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REVIEW

A Focused Clinical Review of Lynch Syndrome

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Abstract: Lynch syndrome (LS) is an autosomal dominant condition that increases an individual's risk of a constellation of cancers. LS is defined when an individual has inherited pathogenic variants in the mismatch repair genes. Currently, most people with LS are undiagnosed. Early detection of LS is vital as those with LS can be enrolled in cancer reduction strategies through chemoprophylaxis, risk reducing surgery and cancer surveillance. However, these interventions are often invasive and require refinement. Furthermore, not all LS associated cancers are currently amenable to surveillance. Historically only those with a strong family history suggestive of LS were offered testing; this has proved far too restrictive. New criteria for testing have recently been introduced including the universal screening for LS in associated cancers. This has increased the number of people being diagnosed with LS but has also brought about unique challenges such as when to consent for germline testing and questions over how and who should carry out the consent. The results of germline testing for LS can be complicated and the diagnostic pathway is not always clear. Furthermore, by testing only those with cancer for LS we fail to identify these individuals before they develop potentially fatal pathology. This review will outline these challenges and explore solutions. Furthermore, we consider the potential future of LS care and the related treatments and interventions which are the current focus of research.

Keywords: genetic counselling, Lynch syndrome, mainstreaming

Introduction

Lynch syndrome (LS) is the most common inherited cancer predisposition syndrome; it is thought to affect over 1:280 people.[1] The condition arises due to germline pathogenic variants within the mismatch repair genes, namely *MLH1, MSH2* (*EPCAM), MSH6* and *PMS2* leading to a lifelong haploinsufficiency. After a somatic second hit, individuals with LS develop a defective DNA repair machinery which decreases DNA fidelity during cellular replication. This machinery, known as the mismatch repair system, is shown as a schema in Figure 1. Typically, in LS numerous insertion, deletion, and mis-incorporation mutations occur with a propensity for such errors in the microsatellites of the DNA.[2] Microsatellites are tandem repeats of DNA in which sequences of bases reoccur such as AAAA or TCTCTC. Without a functional mismatch repair these microsatellites corrupt which in turn has a deleterious effect on protein function and cellular metabolism. As these errors accumulate over time, somatic mutations arise that can lead to carcinogenesis.[3]

These molecular changes enable clinicians to offer accurate tumour-based screening for LS and definitive germline testing to confirm LS. Immunohistochemistry is a technology that uses antibodies to bind and stain specific proteins. However, if a protein is misshapen or absent the antibody will fail to bind and the stain is lost.[4] This enables pathologists to quickly screen cancers for mismatch repair deficiency (MMRd) as they will fail to stain. As a specific protein will be absent, immunohistochemistry can also help clinicians identify the gene that is likely to contain the pathogenic variant. In addition, microsatellite instability is detectable by polymerase-chain-reaction based analysis. This therefore can be used to screen cancers for LS. Unlike immunohistochemistry, microsatellite instability does not indicate which gene could be affected. It has also been shown that the accuracy of microsatellite instability is reliable in colorectal cancer; it may be less accurate in endometrial cancer.[5] Therefore, in endometrial cancer immunohistochemistry is preferentially used. Both methods do not diagnose LS as they are performed on the tumour and so can only speak to the tumours' DNA. Therefore,

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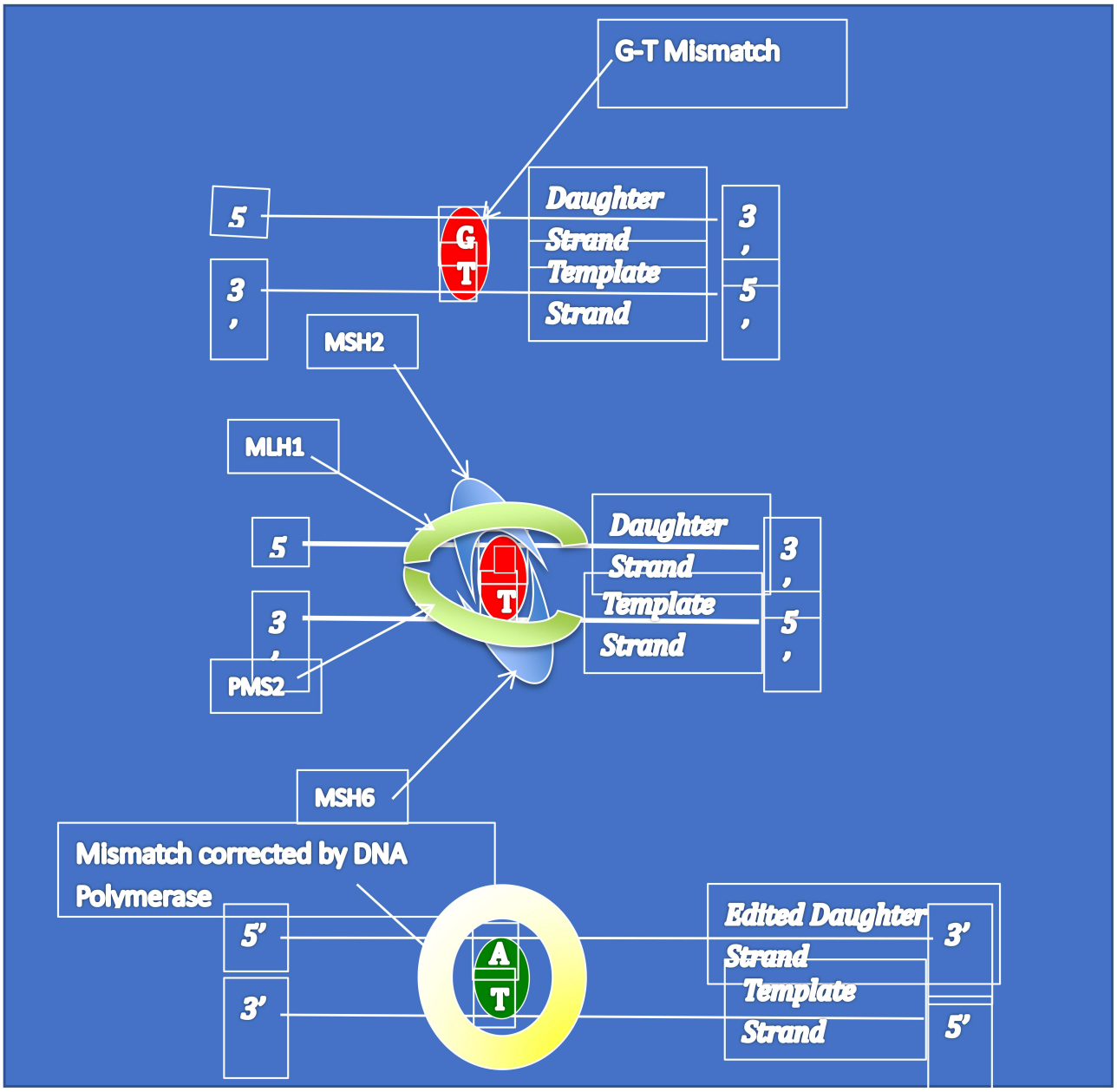

Figure 1 The MMR system. This graphic, in a simplified manor, explains the mechanism of the mismatch repair system. A mismatch repair error occurs, in this case a G-T base pairing. This is identified by the dimer of proteins MSH2/MSH6 identifies the error and recruits MLH1/PMS2 to excise the error. This allows DNA polymerase to insert the correct base leading to a A-T pairing.

germline testing is needed to confirm LS. The number of people sent for germline testing can be reduced by reflex testing for *MLH1* hypermethylation or in colorectal cancer *BRAF V600E* testing.[6] If either *MLH1* hypermethylation of a *BRAF V600E* mutation is found, the individual is very unlikely to have LS.

Diagnosing LS is of clinical importance. Those affected by LS are at an increased lifetime risk of a constellation of cancers. The most closely associated are cancers of the colorectum, endometrium, ovaries, and urinary tract.[7] However, these cancers are in part avoidable with the application of colonoscopic surveillance, aspirin chemoprophylaxis, risk reducing surgery and lifestyle modifications.[8,9] Once correctly diagnosed, those with LS can be enrolled in the risk reducing strategies and cascade testing of their relatives can begin. Cascade testing enables clinicians to find more LS carriers within a family before they develop cancer.[10] Those found to have LS can also be offered risk reducing interventions with the aim of preventing them from ever developing a potentially fatal cancer.

However, which cancers should be screened for LS, who should be offered LS testing, how patients should be counselled for LS testing, what should and can be done to reduce cancer risk in LS are all still, to some degree, matters for debate. In this article, these questions will be discussed with a summary of the current evidence base.

Diagnostic vs Predictive Testing vs Prenatal Diagnosis

Genetic testing processes vary considerably depending on health history and life stage of the individual. With a wide range of risk management and screening options available, identification of LS carriers has been on the forefront of several health systems through universal screening.[11] LS genetic testing can be available in diagnostic, predictive and reproductive stage. In individuals with prior history of LS-related cancer, a test is diagnostic and is thought to help explain the cause of their disease. In the United Kingdom, such tests are often reflex and offered to all patients who have colorectal and endometrial carcinoma. These are often available through secondary care where results are used for ongoing patient management as well as for future health planning.

Cascade Screening

Economically, viability of universal screening programmes for LS relies on cascade screening, which is the onward testing of 1st degree relatives of newly diagnosed individuals.[12–15] It is expected that unaffected family members who are informed of their positive carrier status through cascade genetic testing (also referred to as pre-symptomatic or predictive testing), will engage in risk reducing activities, uptake screening and risk management options and will have a reduced risk of cancer overall or an earlier stage at diagnosis. Menko et al and Griffin et al found that uptake of cascade testing was not very high in LS families; partly due to gender barriers and inadequate patient education.[16,17] As such, one needs to place a lot of attention on factors that facilitate cascade screening; patient awareness, family communication, health system accessibility and national standardisation.[13] A more novel suggestion is the health system-led contact of relatives (with patient consent) that would complement the current traditional method of patient-led dissemination.[17,18]

Predictive Testing

In healthy, unaffected adults, a genetic test is predictive as it is performed to predict whether an individual has an increased risk of LS-related cancers. A predictive test for late onset cancer susceptibilities such as LS has more psychosocial and practical implications (such as life insurance) hence the counselling approach needs more consideration in this context.[19,20] Counselees need to be informed, supported, and offered an assessment by the genetics clinician to ensure they would be well equipped to manage the psychosocial impact and distress linked with an unfavourable result before they consent to a genetic test. Godino et al suggest a multistep approach enabling communication, decision making and action at appropriate timepoints.[21] Given LS is a late onset disease predictive testing in childhood is not available, although families are encouraged to discuss the familial LS status with their children throughout their lives.[11]

Reproductive Options

Prenatal diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD) have broadly been available for LS patients. Chorionic Villus Sampling and Amniocentesis are well established techniques that assist the molecular diagnosis of a foetus, where pregnant individuals are informed of the pregnancy status to make an informed decision on whether to continue with a pregnancy. These have risks to the pregnancy and are known to have limitations in practice (difficult to detect/establish level of mosaicism/sample quality dependent). A further challenge with PND comes with the outcomes of pregnancies identified as positive carriers of genetic disease when parents decide to continue with pregnancy. This is ethically challenging as no individual should have a late onset pre-symptomatic test without their involvement and consent (https://www.rcplondon.ac.uk/file/13314/download). Women and couples undergoing invasive prenatal testing should be offered genetic counselling to help understand the risks, weigh their options, and plan their decisions.

PGD has been available for the last few decades and has supported many individuals with hereditary conditions to conceive an unaffected embryo. This service is offered to couples with a serious hereditary condition; in the United Kingdom LS is licenced for PGD. Although these methods are widely available and offered by healthcare professionals in the context of childhood disease or early onset cancer susceptibility; it is clear that healthcare professionals feel it is

less acceptable to offer these options to families with late onset conditions where some form of prevention/management is available.[22] The increasing availability of risk management options for LS as well as lower penetrance (especially when associated with variants in *PMS2*), have led to ongoing consultations in United Kingdom as to if PND and PGD should be offered. These definitions are summarised in Table 1.

When to Test for Lynch Syndrome

Population Level Testing

LS is thought to affect up to 1:280 people, although large biobank studies put this figure closer to 1:400.[23] Around 95% of those with LS are unaware of their diagnosis.[24] Indeed, with a prevalence of 1:400 we would expect around 200,000 people in the United Kingdom to be affected by LS, however only 10,000 tests for LS have been recorded by NHS digital. With so many undiagnosed and at risk of developing cancer, an argument has been made to introduce population level testing in which there are no restrictions are applied on LS testing.[25] In this scenario, everyone would be eligible to have LS testing; this would either be on a volunteered basis or by a governmental screening program such as the blood spot test to screen for metabolic diseases of the new born.[26] Population level testing has been shown to be cost-effective for high risk ovarian cancer genes.[27] In addition, testing 30yr olds for LS could also be cost-effective.[28]

To date, no country offers state funded population level LS testing. Population-based germline testing has already been carried out in the confines of research programmes.[29] Furthermore, private companies offer LS testing to those who can pay for it without any pre-selection. Therefore, there exists a degree of inequality to access LS testing; those who can pay or those who are enrolled into research can be tested, whereas those who are not can only access LS testing if they meet prespecified criteria.

The cited barriers to population-level LS testing are around informed consent and resource allocation.[30,31] The current model of consent for germline testing involves a lengthy discussion with genetics professional before the test is undertaken. If this was to be rolled out across a population, genetics services would be overwhelmed. In addition, laboratory capacity is limited. With population level testing, demand would increase beyond current capacity leading to systemic issues.[32] Therefore, for the time being, population-level testing for LS remains limited to research projects or to those who pay.

Cancer Testing

LS is closely associated with an increased risk of certain cancers, namely colorectal and endometrial cancer.[33] Therefore, colorectal and endometrial cancer populations are enriched, when compared to the general population, for LS. As such, there is a clear argument to screen those with endometrial and colorectal cancer for LS as has become common practice in North America and Europe.[1] Around 3% of colorectal[34] and endometrial[5] cancers are caused by LS. It has been demonstrated that the universal screening in these groups is cost-effective.[35–37] Therefore, there has been a move away for selected screening, such as based on age or family history, in these cancers. Indeed, universal screening is recommended by international guidelines.[8,9]

LS is also associated with ovarian cancers, however only around 1% of ovarian cancers are associated with LS.[38] Therefore, currently it is not clear if the universal screening of ovarian cancer is cost-effective. Selective screening of

Table 1 Definitions of Different Forms of Genetic Testing

Diagnostic test	Testing of patients germline following abnormal MMR on IHC or MSI (on a tumour sample). Also offered to individuals with history of LS tumours when there is a known pathogenic variant in family.
Predictive/Asymptomatic test (or cascade test)	Testing of asymptomatic adult relatives of a proband, to identify whether they have inherited the pathogenic variant in their family.
Prenatal test	Testing of a pregnancy to identify whether fetus has the familial pathogenic variant.
Preimplantation Genetic Diagnosis	Testing of cells of an early embryo created via IVF for a familial genetic condition. Unaffected embryos are implanted.

ovarian cancer, namely those of an endometrioid histotype or in women less than 50 years old, has been recommended by international guidelines.[8] There is no clear consensus as to if other cancers should also be screened for LS, as again the prevalence of LS is thought to be low outside of colorectal and endometrial cancers.

Screening cancer populations for LS has an innate disadvantage: the individual must have developed a cancer before they are tested. This is counterintuitive as the reason to diagnose LS is to try and prevent cancers. For endometrial cancers an argument can be made. Women often survive endometrial cancer.[39] For women with LS, endometrial cancers are often the sentinel cancer that they develop.[40] Therefore, there is a diagnostic opportunity as they can be diagnosed with LS during their endometrial cancer treatment, go on to survive, and be enrolled in preventative measures that would decrease their risk of a potentially fatal colorectal cancer. Sadly, the universal screening of colorectal cancer is unlikely to have a significant impact on the index case. Yet it does provide the opportunity to enable cascade testing which can in turn find those relatives who are LS carriers before they develop a cancer. On average around 3 LS carriers are found for each index case.[10] Therefore, cancer screening can still identify LS carriers who can benefit from intervention.

Criterion Based Testing

Several different score systems exist that can be used to identify individuals at high risk of being carriers for LS. These can be used in either the general population or to pre-select those with cancers associated with LS. Indeed, it was on the basis of family linage that LS was first described by Aldred Warthin and later Henry Lynch.[41] The Bethesda[42] and Amsterdam[43] criteria were devised in the 1990s as a means to identify those thought to have LS, and as the technology developed, identify those for germline testing. However, these scores suffer from a low sensitivity especially for pathogenic variant carriers of *MSH6* and *PMS*2.[44] More modern criteria have tried to address this such as PREMM5,[45] MMRpredict[46] and MMMRpro.[47] These scores report reasonable sensitives but still fail to reliably identify *MSH6* and *PMS2* pathogenic variant carriers.[1] With these caveats, they can be deployed as to help identify those in the general population who should go on to have germline testing.

Mainstreaming v Traditional Model

As molecular biomarkers become a routine part of the diagnostic work up for the colorectal and endometrial cancers the clinical community is looking at the feasibility and utility of mainstreaming genetic testing in these tumour sites.

The term mainstreaming in the genetic testing describes pre-test counselling and consent process being undertaken by a member of the clinical cancer team caring for the patient instead of referring to a clinical genetics professional. This mainstream approach saves time, is fiscally advantageous and importantly provides continuity of knowledge for both clinician and patient.

The concept of mainstreaming is not new, with the advent of targeted therapies, for example poly(ADP-ribose) polymerase (PARP) inhibitors being used in ovarian cancers, the genetic testing for *BRCA1* & *BRCA2* being a necessary companion test to inform prescribing. A study looking at implementing rapid, robust, cost-effective, patient centred and routine genetic testing in ovarian cancer patients was undertaken by George et al with excellent outcomes demonstrating transferability and scalability to other tumour sites and cancer services.[48]

Since this seminal study in ovarian cancer, the principles have been reproduced with similar positive outcomes,[49] with transferability and scalability in breast and *BRCA* testing[50] to the endometrial pathway[10] looking at Lynch testing, with a systematic review addressing the feasibility of implementing mainstreaming germline genetic testing in cancer care[51] supporting these outcomes.

There are several important elements to achieving a robust mainstreaming service:

- genomic literacy of the clinical team enabled by bespoke education/training programmes.
- job planning to accommodate the mainstreaming consulting time.
- pathway mapping of mainstream service, to include timing, return of results, collaboration with clinical genetics.

In the United Kingdom, these issues are being addressed with the advent of the Genomic Medicine Service Alliances. This organisation is charged, amongst other things, to bring mainstreaming across the National Health Service (NHS) in England.

As genomics now moves from niche to necessity with the nursing and midwifery colleges recognising the importance of genomic literacy in the workforce, cancer nurse specialists are now well placed to take up mainstreaming as part of their role. This will need workforce task analysis and role description to include genomic literacy in the skill set and is being looked at by MacMillan and the leadership of the National Health Service to support this role evolution. Third sector colleagues Macmillan have already undertaken a survey review of cancer nurse specialists attitudes and needs (to include capacity and knowledge current limitations) in order to safely practice and offer genomic support to their patients, we anticipate publication in 2023. The education piece is superbly supported by the Lynch Transformation Programme, Health Education England and The Cancer Alliances have been afforded funding to put Lynch Nurse Specialists in place to across the health service to ensure equity of rollout of mainstreaming across the country, working closely with the national Lynch transformation team.

In summary, the concept of mainstreaming "right test, right place, right time" is proven. Now is the right time for the clinical community to move at a faster pace to implement as the tools in the form of education, training and workforce planning have arrived, with importantly funding support.

Diagnostic Genetic Testing

Diagnostic testing in LS is the genetic testing performed on an individual with history of cancer to confirm or exclude LS. Diagnostic genetic testing is now mainstreamed in routine oncology clinics. The Health Education England's Genomic Education Program (https://www.genomicseducation.hee.nhs.uk) developed competency frameworks to facilitate genomic testing and communicating germline genomic results that can support health care professionals to gain the skills necessary to provide genomic testing. It's important to take into consideration that the frameworks should be interpret in the context in which is going to be used, and not all competencies will be applicable to all situations. In

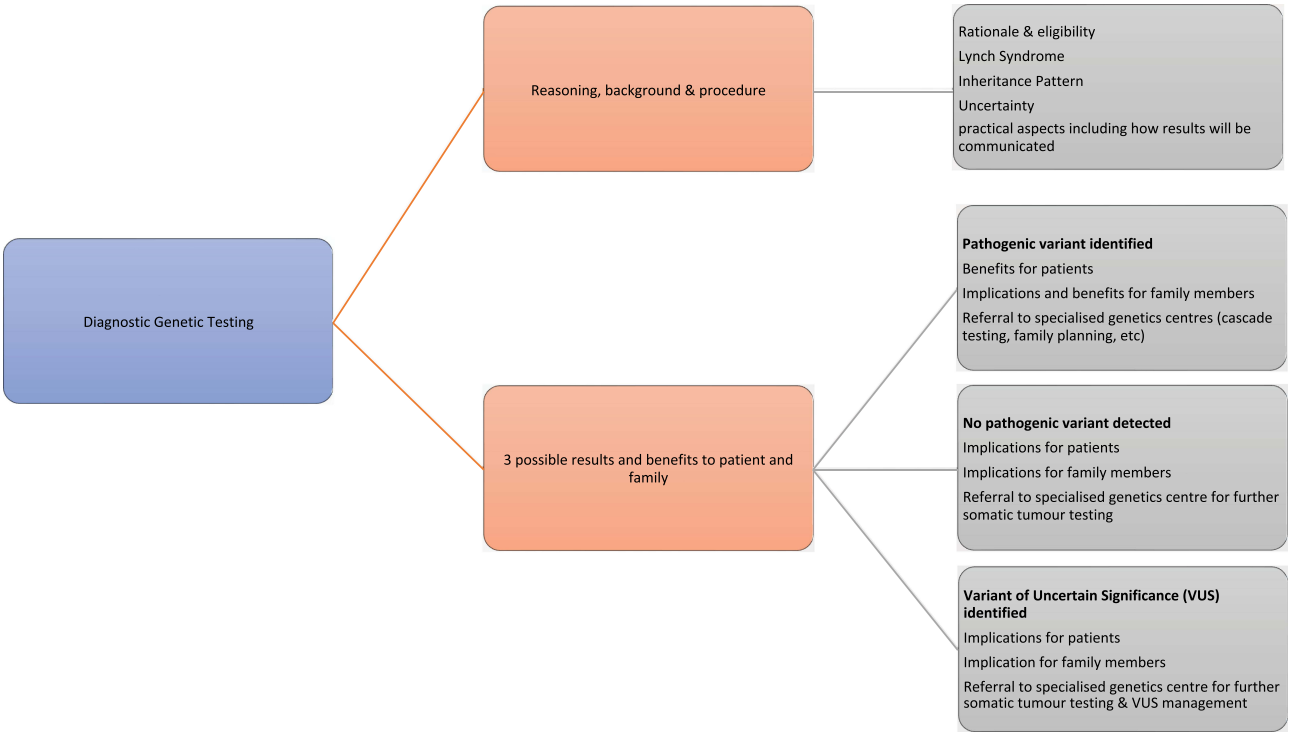

Figure 2 A flow diagram illustrating specific aspects of diagnostic genetic testing for LS not covered by current Health Education England's Genomic Education Program (GEP, 2022) competency frameworks.

addition, it acknowledges that healthcare professionals might already be competent in some of the themes. These frameworks are not intended to be used as an assessment tool, but rather as a resource to support learning and practice. Figure 2 illustrates some of the specific aspects of diagnostic genetic testing for LS not covered by these frameworks.

In combination with the above-mentioned frameworks, there are a wide variety of resources produced as part of the National Lynch Syndrome Project that describes the genomic test consultation, benefits to patients and their family members and the rationale for referring all patients, regardless of their genetic result, to specialised genetic centres. It also explains the responsibilities of specialised genetic centres following results, such as cascade testing should a pathogenic variant be identified, or further somatic tumour testing when a pathogenic variant has not been detected to clarify if the patient has LS.[52] Patients in which LS cannot be ruled out are classified as "Lynch-like syndrome". These patients and their first-degree relatives are eligible for 2 yearly colonoscopic surveillance from the age of 25.[53]

What to Do About the Variant of Uncertain Significance

There are three potential results from diagnostic testing for LS, the identification of a pathogenic variant in an MMR gene (the definition of a diagnosis of LS), no variant detected, or a variant of uncertain significance (VUS). With a VUS the clinical significance of a genetic variant is uncertain, it may represent healthy or disease-associated variation in an MMR gene. With the advent of next generation sequencing platforms high volume genomic analysis has resulted in large scale variant identification which need to be catalogued and categorised systematically. VUS results are dealt with by specialists who will assign the degree of concern for that specific VUS.

Identified pathogenic variants and VUSs in MMR genes should be submitted to the international variant registry supported by InSIGHT (https://www.insight-group.org/variants/databases/), where such variants are curated, may be assigned pathogenicity, and therefore this database may inform interpretation of results.[54] In 2015, the American College of Medical Genetics and Genomics (ACMG) has produced a guideline to support DNA sequence variant interpretation which is widely used in clinical practice worldwide - this utilises clinical information including evidence of tumour MMR status, and segregation within families.[55] We would also recommend that diagnostic services maintain a registry of variants which they might clinically review at regular intervals by working with variant review boards. Coordinated national approaches such as the Cancer Variant Interpretation Group (https://canvaruk.org) in the United Kingdom may facilitate systematic variant review by linking genomics laboratories to multidisciplinary clinical networks.

Barriers to Lynch Syndrome Testing

Given the benefits to discovering that someone has LS, not just for the patient but for their immediate family members, it is expected that most people would welcome genetic testing for LS. In fact, there is good number of studies that suggest that hypothetically there is a high interest in finding out this information.[56,57] By contract, there are good reports that show that there is a high number of people that decline testing.[58] Few studies to date have looked at why some people decline genetic testing. Keogh and her team conducted a couple of qualitative studies looking at this phenomenon in Austria. In the final study conducted in 2017 the team divided the people who declined genetic testing into four groups: people who are uniformed, who have a weak intention, who conditionally decline, and unconditionally decline.[59]

Poor knowledge can be a barrier that can be overcome if identified. The uninformed participants declined due to not being aware that they were eligible for genetic testing or misinterpreting the information that has been given to them. An important factor affecting their risk perception and decision making was the belief their family's cancers have been caused by lifestyle factors, and the information or the test was inappropriate for them. Following the clarification and education provided as part of the research they changed their mind.

There was a second group that was passive or unsure and delayed their result. Barriers in this group were poor knowledge, and fear of changes in their cancer surveillance or insurance discrimination. This second group was classified as having a "weak intention" and could be divided into the level of knowledge they have. People with partial knowledge were undecided because they misunderstood their risk of cancer, believed that the result was not applicable to them at that time and could be delayed. People with fair knowledge were already under colonoscopic surveillance and were afraid of losing their cancer screening or were concerned about insurance discrimination.

The third group called "Conditional decliners" was firm about declining; however, they kept the option open to find out the result in the future. The main barriers in this group were their inability to see the value of genetic testing as if the result wouldn't alter anything, and only cause anxiety. In addition to this, fears found in previous group such as fear of losing their cancer surveillance or insurance discrimination was more evident. Their levels of knowledge range from partial to complete and stated that they would change their mind if the results provide clear benefits, for instance, remove concerns about insurance, if there any signs of cancer, or their children wanted the results. This group was older and was already under surveillance.

The fourth and last group called "unconditional decliners" was firm about declining and would be unlikely that they change their mind in the future. Barriers include the same as previous group, but their belief and confidence was stronger. They expressed a strong need to avoid the anxiety related to a genetic diagnosis. Some talked about their experiences of seeing other family members going through cancer and found the thought of going through it unbearable. People in this group was also under colonoscopic surveillance.

We find that the barriers found in these studies are also pertinent in the United Kingdom and provide important information to guide genetic counselling conversations.[59] The consultation needs to address misconceptions and concerns so patients can make informed decisions. Benefits of testing need to be made clear to patients. For the people who are already under surveillance, the additional surveillance offered as part of LS diagnosis needs to be highlighted, as well as contraindications for people who no longer need it. Lastly, addressing anxieties and fears or living with LS as well as exploring significant family history of cancer, and providing emotional support will be key. The essential information to share with a patient before offering genetic testing is outlined in Box 1.

Figure 3 illustrates some of the more salient barriers and facilitators for germline genetic testing. Some are unique to predictive genetic testing on asymptomatic patients that are not applicable to mainstreaming. However, they should be taken into consideration when offering germline genetic testing as they affect risk-perception and decision making.[59] In addition to these barriers, there are other external barriers that can affect decision making, like for instance family communication and healthcare barriers (eg, lack of specialised services and variability in surveillance packages) that can exacerbate uncertainty and anxiety[13,60] and should be explored during the consultation. On the other hand, other external facilitators to testing are the work undertaken by the Genomic Medicine Service Alliances and the National Lynch syndrome project in mainstreaming, education, and reduction in variation of care.

Cancer Risk Reduction

Colorectal Cancer

Colonoscopy

The cumulative lifetime incidence of CRC in people with LS is gene-specific ranging between 14% in *PMS2* carriers and over 40% in *MLH1* or *MSH2* carriers, considerably higher than average population risk.[5] LS patients have an accelerated pathway to carcinogenesis compared to the general population.[14] Colonoscopy reduces the incidence and mortality associated with CRC in LS.[15] As CRC risk is gene-specific, with earlier age diagnoses with higher risk genotypes, colorectal surveillance with routine colonoscopy every 2 years should start at 25 years for *MLH1* and *MSH2* carriers or at 35 years for *MSH6* and *PMS2* gene carriers.[53,61]

Box 1 Essential Information to Share with Patients Before Offering a Diagnostic Test

- What is Lynch Syndrome?
- Inheritance Pattern
- Uncertainty (genetic tests cannot identify all causes of hereditary cancer, uncertain results may occur)
- Practical aspects including how results will be communicated with patient
- Implication for family members and family planning, advice for patient to talk to family members about test
- Screening/management plan may change for patient and family pending results
- If patient has VUS or pathogenic variant, explain that you will need to refer to specialised genetics centre for further somatic tumour testing & VUS management or for pathogenic variant management/cascade testing

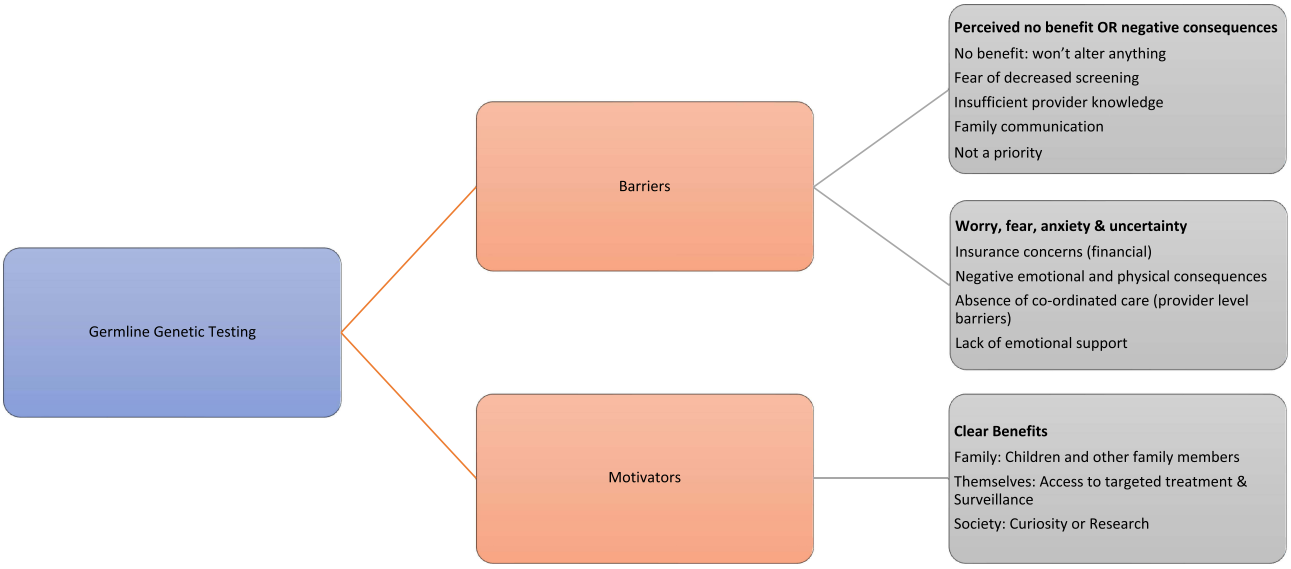

Figure 3 An illustration of barriers and facilitators for germline genetic testing.

Despite adherence to appropriate, good quality endoscopic surveillance there are still high rates of interval CRC in LS. Although the prevalence of colonic polyps in patients with LS seems may not be higher than in the general population, the dMMR pathway to CRC seems to be accelerated at 3–3.5 years compared to 10–15 years in sporadic CRCs.[62] Ahadova et al recently described a "3 pathways" model in LS CRCl carcinogenesis: dMMR usually represents an early and possibly initiating event, while *CTNNB1* and *TP53* mutations occurs in tumours lacking evidence of non-flat morphology polypoid growth.[62]

There is an association with intervals CRCs and quality of colonoscopy. A high proportion of post-colonoscopy cancers in LS are caused by missed lesions as a result of inadequate examination, lack of adherence to surveillance recommendation, and incomplete polyp resection.[63] Reassuringly, a large multicentre study recently showed that rates of post colonoscopy CRC in centres complying with current guidance was 1.2%.[64] Newton et al demonstrated that different hospital recall systems along with clinician and patient factors resulted in variable compliance with the recommended surveillance intervals for LS with a significant risk to patients not on well managed surveillance.[65] In this study, the cumulative incidence of colorectal cancer to the age of 70 was 25% in the surveillance population and 81% in genetically diagnosed LS patients not undergoing colonoscopic surveillance.

In 2016, a United Kingdom multi-society meeting recommended the development of a quality-assured colonoscopic surveillance programme for people with LS,[66] and from April 2023 the national screening programme in England will deliver this surveillance. This new programme will deliver registration, episode recall and high-quality colonoscopy for people with LS.

Aspirin

Meta-analyses of observational data amongst populations taking aspirin revealed an absolute risk reduction of 20% in all cancers, within gastrointestinal cancers the benefit was up to 34% risk reduction. A difference in CRC risk manifests in people taking aspirin compared to a population not taking aspirin after a lag-period of approximately 7–8 years after commencing aspirin.[67]

The CAPP2 trial recruited 861 people with LS. who were randomised to receive either 600mg of aspirin or placebo. Although the primary outcome of a difference in CRC incidence at 5 years was not confirmed, cancer outcomes at a mean of 10 years showed that 9% (40/427) in aspirin group developed CRC and 13% (58/434) in placebo group, in line with the observed "lag period" noted in previous observational meta-analyses.[35] Adverse events were similar across the two groups. Data from CAPP2 suggest that aspirin should be taken daily for at least 2 years, and up to 5 years in total, after which it may be discontinued. In recent years United Kingdom guidelines recommended that aspirin be offered to

people with LS with a linked decision aid developed by NICE to allow people with LS understand the risks and benefits of prophylactic aspirin.[53]

Data from the ASPREE trial suggests a more cautious approach in older patients. This study performed in people aged over 70 years starting aspirin demonstrated an increase of cancer diagnoses, and adverse effect on cancer stage at diagnosis. Although it is unclear, this observation may be due to aspirin suppressing the inflammatory response and facilitating metastasis.[68]

Gynaecological Cancer

Endometrial and ovarian cancers are closely associated with LS. The only proven way of reducing the risk of these cancers in women with LS is prophylactic surgery.[69] This is in the form of hysterectomy and bilateral salpingo-oophorectomy. The age of surgery is one that should be decided on in consultation with the patient. Those who carry pathogenic variants in *MSH6* or *PMS2* can wait until after 45 years of age.[70] However, women who carry pathogenic variants in *MLH1* or *MSH2* should consider risk reducing surgery once their families are complete. If there is a history of early onset gynaecological cancer within the family, this should be taken into account and surgery at an earlier age considered. For most women, risk reducing surgery can be done laparoscopically which allows a short hospital admission.[71] After surgery, those premenopausal women found not to have an occult cancer, should be offered hormone replacement therapy.[8]

The role of gynaecological cancer surveillance in women with LS has been discussed in detail.[72] There is no good evidence to support its use. However, such surveillance is offered in the United Kingdom albeit in an ad hoc fashion.[73] Women with LS should be seen by a gynaecologist every year to two years as to discuss red flag symptoms of gynaecological cancer, family planning and the time of risk reducing surgery.[8] Where there are red flag symptoms, such as irregular or heavy menstrual bleeding, investigations should be considered.[74] In addition, those who can, should be advised to take aspirin. The CAPP2 found that those women taking aspirin had a 50% reduction in the incidence of endometrial cancer; however, it should be noted the study was not powered to explore this outcome and so this finding should be interpreted cautiously.[75] The use of hormonal therapy to reduce endometrial and ovarian cancer risk in women with LS remains controversial. No meaningful trial data exists to support the hypothesis that hormonal therapy reduces gynaecological cancer risk in women with LS. However, in non-LS populations, there is clear observational evidence that the use of the combined pill reduces the risk of endometrial and ovarian cancer.[76,77] In addition, the levonorgestrel intrauterine system has also been shown to greatly reduce endometrial cancer in non-LS populations.[39] Therefore, many clinicians do advise women with LS to use hormonal forms of contraception as to reduce their cancer risk on the assumption that the evidence based within the non-LS population is applicable to women with LS.[73] There is limited evidence that this maybe so, a small prospective biomarker study did find endometrial cellular proliferation was reduced with the use of progesterone/progestins in women with LS.[78]

Other Cancers

There is no reliable evidence as to how best to reduce the risk of the other cancers associated with LS. The use of prostate-specific antigen (PSA) as a means of surveillance for prostate cancer in men with LS is currently being investigated. The results of a prospective screening programme round found that male *MSH2* and *MSH6* pathogenic variant carriers have a higher incidence of prostate cancer.[79] The overall positive predictive value of a PSA threshold of 3.0 ng/mL was 32.1% (20.3–46.0). However, these results are only from the first round of screening and further data is needed from more rounds of screening before the utility of PSA-based surveillance can be decided. Therefore, PSA screening for prostate cancer in men with LS should only be used in the context of a research trial. Another potential technology that could enable urinogenital surveillance in LS is urine cytology.[80,81] However, there is insufficient evidence currently for this to be recommended.

Lifestyle risk factors for cancers should be addressed in those with LS. Namely, those with LS should be advised to exercise, maintain a healthy weight, and eat a healthy diet.[82] In addition, they should not smoke and avoid other environmental carcinogens.[83]

The cancers associated with LS are summarised in Table 2.

Table 2 Salient Clinical Features of Lynch Syndrome Associated Cancers. Sources Data Taken from PLSD (http://www.plsd.eu)

Cancer Site	Main Symptoms	Lifetime Risk				Amenable to Surveillance	Prophylactic Surgery Recommended
		MLH1	*MSH2*	*MSH6*	*PMS2^*		
Colorectal	Bleeding, pain, change in bowel habit	45%	43%	15%	1%	Yes - Colonoscopy around every 2 years	No
Endometrial	Abnormal vaginal bleeding or discharge, postmenopausal bleeding, pain	43%	57%	47%%	26%	No- evidence not clear if of benefit	Yes
Ovarian	Bloating, pain, decreased appetite, nausea	10%	17%	13%	0%	No- evidence not clear if of benefit	Yes
Prostate	Decreased flow, blood in the urine, pain	17%	32%	18%	38%	Yes - prostate specific antigen levels (ongoing study NCT 00261456)	No
Gastric	Pain, decreased appetite, black stool, indigestion, feeling full	7%	8%%	5%	0%	Yes - gastroscopy around every 2 years	No
Bladder/ Ureter/ Kidney	Pain, increased urinary frequency, blood in the urine	8%	25%	11%	0%	No- no reliable test	No
Pancreas	Bloating, pain, decreased appetite, nausea	6%	1%	1%	0%	No	No
Breast	Lump, pain, abnormal nipple discharge/bleeding	12%	12%%	13%	NK	Yes - routine breast screening	No*

Notes: ^PMS2 results limited as very few individuals in source data. *Mastectomy is possible however the lifetime risk in Lynch is not significantly more than a woman's risk of breast cancer who does not have Lynch. Therefore, Mastectomy is not indicated.

The Global Perspective

As the authors practice in the United Kingdom, the perceptive of this article has been focused on clinical practice in the United Kingdom. Herein we detail key areas of practice variation seen globally. Furthermore, clinicians must be culturally aware when applying the guidance in this article. Patients must be viewed and treated holistically and in the context of their culture. Clinicians should seek to follow local guidelines where possible. A summary of the guidelines mentioned is provided in Table 3; this is not an exhaustive list of guidelines however a summary guidance from major professional bodies regionally.

North America

Healthcare in North America is mostly delivered through an insurance-based model. For many, their healthcare will be funded by private providers who charge a premium. One of the barriers not seen in a socialised health care model (such as the National Healthcare Service) is the implications of a positive LS test on insurance premiums. Indeed, the impact of increased premiums secondary to positive LS testing has been cited as a key barrier to testing.[84] Furthermore, there are numerous private labs providing germline testing leading to an array of different report formats and terminology along with varying quality assurance. This in turn can make the interpretation of reporting difficult.[85] Currently in North America, there is no movement towards a national registry of those with LS or nationally directed care.

The universal testing of endometrial and colorectal cancer is recommended by National Comprehensive Cancer Network (NCCN), however it may not be covered by an individual's insurance meaning that the actual coverage is not universal.[86] Conversely, those with more comprehensive insurance may find the spectrum of cancers that undergo MMR

Table 3 Summary of Key Clinical Guidelines on Lynch Syndrome from Around the World

Body	Year	Geographic Area	Colonoscopy	Aspirin	Gynaecology
European Hereditary Tumour Group	2021	Europe	Every 2–3 years (every 5 years if PMS2) from 25 years (MLH1 or MSH2) or 35 years (MSH6 or PMS2))	Yes	As per Manchester Guidelines
European Society of Oncology	2019	Europe	Every 1–2 years from 20–25 years (MLH1 or MSH2) or from 30–35 years (MSH6 or PMS2)	Yes	Pelvic ultrasound, CA125 and endometrial biopsy every year from 30–35 years
Manchester Guideline	2019	International (UK)	Not applicable	Yes	No surveillance. Annual review with gynaecologist for symptom review and education from 25 years
ACOG Practice Bulletin no. 147: Lynch syndrome. Obstet Gynecol 124:1042–1054[1]	2014	USA	Colonoscopy every 1–2 years, beginning at age 20–25 years, or 2–5 years before the earliest cancer diagnosis in the family, whichever is earlier	Consider	Endometrial biopsy every 1–2 years, beginning at age 30–35 years
National Comprehensive Cancer Network (NCCN)	2022	USA	Every 1–2 years from 20–25 years (MLH1 or MSH2)[a] or every 1–3 years from 30–35 years (MSH6 or PMS2)[a]	Yes	Endometrial biopsy every 1–2 years from 30–35 years
American Society of Clinical Oncology	2015	USA	Colonoscopy every 1 to 2 years,	Consider	Pelvic ultrasound and endometrial biopsy every year from 30–35 years
Japanese Society for Cancer of the Colon	2021	Japan	As per NCCN	No	As per NCCN
Australian national guidelines for colorectal cancer screening	2018	Australia	Immunochemical faecal occult blood test (iFOBT) every 2 years and then colonoscopy every 5 years.	No	Not mentioned

Notes: [a]Or 2–5 years prior to the earliest CRC if it is diagnosed before age of recommended colonoscopy initiation. References not included in the manuscript: 1. ACOG Practice Bulletin No. 147: Lynch syndrome. Obstet Gynecol. 2014;124(5):1042–54.

testing is broader than currently seen in the United Kingdom.[87] Whether someone can access PGD is also determined by their level of insurance cover.

Regarding cancer surveillance, the recommendations for colonoscopy are equitable to those discussed within this article although once more, access is determined by an individual's level of insurance. Those women with sufficient provision are often offered gynaecological cancer surveillance with a variety of methods used. This is supported by local guidelines from American Society of Clinical Oncology (ASCO) and NCCN which include gynaecological cancer surveillance for women with LS with either an ultrasound or/and an endometrial biopsy.[88,89] Risk reducing surgery for women is offered around the same time as it is in the United Kingdom.

Europe

European healthcare is tapestry of private and state provided. The issues and barriers with private healthcare discussed above apply to those also paying premiums in Europe. Guidelines for the care of those with LS have been published by two continent wide bodies: The European Hereditary Tumour Group (EHTG) and The European Society for Medical Oncology (ESMO).[9,90]

Regarding gynaecological surveillances, the EHTG guidelines accepted the recommendations made in the United Kingdom Manchester Guidelines, and therefore does not recommend surveillance for gynaecological cancer].[8] However, ESMO guidelines do support the use of annual endometrial biopsy, transvaginal ultrasound and CA125 for

gynaecological cancer surveillance from 30 years of age.[90] It should be noted that the authorship of the ESMO guidelines did not include a gynaecologist. Colonoscopy is recommended every 1–2 years but otherwise is in line with the United Kingdom.

Asia/Australasia

Once more, Asia has a broad range of healthcare systems operating in a diverse spectrum of cultures and economies. The Japanese Society for Cancer of the Colon have published a comprehensive guideline on the clinical management of Lynch syndrome. They accept the recommendations of the NCCN as discussed above and support the universal testing of endometrial and colorectal cancers for MMRd. They do not support the use of Aspirin for chemoprophylaxis in LS. Australian guidelines concentrate on colorectal screening.[91] They recommend a novel approach in that 35–44yrs, those with LS are offered immunochemical faecal occult blood test (iFOBT) every 2 years and then colonoscopy every 5 years. No mention is made to extracolonic cancers.

The Rest of the World

No specific guidelines could be found from South America. The Jerusalem workshop was held in 2010 however this was organised and attended by clinicians from the USA and Europe.[92] The Middle East Network on Hereditary Colorectal Cancer (HCCN-ME) have not produced their own guidelines but have endorsed those of other professional bodies.[93]

The Future

LS is now the focus of a gambit of research that looks to prevent, screen, and treat the cancers associated with the condition.

Vaccination

LS-associated cancers arise in the background of numerous insertion, deletion, and mis-incorporation mutations because of a dysfunctional mismatch repair system. This leads to numerous frameshifts within DNA transcription and translation.[94] The resulting neo-peptides that are produced are immunogenic acting as antigens. Therefore, many LS associated cancers are associated with a strong immune response which will often lead to the destruction of the cancer.[95] The neo-peptides produced by LS-associated cancers are to some degree predictable.[96] As such, similar neo-peptides could be used as the basis of vaccine to inoculate LS carriers so that their immune system recognises cancers early and are able to clear them before they become clinically meaningful. Sadly, no trial data currently exists to support vaccination as a preventative measure in LS. The use of such vaccines in a murine model did lead to a significant decrease in tumour size which is encouraging and could also suggest vaccination could form part of the treatment for those with advanced LS associated cancers.[97] Therefore, there is real excitement about the development of LS cancer vaccinations soon.[98] Phase I and II trials have been undertaken; these have demonstrated LS associated cancers are well tolerated by patients and have an acceptable side effect profile.[99] In addition, immunological analysis from these studies suggests a meaningful immune response secondary to vaccination; however, it is not clear if this will translate into meaningful clinical outcomes such as improved overall survival or a lower incidence in cancer.[99] Vaccines are also being explored as an adjuvant therapy to complement more conventional cancer treatments. These studies are in a pre-clinical stage but have shown overall promise.[97]

New Screening Technologies

Currently, those with LS undergo a colonoscopy every two years.[9] This procedure is uncomfortable, requires bowel preparation and associated with complications; one in 1000 colonoscopies end in visceral perforation.[100] In addition, colonoscopy can miss cancers and provide false reassurance; around 7–10% of people who have undergone a colonoscopy are diagnosed with a colorectal cancer within 3 years.[101] For women there is currently no method that can be reliably used to detect either ovarian cancer or endometrial cancer.[72]

However, new technologies are currently be evaluated to provide non-invasive and reliable methods of cancer surveillance. Faecal immunochemical testing (FIT) is a non-invasive screening test for colorectal cancer which is used in the general population to stratify people for colonoscopy. The test works by detecting occult blood in the stool through an antibody-based assay for human globin.[102] FIT is currently being evaluated for use in the LS population which, if successful, could greatly limit the number of colonoscopies those with LS undergo.[103] For women, cytology-based methods of endometrial cancer surveillance are currently being evaluated in the general population.[104,105] These could be a non-invasive alternative for women with LS, however this is yet to be evaluated. In addition, novel microsatellite analysis of urine has to been used to detect cancers of the urogenital tract and endometrium in those with LS with some success.[106] Larger studies are needed however, to confirm if this could be a viable non-invasive means of cancer surveillance. Finally, the development of technologies that utilise cell-free DNA could mean in the near future a blood test could be used to screen for all LS-associated cancers through the detection of molecular markers.[107,108] These technologies are still unproven in the general population and further work would be needed before they could be applied to high-risk groups like LS.

Immunotherapy

LS-associated cancers arise within a dysfunctional mismatch repair system and therefore the tumours have a high mutational burden.[109] This leads to a high number of immunogenic peptides that stimulate an anti-cancer immune response.[110] To overcome this, LS-associated cancer develops immune escape mechanisms namely they utilise the programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) axis.[111] This is a druggable mechanism; the development of checkpoint immune inhibitors has revolutionised the treatment of cancers with mismatch repair deficiency.[112] Seminal work by Le et al demonstrated a significant survival benefit in mismatch repair cancers that are treated with immune checkpoint inhibitors.[113] These treatments have now become the mainstay of therapy for advanced mismatch repair tumours.[114] As we come to better understand the utility of these treatments, through trial data, it maybe they become maintenance therapies.[115] As our understanding of the immune landscape improves, we may be able to find novel targets for cancers in LS that prove resistant to immune checkpoint inhibition.

Conclusion

LS is a complicated clinical entity. The diagnosis requires people to come forward for testing which is difficult as there are no accurate means by which to identify healthy LS carriers. Universal testing is potentially expensive, will put pressure on already under resourced laboratories and it is not clear how best to take informed consent on such a large scale. Therefore, currently we screened those with LS associated cancers for LS by way of testing their tumours for features of mismatch repair deficiency. As we move to mainstreaming, those more likely to have LS will be offered germline testing by their clinical team. Therefore, only those with confirmed LS will need to be seen by clinical genetics who can go on to organise cascade testing and find those relatives who are healthy LS carriers. They can also aid with the interpretation of VUS results. Not all people wish to undergo testing for LS and having an appreciation of how to communicate risk and the barriers to testing is important so that clinicians can support individuals through the LS testing process.

Once diagnosed with LS, people need to be encouraged and supported to take evidenced-based measures that can reduce their risk of cancer. Sadly, many of these are invasive such as colonoscopy or risk reducing surgery and therefore individualised care is vital based on the individual's risk and preferences. Further research is needed and needs to be funded to improve the care of those with LS. Vaccines hold hope of lifelong cancer prevention. New technologies could mean cancers that do develop are detectable on a blood test and could be treated with immunotherapies before they even became clinically relevant. This future is only realisable if the current focus on LS-related research is maintained, and funding bodies seek to fund it.

In summary, LS care has come a long way over the last twenty years. We know understand the individual cancer risk to inform consent, tests to accurately diagnoses LS and ways by which we can reduce cancer risk. However, more needs to be done to find those who are undiagnosed, develop less invasive cancer surveillance methods and develop new vaccinations and treatments.

Data Sharing Statement

All data contained here within this manuscript is available on request from the corresponding author.

Ethics Statement

All studies were approved by the respective institutional review boards and conducted with appropriate ethical criteria in each country and in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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