A mismatch in care: results of a United Kingdom-wide patient and clinician survey of gynaecological services for women with Lynch syndrome

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Objective To describe the current testing practice, referral pathways and gynaecological services available to women with Lynch syndrome (LS) in the UK.

Design Cross-sectional nationwide survey of gynaecological oncologists and women with LS.

Setting United Kingdom.

Methods Gynaecological oncologists were contacted directly. Women with LS were identified from national and regional clinical databases and the patient support group, Lynch syndrome UK.

Main outcome measures Gynaecological oncologists were asked to report rates of LS testing and current practice regarding risk-reducing strategies and gynaecological surveillance for women with LS. Women with LS were asked to describe their experiences of gynaecological care.

Results In total, 41 gynaecological oncologists and 298 women with LS responded to the survey. Of the gynaecological oncologists surveyed, 37% were unfamiliar with any clinical guidelines for the management of LS. Only 29% of gynaecological oncologists supported universal testing of endometrial cancer for LS; one centre routinely performed such testing. In all, 83% said they perform risk-reducing gynaecological surgery and 43% were aware of a local gynaecological surveillance service for women with LS. Of women with LS, most had undergone a hysterectomy (n = 191/64.1%), most frequently to reduce their gynaecological cancer risk (n = 86/45%). A total of 10% were initially referred for LS testing by their gynaecologist and 55% of those eligible regularly attended gynaecological surveillance; however, 62% wanted more regular surveillance. Regional variation was evident across all standards of care.

Conclusions There is widespread variation in the services offered to women with LS in the UK. As a community, gynaecological oncologists should move towards a nationally agreed provision of services.

Keywords Endometrial cancer, gynaecological surveillance, Lynch syndrome, ovarian cancer, risk-reducing surgery, screening.

Introduction

Lynch syndrome (LS) is an inherited cancer predisposition syndrome that is closely associated with an elevated risk of endometrial and ovarian cancer.1 LS arises from constitutional pathogenic variants affecting the mismatch repair (MMR) genes. It is arguably the most common cancer predisposition syndrome with an estimated population incidence of 1:300. This association increases to around 3% in women with endometrial cancer;2 however, the vast
majority of carriers are unaware that they have the condition. Given these estimates, international expert consensus groups recommend that all women with endometrial cancer are tested for LS. We have shown that women newly diagnosed with endometrial cancer want to be tested for LS and that such strategies are cost-effective. The National Institute for Health and Clinical Excellence (NICE) is currently considering the evidence for endorsing the universal screening of women with endometrial cancer for LS. This recommendation will lead to more diagnoses and, through cascade testing, more healthy LS carriers will be identified.

Identifying women with endometrial cancer who have LS is important, as it informs treatment, prognosis and enables lifelong surveillance for colorectal cancer, which has been shown to improve survival. However, for healthy female carriers of LS, diagnosis poses a clinical challenge. The most effective way to mitigate gynaecological cancer risk is through risk-reducing hysterectomy and bilateral salpingo-oophorectomy. Yet young women may wish to preserve their fertility and/or avoid surgical menopause, and others may not be suitable for surgery. These women may opt instead for risk-reducing interventions such as chemoprevention with hormone therapy or gynaecological surveillance, which aims to identify endometrial and ovarian cancers at an early or even pre-malignant stage.

There are limited data as to current clinical practice in the UK, making it unclear whether such testing and services already exist or need to be developed. This is critical information for current patients, clinicians who look after them and policy-makers who plan clinical services. The aim of this study was to describe the current testing practice, referral pathways utilised and gynaecological services available to women with LS in the UK.

Methods

Study design

The Uterine Protection in Lynch syndrome (UP) study was sponsored by the University of Manchester and approved by the West London Research Ethics Committee (16/LO/1788). We conducted a nationwide survey of gynaecological oncologists and women with known LS to develop an understanding of the current provision of gynaecological services to women with LS. There are no core outcome sets relevant to this area of research.

Gynaecological oncologists

We designed a bespoke survey with input from experts in the field, which used open and closed questions to capture information on level of training, place of work and workload, baseline knowledge of LS, current clinical practice and perceived areas of need. This questionnaire is available upon request. Gynaecological oncologists were identified through the list of gynaecological cancer centres held by the British Gynaecological Cancer Society and were contacted directly by email to participate in the survey. Data were collected and collated with the use of the secure online questionnaire service (http://selectsurvey.net). Clinicians were given the option of completing the survey over the telephone with a member of the research team if they preferred.

Women with LS

Women were identified through Lynch Syndrome UK (a patient advocacy group), the North West regional Lynch syndrome clinical database and utilisation of the National Institute for Health Research Rare Genetic Disease Consortium Agreement. Social media was also used to invite women to complete the survey. Data were collected via direct entry into a bespoke survey developed in partnership with an LS patient focus group facilitated by Lynch Syndrome UK. This questionnaire is available upon request. It was completed online or on a paper copy; paper copies were mailed to women or completed in person during clinical appointments. The use of a paper questionnaire enabled those without access to the internet to participate in the study. Regardless of the means of data collection, all data were collated on the secure online questionnaire service (http://selectsurvey.net). The questionnaire captured information on socio-demographics, health, health behaviours, method of LS diagnosis, cancer surveillance and the psychosocial impact of their LS diagnosis. Where extra information or clarity was needed, women were individually contacted via the contact details they had provided.

Patient and public involvement

This study was developed in partnership with Lynch Syndrome UK following a scoping exercise that revealed differences in gynaecological services offered to Lynch syndrome patients across the UK. The patient survey was co-designed, piloted and advertised by Lynch Syndrome UK through newsletters, blogs and their annual conferences in Bristol, Birmingham and Manchester (2016–2019). A link to the survey was posted on their website: www.lynch-syndrome-uk.org. The results will be presented at the next Lynch Syndrome UK conference and disseminated via their website. Danielle Sedgewick, co-author and patient representative, helped recruit gynaecological oncologists to the study and contributed to data analysis, manuscript preparation and dissemination of the results.

Data analysis

Data were downloaded from the secure online questionnaire into Microsoft EXCEL version 16.30 (Microsoft, California USA) for cleaning and analysis. Statistical analysis was performed using GRAPHPAD PRISM for MacOS...
version 8.3 (GraphPad Software, La Jolla, CA, USA). Data are presented as mean ± standard deviation or as a median with an interquartile range (IQR, 25th to 75th) depending on its Gaussian distribution. For categorical data, proportions and frequencies were given. Survey responses with more than 50% of their data missing were removed from the analysis. Where less than 50% of data were missing, answers were analysed individually. Where multiple respondents from the same institution participated, answers were checked for agreement. If the respondents agreed, percentages were presented following removal of the duplicate response. Where there was internal disagreement, the answer was coded as ‘not known’ for categorical variables or a mean was taken in the instance of a continuous variable. Clinicians were asked about their baseline knowledge regarding the clinical manifestation of LS, clinical guidelines pertaining to its management, and testing strategies. A crude baseline score was calculated by awarding one point for each correct answer with a maximum score of 15.

Results

Gynaecological oncologists

Between January and August 2019, we approached 52 gynaecological oncologists of whom 41 responded to the survey; three by telephone and 38 online. A full list of centres that responded are detailed in Table S1. There was representation from gynaecological oncologists working in England, Scotland, Wales and Northern Ireland. All respondents were subspeciality-trained in gynaecological oncology surgery and worked in centres with more than 50 new diagnoses of endometrial cancer per year.

Regarding baseline knowledge of LS, respondents had a mean score of 7.5 out of 15. All respondents stated that they had heard of LS and identified an association with colorectal and endometrial cancer; however, eight (20%) were unaware of the association between LS and ovarian cancer. Fifteen respondents (37%) were unfamiliar with any clinical guidelines describing the management of LS. Regarding immunohistochemistry staining for the screening of LS in gynaecological cancers, 22 (54%) said they could correctly interpret the results.

In total 14 (34%) gynaecological oncologists said they were supported by familial cancer multidisciplinary teams (MDT) outside of their regular cancer MDT meetings; these were all in large cities. Respondents thought referral for LS testing after an endometrial cancer diagnosis should come from the general gynaecological oncology MDT (n = 16) with the remaining respondents suggesting that referral could come from multiple sources.

Regarding the universal screening of endometrial cancer for LS, one centre said this was already routine practice. Of the remaining respondents, 11 (28%) strongly agreed or agreed with its adoption, 22 (55%) were neutral and 7 (18%) either disagreed or strongly disagreed with it. Reasons for disagreement were either a perceived lack of funding, too low incidence or concerns around increased distress for patients. Those who disagreed with universal screening of endometrial cancer for LS had the same baseline knowledge of LS as those who agreed with it; the mean score of those that agreed was 7.2 and of those who disagreed 6.3 (P = 0.12). Regarding the referral of woman for LS testing, in our cohort of 41 respondents, two gynaecological oncologists (5%) had never referred, nine (22%) had referred fewer than one per year and three (7%) had referred one per year. Seven gynaecological oncologists (17%) referred at least one woman every month for LS testing, with the remaining (n = 20/49%) referring a woman for LS testing around once every 6 months. Of note, there was no significant difference (P = 0.2) in the baseline knowledge score of those who referred rarely (<1 per 6 months) and those who referred regularly (>1 per 6 months). The reasons why women were referred for LS testing are detailed in Table S2. The number of endometrial cancer cases treated per year did not impact the regularity of referral for LS testing. None of the respondents thought invasive epithelial ovarian cancer should be routinely screened for LS, citing a perceived lack of cost-effectiveness as the main reason.

When asked about gynaecological services provided for women with LS, 34 of 41 gynaecological oncologists (83%) said they had performed at least one risk-reducing hysterectomy, but only 3 (7%) reported local guidance outlining the criteria on which this should be offered. Twenty-four gynaecological oncologists (59%) said they would perform risk-reducing hysterectomy for women with a strong family history of early onset endometrial and/or colorectal cancer without germline confirmation of LS. The investigations requested by gynaecological oncologists before undertaking risk-reducing hysterectomy are outlined in Table S3. Regarding gynaecological surveillance for women with LS with an intact uterus, 21 respondents were aware of local provision and 20 stated they did not know. Of the 21 who knew of local services, 18 reported that gynaecological surveillance was available to women with LS and 16 said it was performed within their institution. The gynaecological surveillance available is shown in Table 1.

Women with Lynch syndrome

The online survey was open from 7 November 2016 until 11 December 2019. After exclusions, 298 women were included in the study from a total of 523 respondents (Figure 1). Their demographics are shown in Table 2. The
The majority of respondents (\(n = 141/47.3\%\)) came from the North West region of England, in keeping with our recruitment method. These data are outlined in Table S4; importantly, there was only one respondent from Northern Ireland.

The locality of genetics services attended by respondents is shown in the Supplementary Material. The mean distance travelled by women to their genetics service was 22.6 miles (SD 22.59) with women in the Midlands on average having to travel the furthest (33.9 miles). The majority of respondents do not attend their genetic centres regularly (\(n = 199/66.8\%\)) with this being most commonly the case in the Midlands (\(n = 29/90\%\)). Of those women who did attend their genetics centres regularly, they did so annually, biennially or more frequently in 21, 42 and 36% of cases, respectively.

In total, 112 (37.6%) women were the index case of LS in their family. The diagnosis of LS in the respondent led to other family members undergoing testing in 244 women (81.9%). Most women were referred for LS testing due in part to their family history (\(n = 124/41.6\%\)). The other reasons for their referral are shown in Table S5. Importantly, 10% of women were initially referred for LS testing by their gynaecologist (Table S6).

A total of 261 women surveyed had been pregnant at least once and 173 women had had at least one live birth. The mean number of pregnancies reported was 6.4 (SD 7.2) and the mean number of live births was 1.57 (SD 1.2). Of those women who had been pregnant, 18 had used assisted reproduction technology, two of whom as a result of complications related to their LS. The majority of women did not start their families earlier due to their LS diagnosis (\(n = 169/97.7\%\)) and only 30 women said their LS diagnosis had directly influenced their child-bearing choices (Table S7).

The use of hormone-based contraception was common within our cohort (\(n = 241/80.9\%\)) with a mean duration of use of 8.9 years (SD 11.2): 120 women used the combined oral contraceptive pill, 13 women used the progesterone only pill, eight used an intra-uterine system and 43 used a combination of the progesterone-only pill and combined pill during their reproductive years. The remaining respondents (\(n = 57\)) reported the use of multiple forms of hormonal contraception. Only 13 (5.4%) and six (2.5%) of these 241 women said they had been offered a levonorgestrel intra-uterine system or oral hormone-based treatment for cancer risk reduction. Most of these women (\(n = 17\)) were based in Scotland or the North West of England.

### Table 1. Methods of gynaecological surveillance for women with Lynch syndrome described by gynaecological oncologists

| Investigation                      | Respondents n (%) |
|------------------------------------|-------------------|
| HE + CA125 + TVUSS + EB           | 3 (19)            |
| HE + CA125 + TVUSS + EB + Hys     | 5 (26)            |
| HE + TVUSS                        | 2 (12)            |
| TVUSS + EB                        | 5 (26)            |
| Serum CA125                       | 3 (16)            |
| Cervical screening                | 1 (2)             |

EB, endometrial biopsy; HE, history and examination; Hys, hysteroscopy; TVUSS, transvaginal ultrasound scan.
The majority of women respondents had undergone a hysterectomy \( (n = 191/64.1\%) \); the most common reason was to prevent cancer \( (n = 86/45\%) \). The mean age at which hysterectomy was performed was 46.3 years (SD 8.1). Most women had also undergone a bilateral salpingo-oophorectomy \( (n = 172/57.7\%) \) or unilateral salpingo-oophorectomy \( (n = 2/1.2\%) \) at the mean age of 47.4 years (SD 10.2). This was most commonly performed to prevent cancer \( (n = 111/64.5\%) \) and at the time of hysterectomy \( (n = 160/93\%) \) (Table S8). The region in which the respondent lived did not seem to impact rate of, reason for or age at surgery.

Fifty-nine (19.8\%) women reported they were currently undergoing regular surveillance for gynaecological cancer; when corrected for those who had received a hysterectomy, this represents 55\% \( (59/109) \) of women with an intact uterus. In our cohort, 204 screening episodes were reported. Seven women said they had received a complication from gynaecological surveillance, six reported severe pain and one reported an infection. Most surveillance was organised by a gynaecologist (49\%), the local genetics service (20\%) or the general practitioner (15\%). The mean number of times women reported having undergone some form of gynaecological surveillance was 0.74 (SD 2). Uptake of surveillance is outlined in Figure 2 and Table S9. The majority of women reported attending every year \( (n = 41/69.5\%) \) (Table S10 and S11). The most common method of surveillance was pelvic ultrasound \( (n = 25/42.4\%) \) and/or hysteroscopy \( (n = 33/56\%) \) (Tables S12 and S13). Of the 58 respondents who replied, 36 said their surveillance was performed by a gynaecologist and 22 by a nurse specialist. Nurse specialist-led services were more common in the North West and South West, being responsible for 41 and 75\% of patient-reported gynaecological surveillance episodes, respectively. Women were generally dissatisfied with the frequency of the gynaecological surveillance they received, with 62\% stating they would like more regular investigations. Only 1\% of women reported missing their appointments. Women preferred separating their gynaecological and colorectal surveillance, with 53 versus 25\% stating they would like different-day or same-day appointments, respectively. In total, respondents stated five cancers, and 27 polyps/pre-cancerous changes had been found by gynaecological surveillance. Of all respondents, 229 (77\%) said they felt gynaecological surveillance in LS was very important, with a further 29 (10\%) saying it was important. Only three (1\%) said it was unimportant.

**Discussion**

**Main findings**

Here, we present a comprehensive review of gynaecological services provided to women with LS in the UK. These data indicate that the provision of care is not uniform and varies between regions. We found that clinical practice and experience, as well as the resources available to support women with LS, vary considerably between clinician providers in the UK. From our data, several key themes are evident. First, there is a lack of a broad consensus among gynaecological oncologists regarding the universal screening of endometrial cancer for LS. Second, the majority of surgeons said they had performed risk-reducing surgery for women with LS; however, there was an absence of (or knowledge of) guidelines to enable an informed approach. Third, only half of gynaecological oncologists were aware of a gynaecological surveillance service for women with LS; the format of surveillance varied between clinicians and regions. Regarding women with LS, cascade testing was evident in our cohort, with 82\% of women reporting their diagnosis led to family members

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**Table 2. Demographics of women with LS included in the study**

| Age | 51 (SD 14.1) |
| --- | --- |

| Ethnicity |  |
| --- | --- |
| Arabic | 1 (0.34\%) |
| Asian subcontinent | 2 (0.67\%) |
| SE-Asian | 1 (0.34\%) |
| White British | 280 (93.96\%) |
| White other | 10 (3.36\%) |
| Did not answer | 3 (1.01\%) |

| Affected MMR gene |  |
| --- | --- |
| EPCAM | 7 (2.35\%) |
| MLH1 | 71 (23.83\%) |
| MSH2 | 108 (36.24\%) |
| MSH6 | 52 (17.45\%) |
| PMS2 | 19 (6.38\%) |
| Don’t know | 41 (13.76\%) |

| Country |  |
| --- | --- |
| England | 263 (88.26\%) |
| Northern Ireland | 1 (0.34\%) |
| Scotland | 23 (7.72\%) |
| Wales | 11 (3.69\%) |

| Setting |  |
| --- | --- |
| Urban | 205 (68.79\%) |
| Rural | 87 (29.19\%) |
| Not known | 6 (2.01\%) |

| Personal history of cancer |  |
| --- | --- |
| Yes | 162 (54.36\%) |
| No | 136 (45.64\%) |

| Site of cancer |  |
| --- | --- |
| Endometrial | 79 (26.51\%) |
| Colorectal | 76 (25.5\%) |
| Ovarian | 19 (6.38\%) |
| Skin | 27 (9.06\%) |
| Other | 28 (9.40\%) |
being tested. The majority of women had received gynaecological risk-reducing surgery and viewed gynaecological surveillance as very important, yet only half of those eligible reported attending such a programme.

Strengths and limitations
This study benefits from representation from a broad range of gynaecological cancer centres across the UK. In addition, we were able to curate data from a large number of women...
with LS residing in the UK, the largest such dataset to the authors’ knowledge. This enables direct comparison between clinician and patient perspectives and identifies regional variations. Potential limitations of our study include selection bias, as gynaecological oncologists and women were self-selecting. This is of particular concern due to the reliance on a patient support group for recruitment; those who replied may not represent the wider population. Women from the North West of England were also over-represented in our dataset. This was because women with LS were more easily identifiable and contactable due to the existence of a current and well-maintained LS clinical database. By presenting our data regionally and with summary statistics, we have tried to reduce any North West domination of our conclusions. Finally, we recognise that services will evolve, and that practices may have changed over the time of this study. It is therefore crucial to re-evaluate service provision in the future.

Interpretation and implications for clinical practice

Our data indicate inconsistency of care for women with LS in the UK. The universal screening of endometrial cancer for LS is supported by international consensus.4 It leads to around three in every 100 women with endometrial cancer being diagnosed with LS.2 Cascade testing of index cases leads to about another three LS diagnoses.13 Those found to have LS can be enrolled in colorectal cancer surveillance programmes which improve survival.14 Healthy female carriers can receive tailored family planning advice and gynaecological risk-reducing surgery.12 These benefits have led to NICE commissioning a Diagnostic Assessment Committee to establish the effectiveness and cost-effectiveness of the universal screening of women with endometrial cancer for LS. It is clear that this is what women want6 and, although resources may not yet be in place, it is vital that gynaecological oncologists are pro-active in establishing these services. Our data suggest that few strongly support this practice and very few have yet to offer it. A consequence of the universal screening of endometrial cancer for LS will be the identification of women with pathogenic variants of unknown significance. These pose a diagnostic and clinical dilemma and need expert and multidisciplinary interpretation.15 It is encouraging to see that 34% of gynaecological oncologists already benefit from genetic MDTs; however, this must become standard as we move towards universal screening.

With the universal screening of endometrial cancer for LS, cascade testing will diagnose more women with LS who have yet to have cancer. These women will look to gynaecologists for family planning advice, cancer risk-reducing strategies and interventions. However, very few of the women surveyed reported being offered hormonal treatments for cancer prophylaxis despite it being supported by the literature16 and expert international consensus.4 Risk-reducing surgery is performed widely within the UK and women reported high uptake. There was, however, variation in the timing of and the procedure performed, with surgeons recommending hysterectomy at different age cut-offs and having disparate views on ovarian conservation, as seen elsewhere.17 Again, this may indicate a need for increased awareness among gynaecological oncologists as to the current guidelines.

Gynaecological surveillance demonstrates variation in application and approach across the UK. It is clear from our data that women want to have access to this service and that gynaecological oncologists are generally in favour of it. However, the effectiveness and cost-effectiveness of surveillance remains unproven and its practice is therefore controversial.4 Some studies provide evidence for a potential stage shift in women with surveillance-detected cancers.18,19 Our data indicate its success in detecting pre-malignant disease in 27/32 women whose surveillance found pathology. While awaiting further high-quality research, clinicians should look to standardise and rationalise their approach to gynaecological surveillance to avoid any perception of a ‘postcode lottery’ in the UK. Of interest, where a service was led by a dedicated gynaecologist or nurse specialist, cancer surveillance was performed at more frequent intervals, had better uptake and took a more uniform methodology. This seems to support the adoption of a dedicated service led by a named clinician as opposed to a more ad hoc approach in which women are followed up in a general gynaecology service or rely on primary care for repeated referrals.

Conclusion

In conclusion, we present the most comprehensive survey of NHS gynaecological services for women with LS conducted to date. Our data indicate that the universal screening of women with endometrial cancer for LS is a long way from being implemented in the UK. Furthermore, there is limited knowledge by gynaecological oncologists of the current clinical guidelines. The infrastructure required to process variants of unknown significance is lacking. Women are receiving both risk-reducing surgery and gynaecological surveillance; however, their application varies by region and clinician. Importantly, where there is a dedicated healthcare professional responsible for the care of women with LS, services are more uniform and have better uptake. As we move to more widespread LS testing, gynaecologists will need to rationalise the services they offer women and as a community, we should move to nationally agreed standards of care.

Disclosure of interests

DGE reports personal fees from AstraZeneca and personal fees from Cerexis, outside the submitted work. The
remaining authors declare no potential conflicts of interest. Completed disclosure of interest forms are available to view online as supporting information.

**Contribution to authorship**
EJC was Principal Investigator for the study and is its guarantor. NAJR, DGE and EJC obtained funding for the study. NAJR and EJC designed the study. EJC and DGE supervised study execution. NAJR recruited women and NAJR, MN, DS and ST recruited surgeons to the study. NAJR, MN, DS and ST analysed the results. NAJR, MN, DGE and EJC interpreted the data. NAJR and EJC wrote the manuscript. All authors provided critical comment, edited the manuscript and approved its final version.

**Details of ethics approval**
The Uterine Protection in Lynch syndrome (UP) study was sponsored by the University of Manchester and approved by the West London Research Ethics Committee (16/LO/1788) on 6 October 2016.

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**Supporting Information**
Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Cancer centres that responded to the survey.

**Table S2.** Reasons why gynaecological oncologists refer patients for Lynch syndrome testing.

**Table S3.** Investigations gynaecological oncologists request before performing a risk-reducing hysterectomy for Lynch syndrome.

**Table S4.** Regional breakdown of Lynch syndrome respondents.

**Table S5.** A breakdown of the respondents’ reasons for Lynch syndrome testing.

**Table S6.** A breakdown of the respondents’ initial sources of referral for Lynch syndrome testing.

**Table S7.** A breakdown of the respondents’ reasons as to why they could not have children/their ideal number of children as a result of Lynch syndrome-related issues.

**Table S8.** A breakdown of the respondents’ reasons for hysterectomy and oophorectomy and the age at which their hysterectomy was performed.

**Table S9.** A breakdown of the respondents’ uptake of gynaecological surveillance by region.

**Table S10.** Time interval between gynaecological surveillance episodes.

**Table S11.** Time interval between gynaecological surveillance episodes by regional genetics centre.

**Table S12.** Reported methods of gynaecological surveillance.

**Table S13.** Reported methods of gynaecological surveillance by region.

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