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Knowledge, Attitudes and Referral Patterns of Lynch Syndrome: A Survey of Clinicians in Australia

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Abstract: This study assessed Australian clinicians' knowledge, attitudes and referral patterns of patients with suspected Lynch syndrome for genetic services. A total of 144 oncologists, surgeons, gynaecologists, general practitioners and gastroenterologists from the Australian Medical Association and Clinical Oncology Society responded to a web-based survey. Most respondents demonstrated suboptimal knowledge of Lynch syndrome. Male general practitioners who have been practicing for ≥ 10 years were less likely to offer genetic referral than specialists, and many clinicians did not recognize that immunohistochemistry testing is not a germline test. Half of all general practitioners did not actually refer patients in the past 12 months, and 30% of them did not feel that their role is to identify patients for genetic referral. The majority of clinicians considered everyone to be responsible for making the initial referral to genetic services, but a small preference was given to oncologists (15%) and general practitioners (13%). Patient information brochures, continuing genetic education programs and referral guidelines were favoured as support for practice. Targeted education interventions should be considered to improve referral. An online

family history assessment tool with built-in decision support would be helpful in triaging high-risk individuals for pathology analysis and/or genetic assessment in general practice.

Keywords: Lynch syndrome; referral; risk assessment; genetic services; knowledge; attitudes and practice

1. Introduction

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited cancer syndrome caused by defect in one of the mismatch repair (MMR) genes—*MLH1*, *MSH2*, *MSH6* and *PMS2*. It accounts for about 5% of all colorectal and endometrial cancers diagnosed [1,2]. MMR mutation carriers have high risks of early onset colorectal (25%–70%) or endometrial cancers (30%–70%), and have increased risks of other cancers such as ovarian, gastric, small bowel, pancreatic, urothelial, brain and skin neoplasms [3,4]. Further, women carrying MMR gene mutations who are diagnosed with endometrial cancer have increased risks of second primary colon cancer (about 40-fold) or other extracolonic cancers (up to 28-fold) compared with that for the general population [5]. Nevertheless, at-risk individuals are dependent on their clinicians for diagnosis and surveillance. Though clinicians cannot be expected to have detailed knowledge about the causative genes of Lynch syndrome, it remains their responsibility to recognize the clinical phenotype and family history characteristics of Lynch syndrome, and make a referral to a clinical genetics service or a familial cancer centre if deemed necessary. However, local and international studies have reported that only a small proportion of individuals suspected to have Lynch syndrome were identified and referred to a clinical genetics service/family cancer clinic for further genetic consultation and possible genetic testing [6–10].

Numerous barriers to referral for genetic services (*i.e.*, genetic consultation and/or testing) have been reported in the literature, including lack of knowledge regarding Lynch syndrome and who should be referred, lack of family history information or referral guidelines, or lack of awareness of clinical genetic services [11,12]. Despite the number of studies on Lynch syndrome, only few included Lynch-associated extracolonic malignancies [13,14]. This contributes to the concern that, although there is increasing awareness of Lynch syndrome and colorectal cancer, endometrial and other extracolonic cancers are under-recognized by practicing clinicians. Domanska and colleagues investigated knowledge about key features of Lynch syndrome in 102 clinicians in Southern Sweden reported that not only a majority of clinicians underestimated the risk of endometrial cancer (77%) but also that of colorectal cancer (56%) [14]. In a more recent survey about the knowledge of regarding the genetics and recommended screening for carriers of Lynch syndrome mutations, 201 medical students at an American medical school demonstrated lack of awareness of recommendations for endometrial cancer screening for high risk individuals [15]. As it was unclear whether clinicians in Australia face similar challenges as their peers abroad, a qualitative study was conducted to assess barriers and motivators of genetics referral among 28 clinicians who are likely to diagnose, treat and assess Lynch families in Queensland, the second-largest and third-most populous state in Australia [16]. While the authors reported that a majority of clinicians were positive about referring patients to a clinical genetics service, they also found a lack of knowledge and support needed to make an appropriate referral.

In order to facilitate diagnosis of Lynch syndrome, various guidelines such as the Amsterdam II, revised Bethesda or the Society of Gynecologic Oncologists have been developed [17–19]. Current Australian practice guidelines recommend that young individuals with colorectal cancer, and with a moderate-to-high risk family history of cancer are referred to a clinical genetics service/family cancer clinic, and offered genetic risk assessment and counselling with or without genetic testing *i.e.*, DNA molecular analysis [20]. While the referral of patients to a clinical genetics service/family cancer clinic can be from a general practitioner (GP) or a specialist [21], only specialists apart from geneticist/genetic counsellor can initiate or order tumour molecular analysis *i.e.*, immunohistochemistry (IHC) or microsatellite instability (MSI) testing directly from a pathology service. Routine IHC for MLH1, MSH2, MSH6 and PMS2 proteins has been recommended and supported by the Australian College of Pathologist for all patients diagnosed with colorectal cancer younger than 50 years of age [22], although the actual patterns of care around uptake of this recommendation in Australia is unknown. Further, to our knowledge, such testing has yet to be formally established in Australia and there are currently no standard criteria for referral of individuals with endometrial cancer who are at risk of Lynch syndrome to a clinical genetics service. Genetic testing, on the other hand, is done through clinical genetics services or family cancer clinics, and is free if a patient presents with a high clinical suspicion of an underlying genetic aetiology.

As early identification of mutation carriers allows for more intensive colonoscopic surveillance and consideration of risk-reducing surgeries [23–27], it is important that patients diagnosed with colorectal cancer or endometrial cancer are identified and appropriately triaged for clinical evaluation. We therefore distributed a questionnaire to: (1) investigate clinicians' knowledge of Lynch-associated cancer risks and tumour molecular analysis; (2) assess referral practices among clinicians who are likely to diagnose, treat and survey Lynch families; (3) quantify motivators and barriers to genetics referral for Lynch syndrome in Australia; and (4) explore physician referral preferences (*i.e.*, preferred timing for referral and who they think might be the most appropriate professional to make the initial genetics referral), perceptions of their role and their desired support for the provision of genetic services.

2. Experimental

2.1. Participants and Procedures

We targeted our sample to clinicians who are likely to diagnose, treat and survey Lynch families. Participants therefore included GPs and specialist groups (*i.e.*, gynaecologists, gastroenterologists, medical oncologists, radiation oncologists, gynaecology oncologists, general and colorectal surgeons), who were identified through membership list of the Australian Medical Association. We purchased the list from AMPCo Data direct, a subsidiary of the Association who owns the list of practicing doctors (N = 11,624), who then broadcasted our invitation to their members. An invitation was circulated by email to a randomly stratified sample of 1674 participants. Sample size was calculated to provide 90% power, with a two-sided significant level of $\alpha = 0.06$. The email described the study and confidentiality, and included a link to the online survey and participant information sheet. Participants were asked to read the information brochure prior to commencing the survey. A reminder email was sent a week apart from the initial broadcast. Responders were allowed to save their responses and

return to complete the survey at a later time. Due to the small sample size of oncologists from the Australian Medical Association database, oncologists were also identified from the membership of Clinical Oncological Society of Australia membership directory. An invitation email was sent to gynaecological oncologists, medical oncologists and radiation oncologists by the Society, and was followed-up with a reminder email sent a week after the initial broadcast. Only one reminder email was sent to all invited study participants. Participation was voluntary and no financial incentives were given. Survey response implied consent to participate, and all responses were anonymous. The study was approved by The University of Queensland School of Medicine and Royal Brisbane & Women's Hospital research ethics committees.

2.2. Instrumentation

A web-based survey was developed specifically for this study based on a review of relevant literature [13,28–32], results from our previous qualitative study [16], and using the advice of a panel of experts with expertise in gynaecology oncology, clinical genetics, psycho-oncology, and genetic counselling. The survey items were pilot-tested with a convenience sample of 10 health professionals (*i.e.*, oncologists, geneticists, clinical and social researchers) to assess relevance and face validity of survey items. Changes to the survey were made accordingly using the Delphi method [33] before administration.

The final version of the survey was created using LimeSurvey and consisted of 19 items (see Appendix 1). Items included participant demographics, referral practices, barriers and motivators for genetics referral, physician referral preferences and perceptions of their role and their desired support for the provision of genetic services. In order to evaluate clinicians' knowledge of Lynch syndrome, the authors adapted a pedigree from a previous study that addressed risk assessment abilities and referral patterns to fit the high-risk profile for Lynch syndrome [28]. At the end of the survey, participants were asked to provide additional comments and their email address if they wish to receive a copy of the research summary report. The survey was open for three months from mid-March to end of May 2013.

2.3. Data Analyses

All survey data were collected using LimeSurvey, and data were coded and analysed using SPSS Version 20 (IBM® SPSS® Statistics, Chicago, IL, USA). Descriptive statistics included frequencies and proportions were calculated. χ^2 or Fisher's exact test was used to investigate associations between categorical variables. Throughout the analysis, respondents who selected unsure were designated as missing data. All *p*-values were two-sided, with a statistical significance level set at $p < 0.05$.

3. Results

Of 582 email recipients who "opened" the email, 144 (24.7%) responded to the web survey fully (138/144, 95.8%) or partially (more than 50% of questions answered, 6/144, 4.2%). Demographics of these clinicians are summarized in Table 1. Overall, the study sample consisted of 59 oncologists (40%), 27 surgeons (19%), 24 gynaecologists (17%), 18 GPs (13%) and 11 gastroenterologists (8%); the remaining 5 were designated as other specialties (4%). Most clinicians were <50 years of age

($p = 0.005$), and were in practice for at least 10 years ($p = 0.002$). There were no statistically significant differences between gender or state of residence with provider groups.

Table 1. Sociodemographics of participating health care provider groups ^a.

	Total	GP	GYN	GE	ONC	SURG	Others ^b
	N (%) ^c						
Total	144 (100)	18 (100)	24 (100)	11 (100)	59 (100)	27 (100)	5 (100)
Age (years)							
<50	84 (58)	10 (56)	11 (46)	6 (55)	37 (63)	17 (63)	3 (60)
≥50	60 (42)	8 (44)	13 (54)	5 (46)	22 (37)	10 (37)	2 (40)
Gender							
Female	67 (47)	8 (44)	8 (33)	0	37 (63)	9 (33)	5 (100)
Male	77 (53)	10 (56)	16 (67)	11 (100)	22 (37)	18 (67)	0
Years of Practice in Specialty							
<10	59 (41)	5 (28)	7 (29)	4 (36)	27 (46)	12 (44)	4 (80)
≥10	85 (59)	13 (72)	17 (71)	7 (64)	32 (54)	15 (56)	1 (20)
State ^d							
NSW/ACT	44 (31)	6 (33)	9 (38)	0	18 (31)	9 (33)	3 (60)
VIC/TAS	44 (31)	2 (11)	5 (21)	4 (36)	20 (34)	11 (41)	2 (40)
QLD	29 (20)	5 (28)	11 (46)	2 (18)	9 (15)	3 (11)	0
SA	11 (8)	2 (11)	0	3 (27)	6 (10)	0	0
WA	16 (11)	3 (17)	1 (4)	2 (18)	6 (10)	4 (15)	0

Abbreviations: GPs general practitioners; GYNs gynaecologists; GEs gastroenterologists; ONCs oncologists; SURGs surgeons; NSW New South Wales; ACT Australian Capital Territory; VIC Victoria; TAS Tasmania; QLD Queensland; SA South Australia; WA Western Australia ^a Bolded estimates indicate statistically significant difference between two groups within each practice category; ^b Other medical specialties include cancer care coordinator ($n = 1$), genetic counsellor ($n = 1$), psycho-oncologists ($n = 2$), social worker ($n = 1$); ^c The % reflects the percentage responding within each practice category; ^d ACT and TAS were consolidated with NSW and VIC, respectively, due to low participation rate and similarity in genetic testing protocols.

3.1. Referral to Genetics Services and Ordering Diagnostic Testing for Lynch Syndrome

Table 2 displays clinician likelihood to refer patients to genetic services and ordering diagnostic testing for Lynch syndrome in the past 12 months, by the provider group. Overall, there were no significant differences between specialist groups and likelihood to refer to genetic services. However, GPs, particularly male practitioners who have been in practice for more than 10 years, were less likely to refer patients to genetic services than others ($\chi^2 = 16$; $p = 0.001$; 25% vs. 87%). GPs and gynaecologists were significantly less likely to order IHC testing ($p = 0.002$ and $p = 0.003$, respectively), whereas oncologists and surgeons were more likely to order such testing ($p = 0.03$ and $p = 0.004$, respectively). GPs and gynaecologists were also less likely to order MSI testing ($p = 0.003$ and $p = 0.004$, respectively), but surgeons were more likely than the others to order MSI testing ($p = 0.005$). Oncologists were more likely than other provider groups to order DNA germline testing ($p = 0.007$), whereas gynaecologists were less likely to do so. There were no statistically significant differences between age, gender, state of residence or years in practice and referral to genetic services.

Table 2. Likelihood that clinicians reported referring patients to clinical genetic services or ordering tumour analysis in the past 12 months, by provider group ^{a,b}.

	Total (N = 144)	GP (N = 18)	GYN (N = 24)	GE (N = 11)	ONC (N = 59)	SURG (N = 27)	Others ^c (N = 5)
	N(%; 95%CI) ^d	N(%;95%CI) ^d	N(%;95%CI) ^d	N(%;95%CI) ^d	N(%;95%CI) ^d	N(%;95%CI) ^d	N(%;95%CI) ^d
		<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value	<i>p</i> -value
Referred patients to genetic services	112 (78; 70–84)	9 (50; 29–71) 0.003	19 (79; 60–91) 0.969	10 (91; 62–98) 0.458	50 (85; 73–92) 0.095	22 (81; 63–92) 0.799	2 (50) 0.196
Ordered tumour IHC testing	77 (53; 45–61)	4 (22; 9–45) 0.002	6 (25; 12–45) 0.003	8 (73; 43–90) 0.524	39 (66; 53–77) 0.030	20 (74; 55–87) 0.004	0 -
Ordered tumour MSI testing	55 (38; 31–46)	1 (6; 1–26) 0.002	3 (13; 4–31) 0.004	6 (55; 28–79) 0.527	29 (49; 37–62) 0.075	16 (59; 41–75) 0.005	0 -
Ordered DNA mutation testing	67 (47; 39–55)	6 (33; 16–56) 0.125	7 (29; 15–49) 0.034	3 (27; 10–57) 0.308	36 (61; 48–72) 0.007	15 (56; 37–72) 0.249	0 -

Abbreviations: GP general practitioners; GYN gynaecologists; GE gastroenterologists; ONC oncologists; SURG surgeons; CI confidence interval; IHC immunohistochemistry; MSI microsatellite instability. ^a Category totals may be less than the total number of respondents due to missing values; ^b Bolded estimates indicate significant findings; ^c Other medical specialties include cancer care coordinator (*n* = 1), genetic counsellor (*n* = 1), psycho-oncologists (*n* = 2), social worker (*n* = 1); ^d The % reflects the percentage responding within each practice category.

3.2. Risk and Surveillance Strategies among Clinicians

When participants were presented with a fictitious high-risk Lynch-specific clinical scenario (Appendix 1), only 13/144 (9%) of all respondents were able to answer all Lynch cancer risk-associated questions correctly, *i.e.*, no elevated risk for breast or thyroid cancer, somewhat higher risk for ovarian and gastric cancer, and much higher risk for colorectal and endometrial cancer as compared to the general population. Of all respondents, 65% could correctly identify colorectal cancer risk, followed by 63% for thyroid cancer, 60% for endometrial cancer, 45% for gastric cancer and 42% for ovarian cancer. About a third of all respondents considered the fictitious high-risk asymptomatic individual to be at lower risk of developing colorectal and endometrial cancer when compared to the general population, but half of all respondents considered the individual to have a much higher risk for developing ovarian cancer, and another 15% considered the individual to have a much higher risk for developing gastric cancer. A notable 44% considered the individual to have high risk for breast cancer. There were no statistically significant differences in specialist groups, age, gender, state of residence or years in practice with providing the correct answers. Nevertheless, GPs were less likely than other specialists to recognize high risk for colorectal cancer ($\chi^2 = 9$; $p = 0.003$; 33% vs. 69%) and endometrial cancer ($\chi^2 = 6$; $p = 0.015$; 33% vs. 64%).

When asked if they consider IHC or MSI testing a germline test, 9% of all respondents thought IHC was a germline test, while another 23% considered MSI a germline test. Forty-nine percent and 35% of all respondents did not consider IHC or MSI a germline test, respectively. Forty-two percent of all respondents were uncertain about both tests. GPs (89%) and gynaecologists (75%) were less likely to answer the question on IHC correctly ($p < 0.05$ for both groups), while oncologists (68%) were more likely to answer the question correctly ($p < 0.001$) and refer patients for genetic services ($p = 0.008$).

When a high risk individual was affected with endometrial cancer, respondents indicated they would: assess family history (96%); refer to a geneticist (94%); discuss Lynch syndrome cancers with the patient (82%); offer cancer surveillance (77%); order IHC or MSI tumour testing (58%); discuss risk-reducing surgeries (53%); order germline testing (42%); and refer to non-genetics specialists (38%); and no further action (1%). For those who offered cancer surveillance and discuss risk-reducing surgeries, they recommended colonoscopy (87%), gastroscopy (62%), serum CA125 (48%), hysterectomy and bilateral salpingo-oophorectomy (41%), breast ultrasound (36%), subtotal or segmental colectomy (8%), pelvic ultrasound (7%) and mastectomy (4%).

3.3. Prevalence of Motivators and Barriers to Referral

As shown in Table 3, a number of motivators and barriers for referral to genetic services were examined. Patient disinterest was considered the biggest barrier to referral. Clinicians that have never referred patients for genetic services were more likely to denote the following barriers to referral: unfamiliarity with hereditary cancer syndromes ($p = 0.04$); no knowledge of how to make referral ($p \leq 0.001$); no access to a genetic health service ($p = 0.001$); no recommendation and guidelines for referral ($p = 0.016$).

Table 3. Motivators and barriers of referral of patients suspected with Lynch syndrome for genetic services *.

	Have not Referred for Genetic Services (Total = 30) N (%) ^a		Referred for Genetic Services (Total = 112) N (%) ^a		<i>p-value</i> ^b
Motivators					
To provide genetic counselling for the patient	20	(66)	103	(92)	<0.001
Patient interest or request	20	(66)	92	(82)	0.065
To provided appropriate screening and/or management for the patient’s family	15	(50)	94	(84)	<0.001
To provide appropriate cancer risk assessments for the patient	21	(70)	98	(88)	0.544
To provide genetic testing for germline mutations	14	(47)	83	(74)	0.004
Reassurance for the patient and family	16	(53)	73	(65)	0.234
Ethical and legal responsibility	14	(47)	70	(63)	0.117
To provide appropriate screening and management for the patient	20	(66)	81	(72)	0.544
Others ^c	0		5	(4)	-
Barriers					
Patient was not interested when referral was offered	17	(57)	62	(55)	0.898
Patient may be at risk for insurance discrimination	5	(17)	19	(17)	0.969
Recommendations and guidelines were not available to select patients for referral	8	(27)	11	(10)	0.016
Patient is unlikely to benefit from genetic counselling/testing	1	(3)	16	(14)	0.123
I do not feel familiar with hereditary cancer syndromes	5	(17)	6	(5)	0.040
Long waiting time for appointment at genetics clinic	2	(7)	7	(6)	0.934
I do not know how to make a referral to the local genetic health service	7	(23)	1	(1)	<0.001
I do not have access to genetic health service	6	(20)	2	(2)	0.001
I do not feel it is my responsibility	2	(7)	1	(1)	0.113
Others ^d	0		4	(4)	-

* For referral to genetic services, total respondents were 142 in total. ^a The % reflects the percent responding within each category; ^b Bolded estimates indicate significant findings between clinicians who have referred (*n* = 112) and did not refer (*n* = 30) patients for genetic services; ^c Qualitative answers were provided, which include antenatal diagnosis, significant family history, significant tumour testing results, to provide the necessary routine surveillance and advice regarding screening and risk-reducing options for patients; ^d Qualitative answers were provided, which include lack of resources and no prophylactic treatment or screening available for patients.

3.4. Referral preferences, Perceived Role and Desired Support for the Delivery of Genetic Services among Clinicians

There was no statistically significant difference between provider groups and preferred timing for referral. Clinicians indicated referral should be warranted at any time (51%) and when family history is collected (27%). Although a majority of clinicians felt that everyone is responsible for referring patients to genetic services, a proportion of clinicians believe that oncologists (15%) and GPs (13%) would be best suited for the role ($p = 0.031$). Oncologists were preferred as they would most likely recognize at-risk individuals, whereas GPs were preferred because they are the first point of contact for patients, who have the best knowledge about patients’ family history and are the ones responsible for coordinating care. However, compared to the specialist groups, some GPs did not feel that their role is to identify patients for referral to genetic services ($\chi^2 = 7$; $p = 0.011$; 30% vs. 10%) or to order IHC or MSI testing ($\chi^2 = 11$; $p = 0.001$; 20% vs. 2%). Table 4 further shows clinicians’ perceived roles and referral for genetic services. Clinicians who have referred for genetic services considered themselves to be responsible for (1) identifying and referring individuals to clinical genetics services; (2) interpreting germline DNA mutation testing results; (3) ordering IHC or MSI tests; (4) discussing cancer surveillance and prophylaxis with patients; and (5) providing regular clinical exams and care to patients with hereditary cancer syndromes. The support desired for delivering genetic services is summarized in Figure 1.

Figure 1. Desired support for the delivery of genetic services among health care providers.

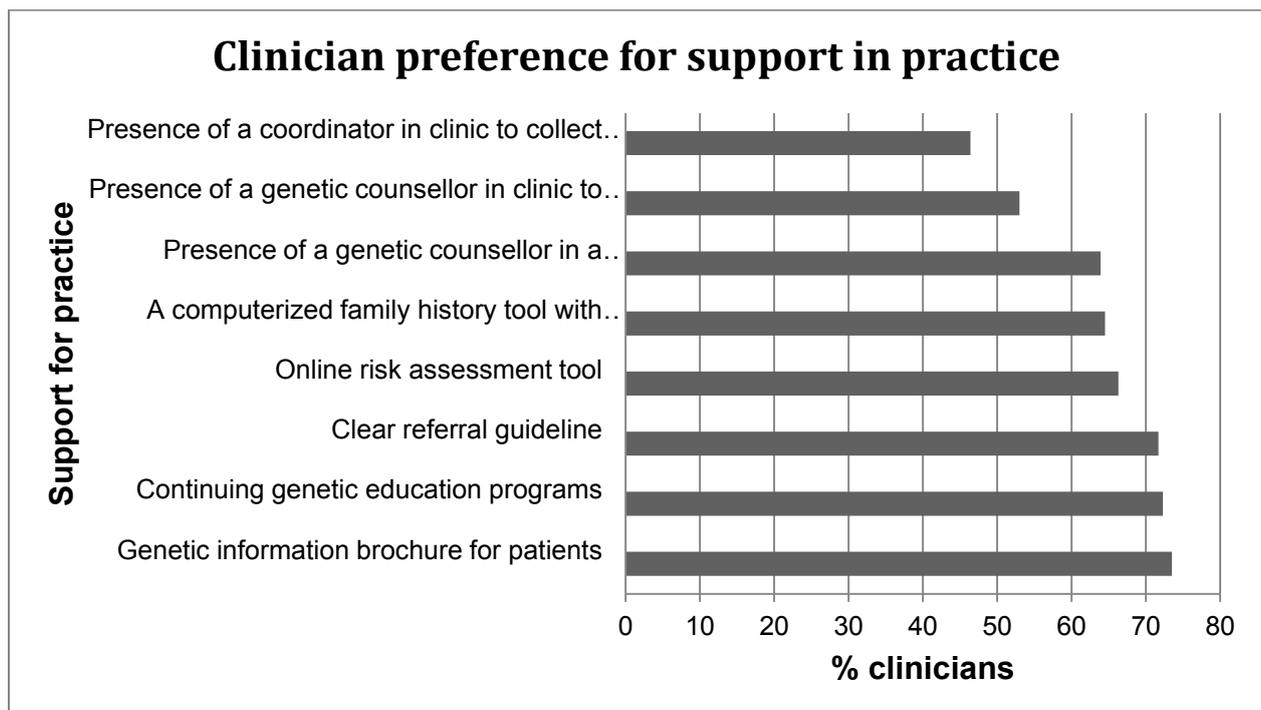


Table 4. Clinicians’ perceived roles and referral of patients suspected with Lynch syndrome genetic services *.

Perceived Roles	Have not referred for genetic services (Total = 30) N (%) ^a	Referred for genetic services (Total = 112) N (%) ^a	p-value ^b
Providing emotional support after genetic testing	21 (70)	64 (57)	0.202
Identifying patients for referral to genetic services	19 (63)	104 (93)	<0.001
Interpreting germline DNA-based genetic test results	0	22 (20)	0.004
Collecting a three-generation family history information	11 (37)	54 (48)	0.260
Ordering pre-genetic testing of tumour tissue (e.g., MSI or IHC)	5 (17)	53 (47)	0.002
Counselling patients about their cancer risks after genetic testing	8 (27)	38 (34)	0.450
Counselling patients about their cancer risks before genetic testing	7 (23)	42 (38)	0.147
Calculating relative risk of cancer associated with family cancer history	4 (13)	25 (22)	0.321
Discussing the need for cancer surveillance or prophylaxis with patients when required	17 (57)	90 (80)	0.011
Providing regular clinical examination and care to patients with hereditary cancer syndromes	15 (50)	82 (73)	0.015
Other	3 (10) ^c	5 (5)	-

* For referral to genetic services, total respondents were 142 in total. ^a The % reflects the percentage responding within each category; ^b Bolded estimates indicate significant findings between clinicians who have referred (*n* = 112) and did not refer (*n* = 30) patients for genetic services; ^c Qualitative answers were provided, which include liaison with genetic services, psychotherapy and specialty specific to one particular general surgeon; ^d Qualitative answers were provided, which include advice on sequence of treatment modalities, antenatal advice and diagnosis, counselling provided in addition to that provided by genetic service, clear documentation to clinicians, ensuring patient informs family of risk, and referring to appropriate services.

4. Discussion

In 2009, a total of 2105 patients were diagnosed with endometrial cancer in Australia [34]. As the prevalence of Lynch-associated endometrial cancer among mutation-positive women is comparable to that reported internationally [35], it would be expected that about 100 cases diagnosed annually would be due to Lynch syndrome. Establishing a pathogenic mutation carrier in a family is important since it enables predictive testing to be offered to family members, and allow decisions to be made about screening, risk-reducing surgery and chemoprevention if found to be MMR mutation positive [23–26]. While genetic testing is typically offered free of charge and always in the context of genetic counselling at an accredited clinic in Australia [36], access to publically funded genetic services requires a referral from either a GP or a medical specialist [37]. It is therefore essential that clinicians in general recognize the classical family history indicators for Lynch syndrome when individuals present in everyday practice. To our knowledge, this is the first study to formally examine the knowledge, attitudes and referral patterns of Lynch syndrome in Australia. Overall, our findings demonstrated suboptimal knowledge of Lynch syndrome. The presented fictitious individual—a female patient—has a remarkable family history of cancer representing that of revised Amsterdam II criteria. However, a third of clinicians, particularly GPs, did not consider the female patient to have high risk of colorectal or endometrial cancer (which is a concern as MMR mutation carriers have the highest lifetime risk for developing colorectal and/or endometrial cancer amongst the general population). In contrary, about half of all clinicians considered the female patient to have high risks of breast or ovarian cancers (which is another concern as MMR mutation carriers have up to 14% increased risk of ovarian cancer, and breast cancer has yet to be recognized as part of the Lynch syndrome spectrum of tumours) [4]. This suggests that clinicians could recognize the underlying genetic predisposition in the female patient, but lack familiarity with Lynch syndrome spectrum of tumours. However, this lack of familiarity with Lynch syndrome is consistent with other studies [29,38–40], reflecting the need to establish new ways to reach out to clinicians who are likely to diagnose, treat and survey Lynch families.

Parallel to this finding, we showed that GPs and gynaecologists were less familiar with IHC or MSI testing compared to the specialists. Nevertheless, this is expected, as only specialists apart from geneticist/genetic counsellor can initiate or order IHC or MSI tests directly from a pathology service. However, a proportion of specialists, including surgeons, was not familiar with IHC or MSI testing and was not certain if they were germline tests. The Royal College of Pathologists of Australia considers both IHC and MSI to be tests that assist in characterizing patient's tumour, and do not constitute genetic testing for a familial disorder [41]. IHC and MSI testing are useful not only to identify patients with suspected Lynch syndrome but also to recognize suspected patients who do not meet the Amsterdam criteria for subsequent germline DNA sequencing. Both IHC and MSI provide predictive and prognostic information that may be used to guide treatment decisions. It is therefore important that clinicians know what these tests are so that accurate diagnosis and proper clinical management are warranted for at-risk patients and their family members to reduce cancer risk. Our above results raise concerns, as this implies that the clinicians might not know the purpose of IHC or MSI testing, and may not be able to interpret the results correctly even when patients are tested. Thus, adoption of universal, or even age-selected, IHC testing of colorectal and endometrial tumours will reduce issues

around poor identification of Lynch syndrome cases based on family-history selection criteria. However, there will still be need for targeted genetic education to improve physician understanding of IHC results, and subsequent referral of patients and their relatives for genetic testing and appropriate medical management.

Our results also show that clinicians were not familiar with cancer risk management associated with Lynch syndrome. Although the majority of clinicians recommended colonoscopy for high-risk patients, they also recommended gastroscopy, serum CA125, pelvic ultrasound and mastectomy. According to the eviQ Australian guideline (Appendix 2) and international recommendations [3,42], there is currently no evidence to support a survival benefit from gastroscopy, CA125 or pelvic ultrasound. Current recommendation for breast cancer, which is yet to be considered as part of Lynch syndrome tumour spectrum, is biannual mammography from age 45 or 50 years. Our results suggest that referral, if made, will not always be appropriate, as is unnecessary referral for screening and prophylactic surgeries.

While the majority of clinicians reported that they would assess family history and refer for genetic services when an asymptomatic individual present with a significant family history suggestive of Lynch syndrome, numerous barriers in collecting the information have been reported [43–46]. These include limitations of patients' family history knowledge, time available for collection, knowledge and skills to collect and interpret family history data to provide appropriate risk assessment and clinical care recommendations. Nonetheless, it is important to collect a three-generation pedigree from individuals with a diagnosis of cancer, as this informs eligibility for mutation testing, and readily identifies members in the extended family who are eligible for predictive testing if a pathogenic mutation is identified in the proband. Published data have shown that time devoted on family history collection was often minimal in general practice [43], and inadequate even when documented for cancer patients [8,47–49].

Clinicians in our study considered patient disinterest to be a barrier to uptake of referral. Several published reports have demonstrated low rate of uptake of genetic counselling and testing by at-risk relatives (23% and 44%, respectively) [50,51]. An investigation by Wakefield *et al.* [52] involving 39 high-risk Australian patients for breast and/or ovarian cancer revealed positive attitude toward genetic counselling and testing but patient barriers to clinical attendance and testing uptake were poor understanding of cancer risk and eligibility for genetic testing [52]. It is possible that individuals at risk of Lynch syndrome may face similar challenges; however, no study to date has explicitly assessed Lynch cancer patients' information needs. Our findings also suggest a slight preference by all respondents for the oncologists and GPs to make the initial referral for genetic services; however, a significant proportion of GPs did not feel that their role is to identify patients for genetics referral or to order IHC or MSI testing. As such, it is important to consider alternative methods to triage patients with suspected Lynch syndrome. Universal testing should be considered in Australia; however, to our knowledge such testing has yet to be formally established. Also, due to limited resources, more studies are needed to assess cost-effectiveness of universal testing prior to nationwide implementation.

In our previous study, we showed that a research-based self-administered family history questionnaire can be considered for use in specialist clinics to facilitate and improve family history documentation [8]. Indeed, a review has reported that a systematic family history tool may add

significant family health information to current primary care practice [53], and a computer-based decision support system can further facilitate appropriate referral of high risk individuals for genetic services [54,55]. An automatic prompt for IHC or MSI testing may also be incorporated into such a system once routine universal testing is formally established in Australia to improve diagnosis and referral of patients for genetic services. Development of patient information brochure should further assist clinicians when consulting patients as well as to aid patients in making informed decisions about genetic testing.

There are several limitations to this study. Firstly, the response rate was low. This may be in part due to unwillingness to complete a web-based survey or lack of interest in hereditary cancer syndromes. A larger sample size and greater response rate would certainly provide a more accurate view on clinicians' attitudes to genetics referral, however, the response rate in our study is comparable to other web-based studies conducted [56–59]. Selection bias may have occurred because participants had greater interest in hereditary cancer syndromes, more genomic knowledge, or stronger beliefs about their role in providing genetic services. Should this be true, our results would indicate even more strongly a need for improved education and support for clinicians to triage patients with suspected Lynch syndrome. Another limitation faced by our web-based data collection includes the inability to assess the representativeness of Australian healthcare providers due to lack of a national email registry, which may potentially bias our original sampling frame. We also did not know how many men and women within each practice category were asked for the survey initially, as the email broadcast was blinded by the Association for confidential reasons. Although clinicians were not evaluated for low or moderate risk Lynch syndrome-related clinical scenarios, the purpose of this study was to explore recognition of a classical family history suggestive of Lynch syndrome. Despite the abovementioned caveats, findings from this Australian study offer insight into clinicians' knowledge of Lynch syndrome, and their attitudes toward genetic services and referral practices.

5. Conclusions

Our study suggested that genetics education is necessary for clinicians in order to improve genetic referral. Further studies should be conducted to examine educational topics selected by clinicians (e.g., genetic risk assessments, basic genomic concepts), and more behavioural research is needed to investigate barriers to patient uptake of referral as well as patients' information needs. An online family history tool with built-in decision support for genetics referral would be helpful in triaging high-risk individuals in general practice. Future research should also focus on feasibility and impact assessment of reflex IHC or MSI and *MLH1* methylation testing to identify Lynch syndrome patients as a way to prevent second cancers, and identify carrier relatives for predictive testing.

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Author Contributions

Yen Y. Tan was responsible for conception and design; collection, assembly and analysis of data. All authors were responsible for data interpretation, manuscript writing, and final approval of manuscript. Andreas Obermair also provided financial support for the study.

Conflicts of Interest

The authors declare no conflict of interest.

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Appendix 1: Questionnaire

Health Professionals' Knowledge and Attitudes towards Genetic Services for Patients with or at High-Risk of Lynch syndrome

This survey is about health professionals' knowledge and attitudes towards genetic services. Genetic services refer to the delivery of genetic counselling and risk assessment, and testing for patients and families with or at high-risk of hereditary syndrome.

Demographic of Respondents

1. What is your gender?
 - Male
 - Female
2. What is your age?
 - 18–29
 - 30–39
 - 40–49
 - 50–59
 - 60 +

3. What is your current specialty?
 - General practice
 - Gynaecology
 - Gastroenterology
 - Gynaecology oncology
 - Medical oncology
 - Radiation oncology
 - General surgery
 - Colorectal surgery
 - Other (please specify _____)

4. How long have you been practicing in your current field?
 - 0–5 years
 - 6–10 years
 - 11–20 years
 - More than 20 years

5. What is the postcode of your primary location of practice?
Please specify _____

You and Your Practice

The following section is about you and your referral practice. This is not a test. Your replies are anonymous and will be treated confidentially. Please answer all items.

6. In the past 12 months, have you referred patients for:

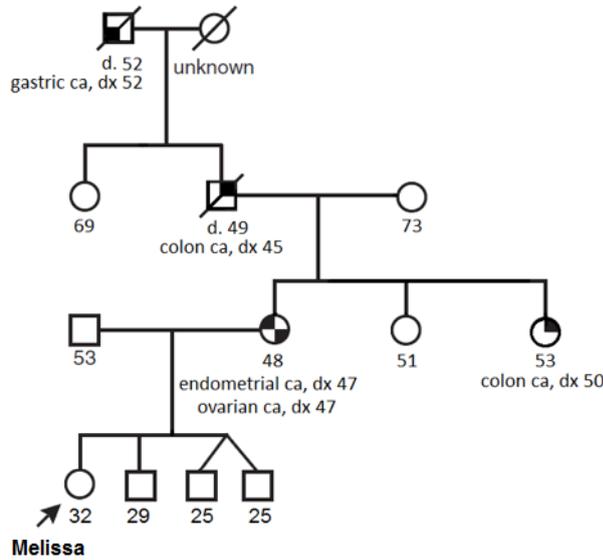
	Yes	No	Not sure
a. Genetic services?	<input type="checkbox"/> ¹	<input type="checkbox"/> ²	
b. DNA mutation testing?	<input type="checkbox"/> ¹	<input type="checkbox"/> ²	<input type="checkbox"/> ³
c. Tumour immunohistochemistry (IHC) testing	<input type="checkbox"/> ¹	<input type="checkbox"/> ²	<input type="checkbox"/> ³
d. Tumour microsatellite instability (MSI) testing	<input type="checkbox"/> ¹	<input type="checkbox"/> ²	<input type="checkbox"/> ³

7. Do you consider the following testing a germline test?

	Yes	No	Not sure
a. IHC testing?	<input type="checkbox"/> ¹	<input type="checkbox"/> ²	<input type="checkbox"/> ³
b. MSI testing?	<input type="checkbox"/> ¹	<input type="checkbox"/> ²	<input type="checkbox"/> ³

Case Scenario

Please read the following patient background before answering Questions 8 and 9. This is not a test. Your replies are anonymous and will be treated confidentially. Please answer all items. If you are unfamiliar with a pedigree format and need more explanation, please read the paragraph next to the pedigree below.



- Legend**
- Male
 - Female
 - Colon cancer
 - Ovarian cancer
 - Gastric cancer
 - Endometrial cancer
 - d. Died
 - dx. Diagnosed

A new patient Melissa, 32 year old, visits you for the first time for a routine annual examination. Her physical examination shows that she is in good health. During the visit, she mentions to you that she has a family history of cancers. Her maternal aunt, aged 53, had colon cancer at 50, and her mother (now aged 48 years) had endometrial and ovarian cancer at 47. Her maternal grandfather had colon cancer at 45, and her maternal great grandfather had gastric cancer at 52. Her paternal family history is unremarkable. She is very concerned about her risk of developing cancer.

8. In your medical opinion, what is Melissa’s risk for developing the following cancers as compared to the general population? (Please answer all items).

	Much higher	Somewhat higher	Same	Somewhat lower	Not sure
a. Breast cancer	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
b. Gastric cancer	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
c. Ovarian cancer	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
d. Thyroid cancer	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
e. Colorectal cancer	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
f. Endometrial cancer	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹

9. About a year later, Melissa was diagnosed with endometrial cancer. How would you proceed?

	Very likely	Somewhat likely	Not likely	Very unlikely	Not sure
a. Offer surveillance	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
b. Referral to a geneticist	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
c. Family history assessment	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
d. Discussion of risk-reducing surgery	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
e. Referral to a non-genetics specialist	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
f. Order genetic testing for germline mutations	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
g. Order pre-genetic testing of tumour tissue (e.g., MSI or IHC)	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
h. Discussion about Lynch syndrome cancers with patient	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
i. No action	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹

10. If you have chosen to offer surveillance, what would you offer? (check all that apply)
- Colonoscopy
 - Gastroscopy
 - CA125
 - Mammography
 - Other, please specify _____
11. If you have chosen to discuss risk-reducing surgery with patients, what kind of risk-reducing surgery would you discuss with the patient?
Please specify _____

General Attitudes about Genetic Services

The following section is about why you would or would not refer patients for genetic services. We would like you to answer the questions whether or not you currently use genetic services.

12. In your opinion, which of the following factors play a role in your decision to refer a patient for genetic services? (Check all that apply)
- ¹ Patient interest or request
 - ² Ethical and legal responsibility
 - ³ Reassurance for the patient and family
 - ⁴ To provide genetic counselling for the patient
 - ⁵ Genetic testing for germline mutations
 - ⁶ To provide appropriate cancer risk assessment for the patient
 - ⁷ To provide appropriate screening and management for the patient
 - ⁸ To provide appropriate screening and/or management for the patients' family
 - ⁹ Other, please specify: _____
13. In your opinion, which of the following factors play a role in your decision to NOT refer a patient for genetic services? (Check all that apply)
- ¹ I do not feel it is my responsibility
 - ² I do not have access to a genetic health service
 - ³ Patients may be at risk for insurance discrimination
 - ⁴ Long waiting time for appointment at a genetic clinic
 - ⁵ Patient was not interested when referral was offered
 - ⁶ I do not feel familiar with hereditary cancer syndromes
 - ⁷ Patient is unlikely to benefit from genetic counselling and/or testing
 - ⁸ I do not know how to make a referral to the local genetic health service
 - ⁹ Recommendations and guidelines are not available to select patients for referral
 - ¹⁰ Other, please specify: _____

14. Who do you think is best to refer patients for genetic services (*i.e.*, to make the initial offer)?
(Please choose only one of the following, and provide the reason(s) for your selection)

- General practitioners
- Gynaecologists
- Gastroenterologists
- Gynaecology oncologists
- Medical oncologists
- Radiation oncologists
- Colorectal surgeons
- General surgeons
- Any of the above

Make a comment on your choice here: _____

15. When is the best time for the initial referral for genetic services to be made to the patient? (Please choose only one of the following, and provide the reason(s) for your selection)

- When family history is collected
- At diagnosis of cancer
- After surgery and before commencement of adjuvant therapy
- During adjuvant therapy
- After treatment is finished
- At any time

Make a comment on your choice here: _____

16. I feel my role as a physician includes: (Check all that apply)

- ¹ Providing emotional support after genetic testing
- ² Identifying patients for referral to genetic services
- ³ Interpreting germline DNA-based genetic test results
- ⁴ Collecting a three-generation family history information
- ⁵ Ordering pre-genetic testing of tumour tissue (e.g. MSI or IHC)
- ⁶ Counselling patients about their cancer risks **after** genetic testing
- ⁷ Counselling patients about their cancer risks **before** genetic testing
- ⁸ Calculating relative risk of cancer associated with family cancer history
- ⁹ Discussing the need for cancer surveillance or prophylaxis with patients when required
- ¹⁰ Providing regular clinical examination and care to patients with hereditary cancer syndromes
- ¹¹ Other, please specify: _____

17. In your opinion, which of the following would support your practice? (Please choose the appropriate response for each item)

	Very likely	Somewhat likely	Not likely	Very unlikely	Not sure
a. Clear referral guideline	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
b. Online risk assessment tool	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
c. Continuing genetic education programmes	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
d. Genetic information brochure for patients	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
e. A coordinator in clinic to collect patient family history	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
f. A genetic counsellor in clinic to assess risk and to facilitate referral	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
g. A computerized family history tool with decision support for referral	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹
h. The presence of a genetic counsellor in a multidisciplinary tumour board meeting	<input type="checkbox"/> ⁵	<input type="checkbox"/> ⁴	<input type="checkbox"/> ³	<input type="checkbox"/> ²	<input type="checkbox"/> ¹

18. Is there anything else you would like to tell us about?

19. If you would like to receive a copy of the research summary report, please enter your email address here: _____

Appendix 2. Risk Management for Lynch Syndrome (eviQ version 2)

Risk Management for Lynch Syndrome



ID: 001410 (V2) Approved: 18 Oct 2009 Last Modified: 29 Jan 2014 Review Due: 29 Aug 2014

- Information for families with Lynch Syndrome**
- Contacting family members about hereditary cancer**

Lynch Syndrome is an autosomal dominant condition caused by germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6* or *PMS2*.

Target group

- n known mismatch repair (MMR) gene mutation carrier
- n 50% risk of being a MMR gene mutation carrier

Exclusion criteria

Not suitable for:

- n individuals from families fulfilling **Amsterdam I or II** clinical criteria with **active exclusion of MMR defect** by tumour testing or in whom no molecular tumour testing or germline testing is possible
- n familial gastric cancer syndrome
- n individuals and first degree relatives of individuals with a tumour showing loss of functional MMR pathway but in whom no germline MMR mutation has been identified

Lifetime risk of cancer

Cancer	Lynch syndrome to age 70 yrs*, **, 1	General population to age 85 yrs
Colorectal (male)	38%	10%***
Colorectal (female)	31%	6.6%***
Endometrial	33%	? - 3%
Gastric	7%	?%
Ovarian	9%	? - 2%
Urothelial	≤3%	?%
Brain	≤3%	?6%
Small Bowel	≤3%	0.01%

* Higher figures obtained in papers not corrected for ascertainment bias

** Combined data for *MLH1*, *MSH2*, *MSH6*, **but risks shown do vary per gene**

*** This data does not take into account the impact of surveillance.
Data Source: NSW Central Cancer Registry 2008 final dataset and NSW Health Outcomes Information Statistical Toolkit (HOIST).

Cancer risk management guidelines

All patients should be entered on a local hereditary cancer registry for information and surveillance reminders. ([Link to Hereditary Cancer Registry](#))

Cancer type	Recommendations
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Risk Management for Lynch Syndrome

Colorectal	Surgical	<ul style="list-style-type: none"> consider subtotal colectomy in selected individuals
	Surveillance	<ul style="list-style-type: none"> annual colonoscopy from age 25 yrs or 5 yrs younger than youngest affected if <30yrs review frequency of colonoscopy at age 60 yrs with a view to reduced frequency
	Risk-reducing medication	<ul style="list-style-type: none"> there may be a reduction of risk in taking aspirin however the appropriate dose is not yet defined (preliminary data)
Endometrial	Surgical	<ul style="list-style-type: none"> recommend hysterectomy after childbearing complete or from age 40yrs
	Surveillance	<ul style="list-style-type: none"> there is no evidence for transvaginal ultrasound (TVU) and/or aspiration biopsy
Ovarian	Surgical	<ul style="list-style-type: none"> recommend risk reducing salpingo-oophorectomy (RRSO) at time of hysterectomy
	Surveillance	<ul style="list-style-type: none"> there is no evidence for serum CA125 and/or transvaginal ultrasound (TVU)
Gastric	Surveillance	<ul style="list-style-type: none"> consider second yrly gastroscopy from age 30 yrs in families with gastric cancer or those at high ethnic risk - e.g. Chinese, Korean, Chilean and Japanese
Urothelial	Surveillance	<ul style="list-style-type: none"> no evidence of benefit but patients encouraged to report symptoms e.g. haematuria

Management of associated health problems and side effects

Management of early menopause

As there is no conclusive data regarding an increased risk of breast cancer in Lynch Syndrome the use of Hormonal Replacement Therapy (HRT) after oophorectomy is not contraindicated.

Evidence for risk management guidelines

Colorectal cancer

Surgical

No controlled trials regarding partial versus total colectomy for the management of colorectal cancer (CRC) are available. One decision analysis has reported an increase in life expectancy with subtotal colectomy².

Surveillance

A study of 114 Lynch Syndrome families comparing outcomes of screening at intervals of <2yrs with >2yrs demonstrated CRCs diagnosed at higher stage with longer interval surveillance. Evidence supports screening 1-2yrly³.

Since 57% of the neoplasms in Lynch Syndrome occur proximal to the splenic flexure⁴, visualisation to the caecum is essential. Given the high metachronous CRC risk in Lynch Syndrome (16% 10 yrs after a partial colectomy)³, total colectomy should be discussed if a CRC is detected on surveillance.

Endometrial cancer

Surgical

Hysterectomy and RRSO are the only proven interventions which significantly reduce the risk of both endometrial and ovarian cancer⁵.

Risk Management for Lynch Syndrome

Surveillance

There is no evidence to support a survival benefit from TVU and aspiration biopsy³. Where possible, surveillance should be offered in the context of a clinical trial⁵.

Ovarian cancer

Surgical

Risk reducing salpingo-oophorectomy (RRSO) reduces the risk of developing ovarian cancer in mutation carriers. One study demonstrated no cases of ovarian cancer amongst women who had undergone RRSO compared with 5% of controls being diagnosed with ovarian cancer with mean follow up of 7yrs⁶.

Surveillance

Data extrapolated from other high risk groups demonstrates annual TVU and serum CA125 levels do not detect ovarian cancers at an earlier stage, nor do they affect outcomes⁵. This form of screening is also associated with a high false positive rate requiring surgical intervention⁷.

Gastric cancer

Surveillance

There is no evidence supporting the role of gastroscopy in the surveillance for gastric cancer in Lynch syndrome patients⁸, however, InSiGHT has recommended gastroscopy in families at high risk of gastric cancer⁹.

Urothelial transitional cell carcinoma

Surveillance

There is no evidence for the role of urine cytology in the surveillance of urothelial carcinomas in MMR gene carriers. One study of individuals with confirmed or suspected Lynch Syndrome demonstrated urine cytology had a sensitivity for malignancy of only 29%¹⁰.

Support and information

First degree relatives, (parents, brothers/sisters and children) are at 50% risk of having inherited the condition. First degree relatives should be referred to a local Family Cancer Clinic.

Link to an [information sheet on contacting relatives](#)

Website resources

Centre for Genetics Education NSW Health
Association of Genetic Support of Australasia INC (AGSA)
[Link to Hereditary Cancer Registry](#)

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Risk Management for Lynch Syndrome

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