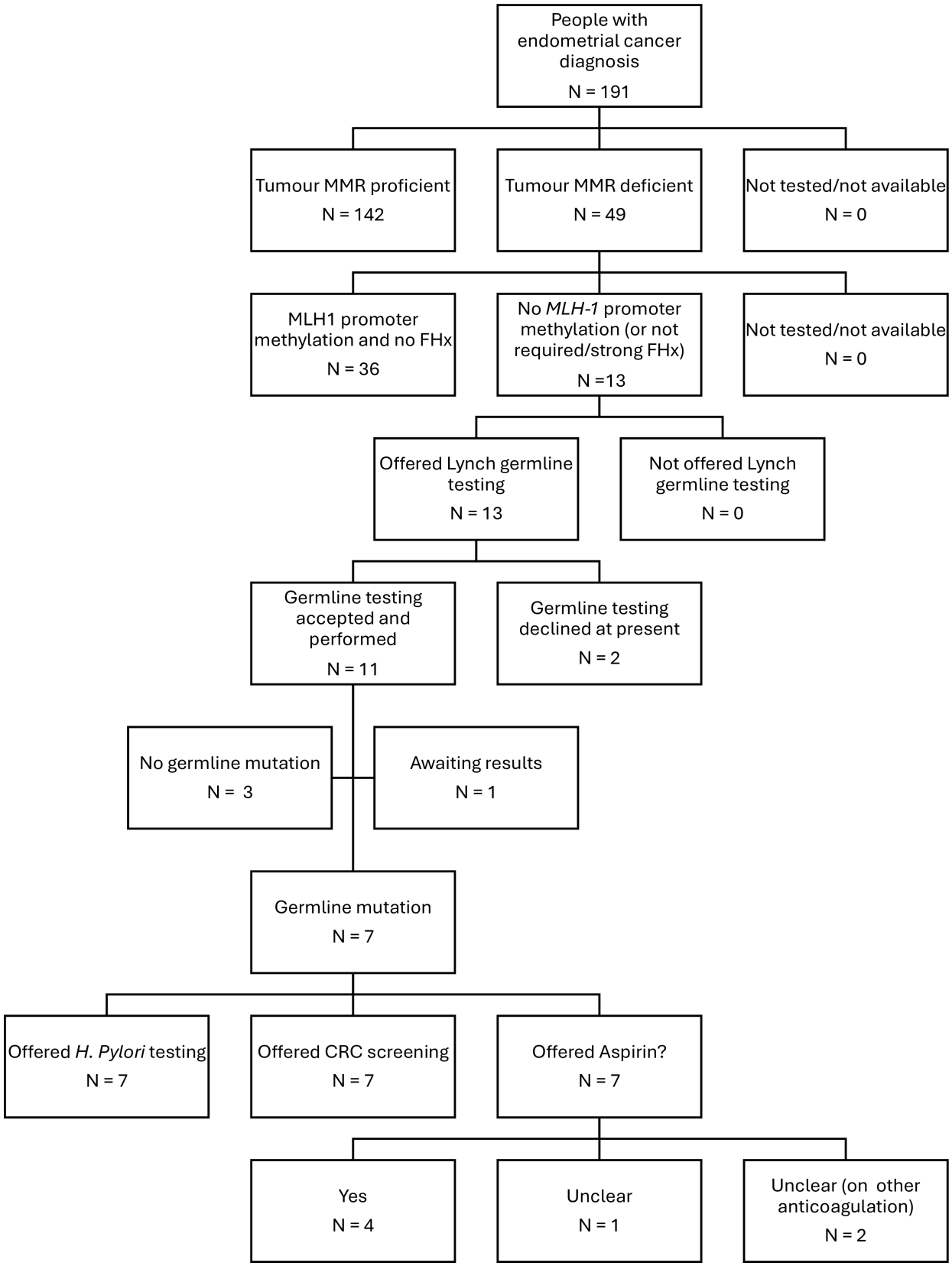

Figure 1 Flowchart showing numbers and outcomes of tumour testing for MMR protein immunohistochemistry, *MLH-1* gene promoter methylation testing (*MLH-1*), germline testing for Lynch syndrome and where preventative healthcare measures are offered. FHx, family history; *H. pylori, Helicobacter pylori*; MMR, mismatch repair; n, number of patients.

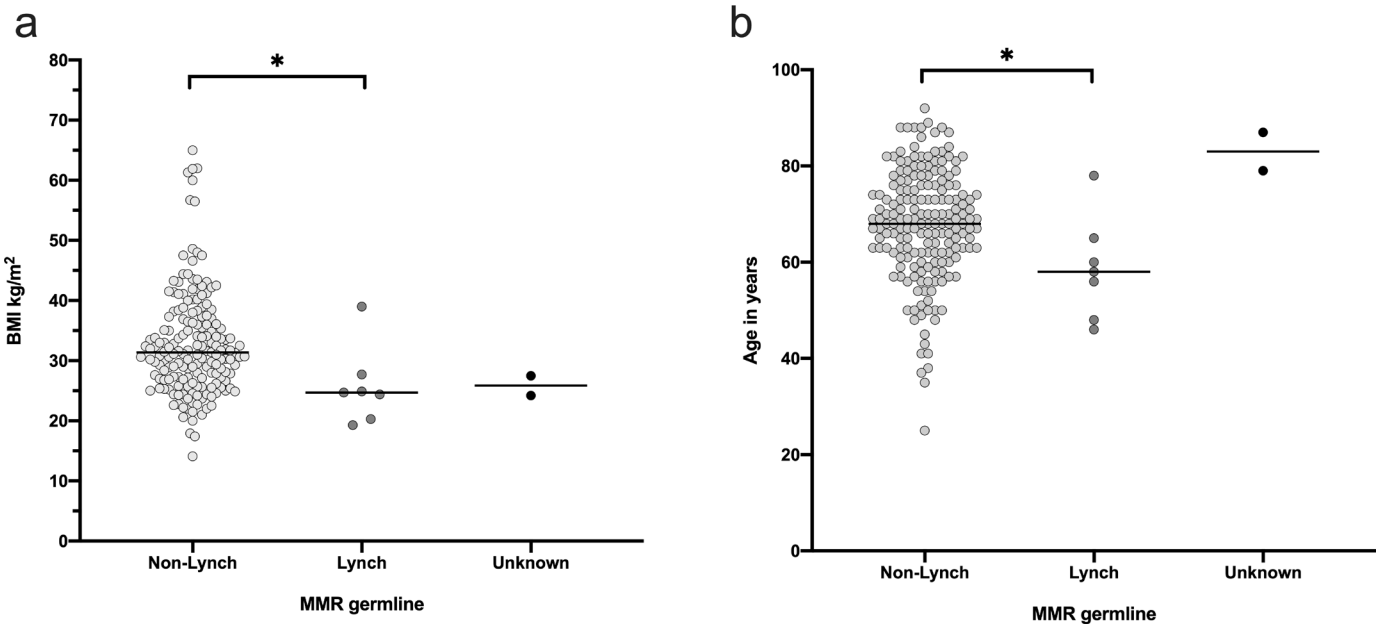

Figure 2 Relationship between diagnosis of Lynch syndrome and (A) BMI and (B) age in women diagnosed with endometrial cancer. BMI, body mass index; MMR, mismatch repair.

team (MDT) between January 2022 and December 2023. Prior to that, MMR testing had been performed routinely since early 2021, but we had not introduced a formal system for result and management tracking. The gynaecological oncology CNS team had an automatic alert and tick box to update the database on the weekly MDT patient list and liaised with the clinical genetics team. They discussed germline testing with those eligible, with clinical genetics nurses initially, as part of formal training to allow them to carry out mainstream testing. We tracked results sent for genetic testing on tumour and blood samples and subsequent risk reduction management. We also recorded body mass index (BMI), with an urgent referral pathway to our local bariatric service for those (with or without Lynch syndrome) in whom obesity was a factor in their disease aetiology.

The aim was for:

- All patients diagnosed with endometrial cancer have:
  - MMR IHC tumour testing.
  - *MLH-1* promoter methylation for those with MLH-1 and/or PMS-2 loss.
  - Offer germline testing to all with likely Lynch syndrome.
- Those with Lynch syndrome:
  - Referral for a 2-yearly colonoscopy from age 35 to 75 years and review at 75.
  - *H. pylori* testing and eradication treatment to reduce gastric cancer risk.
  - Chemoprevention is to be offered from age 25 to 65 (general practitioners to prescribe) with the following dose: 150 mg once daily if ≤70 kg or 300 mg once a day if >70 kg.

All patients were considered for hysterectomy and bilateral salpingo-oophorectomy for treatment of their endometrial cancer, so consideration of risk-reducing surgery was not required in this cohort.

RESULTS

191 women with endometrial cancer were identified, and all were tested for MMR IHC (figure 1). All 13 with MMR-deficient tumours without *MLH1* promoter hypermethylation and without a family history were offered germline testing; two declined, and one is awaiting review by clinical genetics. Seven women were diagnosed with Lynch syndrome (7/49 (14.3%) of those with MMR-deficient (MMRd) cancers and 7/191 (3.7%) of those with endometrial cancer). All were referred for bowel cancer surveillance and have had *H. pylori* testing; only four (57.1%) had evidence they were recommended to take aspirin, but we do not have a copy of the clinical genetics advice letter for three patients (all from our cancer unit), two of whom were on anticoagulation for other reasons, so may be contraindicated. A quarter (25.7%) of tumours were found to be MMRd. Those with MMR-proficient tumours had a BMI of 31.60 kg/m^2 versus 29.40 kg/m^2 for MMRd (p=0.138), and women with a diagnosis of Lynch syndrome versus those without had a lower BMI (median 24.7 kg/m^2 vs 31.35 kg/m^2; p=0.0156; figure 2a) and age (median 58 years vs 68 years; p=0.0139; figure 2b).

DISCUSSION

We achieved high compliance rates of tumour testing and onward referrals. Further management of Lynch syndrome was less consistent. This is significantly better than a recent national audit of MMR testing for 2095 patients with endometrial cancer, where only 96% had undergone MMR testing, 43% were referred for germline

testing, and the Lynch syndrome diagnosis rate was only 1%, suggesting many patients were undiagnosed as a result.[9] Our proactive approach, with a nominated 'Lynch Champion' and an engaged CNS team, who have trained to offer mainstream Lynch testing, has been extremely effective.

Limitations

We do not have data for rates of referrals or time to testing prior to the introduction of routine MMR tumour testing, which is a limitation of this study. However, our impression is that only a small percentage of those with endometrial cancer were offered onward referral to clinical genetics, and prior to the introduction of mainstream testing by our CNS team, wait times for germline testing were many months. National data demonstrate that prior to the introduction of NICE guidance,[4] 37% of centres were unaware of guidelines on Lynch syndrome testing, less than a third of centres were supportive of routine Lynch testing, and only one centre routinely performed tumour testing for MMR IHC.[10] We also did not formally explore patients' and healthcare professionals' perspectives as part of the implementation strategy. The introduction of the strategy, based on national guidelines,[4 5] was well supported by the team. Our previous 10-year follow-up of outcomes of patients with low-risk endometrial cancer had found that a few were diagnosed with a second malignancy and were not previously known to have Lynch syndrome.[11] Routine MMR IHC testing appeared to be appreciated by patients, since the majority could be reassured that there was no genetic link, so there were no implications for their families, although this was not formally assessed. Those who were found to have MMRd tumours were informed that this offered access to new treatment options, and the few found to have Lynch syndrome felt empowered by being able to take preventative action.

CONCLUSIONS

Patients with Lynch syndrome may benefit from multiprofessional teams, through a regional genetic MDT for further management, but these data demonstrate that much can be done at a local level. Mainstreaming of germline testing, offered by a CNS-delivered service within gynaecological oncology, requires some local resources, mainly time for training, but allows specialist clinical genetics resources to be used for more complex patients.

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