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ARTICLE

Uptake of genetic testing by the children of Lynch syndrome variant carriers across three generations

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Many Lynch syndrome (LS) carriers remain unidentified, thus missing early cancer detection and prevention opportunities. Tested probands should inform their relatives about cancer risk and options for genetic counselling and predictive gene testing, but many fail to undergo testing. To assess predictive testing uptake and demographic factors influencing this decision in LS families, a cross-sectional registry-based cohort study utilizing the Finnish Lynch syndrome registry was undertaken. Tested LS variant probands (1184) had 2068 children divided among three generations: 660 parents and 1324 children (first), 445 and 667 (second), and 79 and 77 (third). Of children aged >18 years, 801 (67.4%), 146 (43.2%), and 5 (23.8%), respectively, were genetically tested. Together, 539 first-generation LS variant carriers had 2068 children and grandchildren (3.84 per carrier). Of the 1548 (2.87 per carrier) eligible children, 952 (61.5%) were tested (1.77 per carrier). In multivariate models, age (OR 1.08 per year; 95% CI 1.06–1.10), family gene (OR 2.83; 1.75–4.57 for *MLH1* and 2.59; 1.47–4.56 for *MSH2* compared with *MSH6*), one or more tested siblings (OR 6.60; 4.82–9.03), no siblings (OR 4.63; 2.64–8.10), and parent under endoscopic surveillance (OR 5.22; 2.41–11.31) were independent predictors of having genetic testing. Examples of parental adherence to regular surveillance and genetically tested siblings strongly influenced children at 50% risk of LS to undergo predictive gene testing. High numbers of untested, adult at-risk individuals exist even among well-established cohorts of known LS families with good adherence to endoscopic surveillance.

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INTRODUCTION

Lynch syndrome (LS) predisposes to high lifetime risk of malignancies, including colorectal (CRC) and endometrial cancers, and tumours at several other extracolonic sites, such as gastric, ovarian, hepatobiliary, urinary tract, small bowel, central nervous system, pancreas, prostate, and breast cancer. The cumulative prospective risks for any cancer in patients with LS at the age of 70 years vary according to the mismatch repair (MMR) gene affected: *MLH1* 75%, *MSH2* 79%, *MSH6* 53%, and *PMS2* 37%, although the overall 10-year survival after any first cancer is generally good, at 87%.[1] However, the majority of LS variant carriers are unaware of their condition and the underlying cancer risk[2] despite the recommendations for universal immunohistochemistry screening of all new CRC cases.[3–6] Unfortunately, some guidelines, such as those of the National Comprehensive Cancer Network,[7] recommend genetic testing of LS only for individuals who meet clinical criteria (Amsterdam II or the revised Bethesda guidelines) that are known to miss a large proportion of LS carriers.[8] As a consequence, recommendations for universal tumour screening are not widely followed that decreases the numbers of LS diagnoses. In addition, the cost-effectiveness of universal LS screening of CRC with immunohistochemistry and *BRAF* mutation status depends on the predictive testing (PT) uptake rate among relatives.[9]

In particular, subjects without personal cancer history but belonging to LS families with an ascertained gene variant are able to obtain risk assessment and genetic counselling via national LS registries and health-care professionals. The clinical management of first-, second-, and third-degree relatives of LS probands begins with the provision of information regarding the benefits of family member genetic counselling followed by PT.[3] PT is available to all at-risk relatives in families with known MMR gene variants affecting function.[8] Overall, improved diagnostics of LS offers several advantages. First, increased surveillance, including frequent colonoscopy at a 1–3-year interval, is offered to those with a proven gene variant.[3,6,10,11] Surveillance colonoscopy of known LS carriers improves the detection rate of CRC and greatly improves survival compared with those not under surveillance.[12] Second, new additional treatment and prevention modalities for MMR-deficient cancers such as checkpoint inhibitors, vaccines, and chemoprevention are under development, which may improve the prognosis of LS. Third, tested non-carriers are released from the requirement for burdensome surveillance, because their risk is at the general population level.

However, the uptake of genetic counselling and PT is known to be poor among first-degree relatives (FDRs) of identified probands. Only 30–52% of LS proband relatives receive counselling although the frequency of genetic testing among those counselled is 95%.[13–15] The major problem is that the parents' or relatives' disclosure (or non-disclosure) of carrier status does not effectively lead to genetic counselling. On average, only three unaffected relatives are tested per one identified carrier.[3,13–15] Together, these observations indicate that most LS carriers are not identified and thus the potential for cancer prevention is missed, which is unsatisfactory in the era of precision medicine.[16]

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The Finnish LS registry (LSRFi) has recorded patients with LS since the 1980s, prior to the availability of PT. In many of the families, three generations of carriers have already been tested. However, there are no reports regarding the potential change in counselling and PT uptake from one generation to the next in known LS families. The objective of this analysis was to identify factors in the LS families that predict the decision to undergo PT.

Table 1 Clinical characteristics of the MMR variant carriers and their offspring

	First generation	*Second generation*	*Third generation*	*All*
Parents				
MMR variant carriers, *n*	660	445	79	1184
Sex				
Female (%)	352 (53.3)	219 (49.2)	32 (40.5)	603 (50.9)
Male (%)	308 (46.7)	226 (50.8)	47 (59.5)	581 (49.1)
Vital status				
Deceased (%)	158 (23.9)	26 (5.8)	1 (1.3)	185 (15.6)
Number from cancer	99	20	0	119
Living (%)	502 (76.1)	419 (94.2)	78 (98.7)	999 (84.4)
Age (parents alive)				
Mean (SD)	60.4 (12.4)	42.6 (11.6)	31.8 (8.1)	50.7 (15.5)
Cancer status				
Cancer (%)	449 (68.0)	133 (29.9)	5 (6.3)	587 (49.6)
No cancer (%)	211 (32.0)	312 (70.1)	74 (93.7)	597 (50.4)
Number with children				
Has children (%)	539 (81.7)	298 (67.0)	36 (45.6)	873 (73.7)
No children (%)	121 (18.3)	147 (33.0)	43 (54.4)	311 (26.3)
Number of children				
Mean (SD)	1.9 (1.4)	1.5 (1.4)	1.0 (1.3)	1.7 (1.4)
Range	0–10	0–9	0–4	0–10
Under surveillance (of those alive)				
Yes (%)	465 (93.8)	390 (94.9)	73 (96.1)	928 (94.4)
No (%)	31 (6.3)	21 (5.1)	3 (3.9)	55 (5.6)
Missing	6	8	2	16
Gene affected				
MLH1 (%)	500 (75.8)	340 (76.4)	66 (83.5)	906 (76.5)
MSH2 (%)	109 (16.5)	79 (17.8)	8 (10.1)	196 (16.6)
MSH6 (%)	51 (7.7)	26 (5.8)	5 (6.3)	82 (6.9)
Children				
Number of children	1324	667	77	2068
Sex[a]				
Female (%)	641 (48.4)	320 (48.1)	40 (51.9)	1061 (51.3)
Male (%)	679 (51.3)	345 (51.7)	37 (48.1)	1001 (48.4)
Missing	4 (0.3)	2 (0.3)	0	6 (0.3)
Vital status				
Deceased (%)	36 (2.7)	8 (1.2)	0	44 (2.1)
Living (%)	1288 (97.3)	659 (98.8)	77 (100.0)	2024 (97.9)
Age (of those alive)				
Mean (SD)	40.4 (15.2)	20.0 (12.0)	12.8 (7.6)	32.7 (17.4)
>18 years (%)	1189 (92.3)	338 (51.3)	21 (27.3)	1548 (76.4)
<18 years (%)	99 (7.7)	321 (48.7)	56 (72.7)	476 (23.6)
Tested (of those alive)				
Tested aged >18 years (%)	801 (62.2)	146 (21.9)	5 (6.5)	952 (46.0)
Not tested aged >18 years (%)	388 (30.1)	192 (28.8)	16 (20.8)	596 (28.9)
Not tested aged <18 years (%)	99 (7.7)	321 (48.1)	56 (72.7)	476 (22.9)
Parent gene affected				
MLH1 (%)	1019 (77.0)	517 (77.5)	68 (88.3)	1604 (77.6)
MSH2 (%)	203 (15.3)	112 (16.8)	4 (5.2)	319 (15.4)
MSH6 (%)	102 (7.7)	38 (5.7)	5 (6.5)	145 (7.0)
Number of siblings				
Mean (SD)	2.1 (1.6)	1.8 (1.3)	1.6 (1.0)	2.0 (1.5)
Range	0–9	0–8	0–3	0–9

[a]Sex was missing for six subjects.

METHODS

Data collection

The study subjects consisted of members of LS families in the LSRFi, which includes demographic, genetic, and clinical information on patients and carriers of identified LS families. The registry works as a national research database of patients and high-risk family members. The families have been included in the registry based on clustered LS cancers, and after verification of the proband germline variant, the pedigrees of the families have been created. The genealogical survey was based on the Finnish Population Register, which has enabled the complete registration of all offspring of the LS variant carriers.

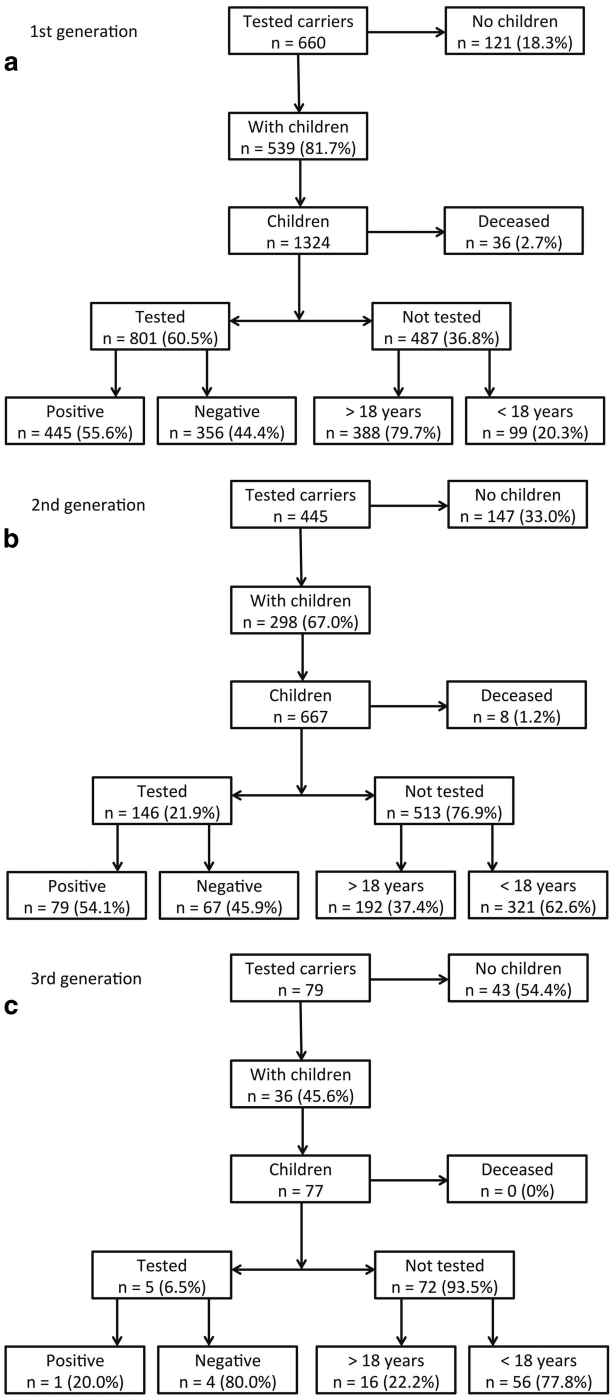

Figure 1 Flowcharts of (**a**) first generation, (**b**) second generation, and (**c**) third generation.

A written informed consent to include them in LSRFi was obtained from each tested individual. The administration of the Central Finland health-care district approved this registry study, which did not require any direct contact with individuals in the registry.

At the time of analysis (October 2015), the LSRFi consisted of 270 families with 1184 tested LS variant carriers that had a total of 2068 known children. The database included all at-risk relatives who had not opted for testing but carried a risk of harbouring an LS variant as direct offspring.[17] The original cohort of 660 first-generation LS carriers, who were not children of any other registered LS probands themselves, was analysed with their offspring forming the second and third generations of tested and non-tested subjects. Age, sex, family structure, family history of cancer, cause of death, and adherence to colonoscopy surveillance in each generation was recorded for this report.

Genetic testing

Relatives of known LS probands were eligible for genetic testing after 18 years of age. The children of LS carriers were mainly offered testing (i) when the subject contacted the LS registry genetic counsellor upon encouragement by a relative (known proband); (ii) when the subject attended genetic counselling based on family cancer history; or (iii) in case of LS cancer of their own. In 2003, 286 subjects of the registry were sent a letter as part of a direct-contact approach (DCA) study resulting in 112 subjects being tested, of which 32 were tested positive.[18] In 1995–1998, 446 subjects were contacted by their family member with a letter from the LS registry as a part of a family-mediated approach (FMA) study, resulting in 334 subjects being tested, of which 99 were tested positive.[19] Subjects of these two contact studies represented carriers and non-carriers of the first and second generation of this study. Outside of these two studies, no direct contact by the registry personnel was established.

Statistical analysis

A chi-square test was used for categorical variables and an independent sample *t*-test was used for continuous normally distributed variables when determining the statistical significance between tested and untested subjects. One-way ANOVA was used for multiple comparisons of continuous variables. Logistic regression analysis was used as a multivariate model for continuous and categorical variables. Variables with $P<0.2$ in univariate analysis were included in the model. Otherwise, $P<0.05$ was considered as a limit for statistical significance. All statistical tests were two sided. Some continuous variables such as number of siblings were categorized to provide more readable results. To fit most subjects to the multivariate model, the age of a deceased parent was categorized as 'dead' and compared as a single age group. Statistical analyses were conducted using SPSS for Mac 23.0.0.0 (IBM Corp., Armonk, NY, USA).

RESULTS

In total, 1184 tested LS probands had 2068 children of which 2024 (97.9%) were alive at the time of the study. Of those aged >18 years ($n=1548$, 76.4%), 952 (61.5%) had undergone PT and 596 (38.5%) had not. Those aged <18 years ($n=476$, 23.6%) were not tested.

The data were divided into generations of LS carriers and their offspring and are presented in Table 1 together with data of the whole cohort. The first generation was formed by 660 probands, of which 539 (81.7%) had 1324 children (mean 2.5 children), of which 1288 (97.3%) were alive. Of those, 1189 (92.3%) were aged >18 years and eligible for PT. Out of the 1189, 801 (67.4%) underwent PT with 445 (55.6%) subjects testing positive for a germ line variant of an MMR gene affecting function, forming the second generation of LS variant carriers.

In the second generation, out of the 445 carriers, 298 (67.0%) had 667 children (mean 2.2 per carrier with children), of which 659 (98.8%) were alive at the time of the study. Of the living children, 338 (51.3%) were aged >18 years and eligible for PT. Among those, 146 (43.3%) underwent testing, of which 79 (54.1%) were positive for germline LS gene variant, thus forming the third generation of carriers.

In the third generation, the mean age of variant carriers was 31.8 years, of whom only 36 (45.6%) had children. Of the 77 total children, all were alive and 21 (27.3%) were eligible for PT. Five (20.8%) subjects at 50% risk had already opted for PT, with one testing positive for germ line variant, starting the fourth generation of tested carriers.

Taken together, 539 variant carriers of the first generation had 2068 children and grandchildren (3.84 per carrier), of which 1548 (2.87 per carrier, 76.5%) were alive and eligible for PT, with 952 (61.5%) having been tested (1.77 per carrier). Flowcharts of the formation of each generation are presented in Figure 1a–c. The numbers of children of each generation of carriers are presented in Figure 2.

The offspring of the first generation (40.4 years) were generally older than the children of the second (20.0 years) and the third (12.8 years) generation of LS variant carriers. Our analysis was focussed on those eligible for testing, that is, >18 years of age, and on the demographic covariates of their decision to undergo PT.

Factors influencing the uptake of genetic testing

In three generations, 1548 subjects were eligible for PT. Those having had PT were older than those who had not undergone PT (44.8 *vs* 31.4 years, $P<0.001$) although they did not differ statistically by sex. Of those who were not tested, 57.7% were aged <30 years, whereas 88.6% of the tested were aged >30 years. Children of *MSH6* variant carriers were less likely to be tested compared with those of *MLH1* and *MSH2* variant carriers. In addition, having a female parent as a carrier was statistically significantly associated with offspring being tested. Cancer or death of a carrier parent (but not cancer death) represented the strongest predictors of PT. In addition, higher age of a parent and one or more siblings chosen to take PT were associated with the probability of being tested. Comparison of adults who underwent and who did not undergo genetic testing in each generation are presented in Table 2.

Of the 55 tested carriers not under regular surveillance at the time of the analysis, 23 were living abroad. Of the remaining 32, 19 were first-generation, 12 second-generation and 1 third-generation carriers. Only 26 actually declined surveillance, but 6 repeatedly did not attend the scheduled appointment.

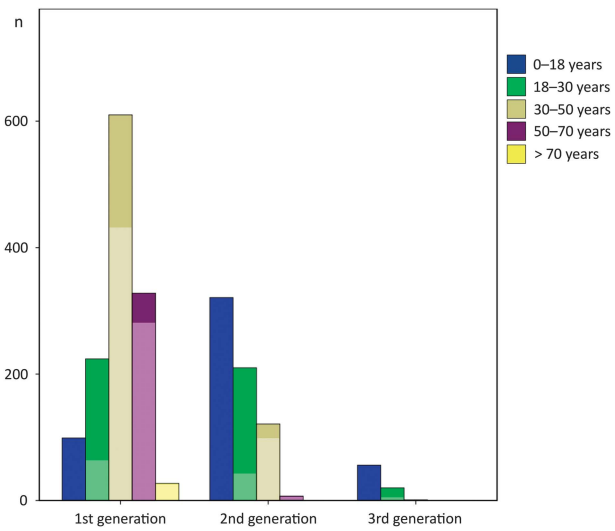

Figure 2 Number of children of carriers in each generation grouped by age. The separated portion of each bar represents the percentage tested within the group.

Multivariate analysis

Variables with $P<0.2$ in univariate analysis included the age of the subject age (continuous), affected gene or sex of the parent, categorized number of siblings, whether a sibling was tested, and categorized age, cancer status, and endoscopic surveillance of the parent. For those whose parent was deceased, endoscopic surveillance was categorized as 'yes' and parent age was categorized as 'dead'. Out of the 1548 subjects, a total of 1525 were included in the logistic regression model (Table 3).

From the covariates tested in the multivariate model, age, gene, number of siblings, siblings having been tested, and prior or ongoing endoscopic surveillance of the parent were independent factors of the decision of having had PT. Parent sex and prior cancer of a parent were statistically non-significant in the logistic regression model. Being an only child (OR 4.63), a sibling to a tested carrier (OR 6.60) or having a parent under endoscopic surveillance (OR 5.22) represented the strongest predictors of having opted for PT. To avoid bias that may have been derived from a high number of 18–25-year-old subjects who may still be in the process of considering having PT, we conducted the multivariate model on those aged >25 years. The same variables were independent predictors of PT, and in addition, prior cancer in a parent was identified as a statistically significant covariate as well (OR 1.40; 1.01–1.95).

DISCUSSION

In the current study, 67.4% of disclosure-aged children of the first generation, 43.2% of the second and 23.8% of the third had chosen to undergo PT. The decrease of uptake rate by generation may be explained by the age distribution of the offspring: even though the limit of 18 years of age enables the possibility to undergo PT, the average age of getting tested was 32.5 years. However, as the PT became available in the mid-1990's, many of the first-generation children underwent testing when they were older than the tested individuals among the second- and third-generation children. It is reasonable that older subjects have become more adjusted over time to the idea of possibly having LS and also simply had more time to get tested than the younger individuals. It also appears possible that at-risk persons currently become tested at younger age when testing is available in their youth; conversely, the uptake of PT may decrease as the prognosis of common LS-related cancers has improved.

It is known that the disclosure of personal test results to children among LS carriers is generally good. Nearly 90% of tested individuals with children informed their offspring of the test result[20]; however, the resulting uptake of children to undergo PT was not reported in the study, as this factor is infrequently documented and is therefore generally not known. Instead, the majority of previous studies have addressed the proportion of FDRs at risk to undergo genetic testing, including siblings, parents, and children.

For example, 90% of FDRs in a Finnish FMA study in 2000 consented to the study, 78% consented to genetic counselling, and 75% (334/446) underwent PT.[19] After completing the FMA study in 2003, a DCA study was carried out, wherein 51% of relatives consented to the study, 40% (113/286) consented to counselling, and 39% (112/286) underwent PT.[18] The lower figures of participation were obviously a consequence of the fact that the non-consented relatives were partly the same in both studies. In the latter study, the low proportion of LS variant-positive individuals (32/112, 28%) among the tested subjects is also reflective of inclusion of the cohort of relatives at 25% risk.[18] Both previous interventions may have increased PT uptake rate at the time.

Table 2 Characteristics of adults who underwent and did not undergo genetic testing in three generations

	First-generation children aged > 18 years			*Second-generation children aged > 18 years*			*Third-generation children aged > 18 years*			*All*		
	Tested	*Not tested*	*P-value*	*Tested*	*Not tested*	*P-value*	*Tested*	*Not tested*	*P-value*	*Tested*	*Not tested*	*P-value*
Number												
n (%)	801 (67.4)	388 (32.6)		146 (43.2)	192 (56.8)		5 (23.8)	16 (76.2)		952 (61.5)	596 (38.5)	
Sex												
Female (%)	399 (49.8)	181 (46.6)	0.550	66 (45.2)	87 (45.3)	1.000	3 (60.0)	7 (43.8)	0.635	468 (49.2)	275 (46.1)	0.424
Male (%)	399 (49.8)	206 (53.1)		80 (54.8)	105 (54.7)		2 (40.0)	9 (56.3)		481 (50.5)	320 (53.7)	
Missing[a]	3 (0.4)	1 (0.3)								3	1	
Age												
Mean (SD)	46.6 (12.1)	35.0 (11.8)	<0.001	35.4 (8.0)	24.9 (6.3)	<0.001	28.2 (2.1)	21.7 (2.3)	<0.001	44.8 (12.3)	31.4 (11.3)	<0.001
18–25 years (%)	14 (1.8)	88 (22.8)	<0.001	12 (8.2)	122 (63.9)	<0.001	0	0	0.001	26 (2.7)	224 (37.8)	<0.001
25–30 years (%)	49 (6.1)	72 (18.7)		30 (20.5)	44 (23.0)		0	14 (87.5)		83 (8.7)	118 (19.9)	
30–40 years (%)	197 (24.6)	102 (26.4)		66 (45.2)	21 (11.0)		4 (80.0)	2 (12.5)		264 (27.8)	123 (20.7)	
40–50 years (%)	234 (29.3)	76 (19.7)		32 (21.9)	2 (1.0)		1 (20.0)	0		266 (28.0)	78 (13.2)	
> 50 years (%)	306 (38.3)	48 (12.4)		6 (4.1)	2 (1.0)		0	0		312 (32.8)	50 (8.4)	
Missing[b]	1	2		0	1		0	0		1	3	
Age at genetic test												
Mean (SD)	33.9 (9.9)			25.8 (5.8)			22.0 (1.6)			32.5 (9.8)		<0.001
Number of siblings												
Mean (SD)	2.29 (1.76)	1.88 (1.36)	<0.001	1.46 (0.77)	2.07 (1.67)	<0.001	2.00 (1.00)	2.25 (0.86)	0.549	2.16 (1.67)	1.95 (1.46)	0.008
≥3	264 (33.0)	82 (21.1)	<0.001	11 (7.5)	48 (25.0)	<0.001	2 (40.0)	7 (43.8)	NA[c]	277 (29.1)	137 (23.0)	0.030
1–2	474 (59.2)	273 (70.4)		123 (84.2)	126 (65.6)		3 (60.0)	8 (50.0)		600 (63.0)	407 (68.3)	
0	63 (7.9)	33 (8.5)		12 (8.2)	18 (9.4)		0	1 (6.3)		75 (7.9)	52 (8.7)	
Parent gene affected												
MLH1 (%)	636 (79.4)	279 (71.9)	<0.001	121 (82.9)	144 (75.0)	0.105	4 (80.0)	12 (75.0)	0.426	761 (79.9)	435 (73.0)	<0.001
MSH2 (%)	121 (15.1)	56 (14.4)		14 (9.6)	34 (17.7)		1 (20.0)	1 (6.3)		136 (14.3)	91 (15.3)	
MSH6 (%)	44 (5.5)	53 (13.7)		11 (7.5)	14 (7.3)		0	3 (18.8)		55 (5.8)	70 (11.7)	
Sex of parent carrier												
Female (%)	461 (57.6)	188 (48.5)	0.003	77 (52.7)	112 (58.3)	0.321	2 (40.0)	6 (37.5)	1.000	540 (56.7)	306 (51.3)	0.041
Male (%)	340 (42.4)	200 (51.5)		69 (47.3)	80 (41.7)		3 (60.0)	10 (62.5)		412 (43.3)	290 (48.7)	
Parent vital status												
Deceased (%)	270 (33.7)	66 (17.0)	<0.001	24 (16.4)	10 (5.2)	0.001	0	0		294 (30.9)	76 (12.8)	<0.001
Living (%)	531 (66.3)	322 (83.0)		122 (83.6)	182 (94.8)		5 (100)	16 (100)		658 (69.1)	520 (87.2)	
Cause of parent death												
Deceased from other cause (%)	104 (38.5)	25 (37.9)	0.495	3 (12.5)	1 (10.0)	1.000	0	0		107 (36.4)	26 (34.2)	0.687
Deceased from cancer (%)	159 (58.9)	40 (60.6)		16 (66.7)	9 (90.0)		0	0		175 (59.5)	49 (64.5)	
Missing[d]	7 (2.6)	1 (1.5)		5 (20.8)	0		0	0		12 (4.1)	1 (1.3)	

Table 2 (Continued)

	First-generation children aged > 18 years			*Second-generation children aged > 18 years*			*Third-generation children aged > 18 years*			*All*		
	Tested	*Not tested*	*P-value*	*Tested*	*Not tested*	*P-value*	*Tested*	*Not tested*	*P-value*	*Tested*	*Not tested*	*P-value*
Age of living parent carrier												
<50 years (%)	8 (1.5)	44 (13.5)	<0.001	17 (14.0)	105 (57.7)	<0.001	5 (100.0)	16 (100.0)	1.000	30 (4.6)	165 (31.5)	<0.001
50–70 years (%)	339 (63.6)	241 (74.2)		98 (81.0)	77 (42.3)		0	0		437 (66.3)	318 (60.8)	
70–100 years (%)	186 (34.9)	40 (12.3)		6 (5.0)	0 (0)		0	0		192 (29.1)	40 (7.6)	
Cancer status of parent carrier												
Cancer (%)	614 (76.7)	232 (59.8)	<0.001	99 (67.8)	72 (37.5)	<0.001	0	2 (12.5)	1.000	713 (74.9)	306 (51.3)	<0.001
No cancer (%)	187 (23.3)	156 (40.2)		47 (32.2)	120 (62.5)		5 (100.0)	14 (87.5)		239 (25.1)	290 (48.7)	
Parent carrier in surveillance (parent living)												
Yes (%)	513 (96.7)	299 (92.9)	0.042	122 (100.0)	171 (94.0)	0.004	5 (100.0)	15 (93.8)	1.000	640 (97.3)	487 (93.7)	0.004
No (%)	18 (3.4)	21 (7.1)		0 (0)	11 (6.0)		0	1 (6.3)		18 (2.7)	33 (6.3)	
Siblings												
Yes (%)	738 (92.1)	355 (91.5)	0.734	134 (91.8)	174 (90.6)	0.847	5 (100.0)	15 (93.8)	1.000	877 (92.1)	544 (91.3)	0.569
No (%)	63 (7.9)	33 (8.5)		12 (8.2)	18 (9.4)		0	1 (6.3)		75 (7.9)	52 (8.7)	
Sibling deceased												
Yes (%)	15 (1.9)	4 (1.0)	0.333	1 (0.7)	2 (1.0)	1.000	0	0	1.000	16 (1.7)	6 (1.0)	0.378
No (%)	786 (98.1)	384 (99.0)		145 (99.3)	190 (99.0)		5 (100.0)	16 (100.0)		936 (98.3)	590 (99.0)	
One or more siblings tested												
Yes (%)	661 (82.5)	163 (42.0)	<0.001	110 (75.3)	35 (18.3)	<0.001	2 (40.0)	6 (37.5)	1.000	773 (81.2)	204 (34.2)	<0.001
No (%)	140 (17.5)	225 (58.0)		36 (24.7)	157 (81.7)		3 (60.0)	10 (62.5)		179 (18.8)	392 (65.8)	

[a]Sex was missing for four subjects.
[b]The exact age was missing for four subjects.
[c]Numbers were too small for statistical comparison.
[d]Cause of death was missing for 13 subjects.

Table 3 Logistic regression analysis of covariates that were statistically significant in the univariate analysis

	Children aged > 18 years *Genetic testing as end variable* n = *1525*		*Children aged > 25 years* *Genetic testing as end variable* n = *1279*	
Covariates	*OR (95% CI)*	P	*OR (95% CI)*	P
Age per year	1.08 (1.06–1.10)	<0.001	1.05 (1.03–1.07)	<0.001
Parent gene affected				
MSH6	1.00 (reference category)		1.00 (reference category)	
MSH2	2.59 (1.47–4.56)	0.001	2.37 (1.32–4.25)	0.004
MLH1	2.83 (1.75–4.57)	<0.001	2.77 (1.70–4.54)	<0.001
Parent sex				
Female	1.00 (reference category)		1.00 (reference category)	
Male	1.30 (0.99–1.70)	0.064	1.34 (0.99–1.81)	0.051
Number of siblings				
≥3	1.00 (reference category)		1.00 (reference category)	
1–2	1.51 (1.08–2.10)	0.015	1.43 (0.99–2.03)	0.051
None	4.63 (2.64–8.10)	<0.001	4.86 (2.63–10.61)	<0.001
Siblings tested				
None	1.00 (reference category)		1.00 (reference category)	
≥1	6.60 (4.82–9.03)	<0.001	7.00 (4.99–9.82)	<0.001
Parent age				
24–50 years	1.00 (reference category)		1.00 (reference category)	
50–70 years	2.01 (1.21–3.33)	0.007	1.24 (0.61–2.50)	0.557
70–100 years	1.96 (0.92–4.18)	0.081	1.55 (0.62–3.83)	0.340
Dead	1.74 (0.89–3.39)	0.104	1.28 (0.54–2.99)	0.577
Parent under endoscopic surveillance				
No	1.00 (reference category)		1.00 (reference category)	
Yes[a]	5.22 (2.41–11.31)	<0.001	4.90 (2.27–10.61)	<0.001
Parent had cancer				
No	1.00 (reference category)		1.00 (reference category)	
Yes	1.34 (0.99–1.81)	0.055	1.40 (1.01–1.95)	0.043

[a]If deceased, the parent was categorized as 'yes' for endoscopic surveillance.

Furthermore, in a recent study, 56% (329/591) of FDRs of LS variant carriers had undergone PT.[21] Similarly, in a Dutch study by Ramsoekh *et al.*,[22] 52% (330/640) of FDRs underwent PT, with 51% (56/111) of FDRs choosing to undergo genetic testing after education and counselling in another study.[23] Conversely, two earlier studies reported 43%[24] and 60%[25] uptake percentage, whereas in a large multicentre study of *MSH6* variant families, only 17% (525/3104) of the relatives were tested, although the degree of the relatives was not reported.[26] In a South-African study, 63% of the tested probands informed their children of the hereditary cancer risk and 73.6% (64/87) of the eligible children underwent PT, which was lower than the proportion of siblings tested (97%).[27] In a systematic review, eight eligible studies including FDRs of LS variant carriers were combined to assess uptake to genetic testing. Less than 52% received genetic testing and on average 3.6 relatives per proband were tested.[15] Furthermore, an original evidence review was undertaken by Palomaki *et al.*[14] to provide background data for an Evaluation of Genomic Applications in Practice and Prevention Working Group recommendation. There was adequate evidence to document the uptake of counselling among 1886 FDRs who were contacted (52%) and subsequently targeted for PT (95% of those counselled). If the study of Aktan-Collan *et al.*[19] was not included, the uptake for counselling would have been 46% and the uptake for testing 95%.[14]

As demonstrated by these reports, the results of PT uptake have been variable, and the uptake of PT by offspring has been infrequently reported separately. Most often, the reported uptake rates have been results of a questionnaire or other intervention. Our results do not contradict earlier studies but rather provide a different viewpoint from one generation of carriers to the next over the natural course of family history. The strength of the current study is that it was not an interventional study based on a questionnaire but a registry observation of results reflecting continued work carried out since the 1980s using primarily FMA (plus one limited DCI study). The difference from earlier reports is that we did not study PT uptake of all FDRs but only the children and grandchildren of the original carriers. This yielded a result of only 1.8 tested children/grandchildren per original first-generation carrier, keeping in mind that some of these families were related to each other.

Death of a parent and prior cancer history in the family have been considered as warning examples for offspring to become tested in order

to prevent and detect upcoming cancers. Our study corroborated the former assumption, even though the results were inconsistent in multivariate analysis. The finding that having an *MSH6* carrier as a parent was associated with a lower probability of PT may be explained by the same phenomenon: recent studies indicate that *MSH6* carriers have a slightly lower risk of cancer, especially at a young age, than *MLH1* and *MSH2* carriers,[1] which may modify the behaviour for testing uptake in the family. Surveillance may also begin later in life, and be less strict than for other genes, although this is not recommended in Finland. In addition, our analysis identified new possible factors that may influence the PT uptake. Being an only child was a strong positive predictor to become tested, as was having a tested sibling. Belonging to a family where some of the children have been tested is an indicator of full disclosure of the variant in the family, which increases the probability of PT for all siblings. A parent being under endoscopic surveillance is an indicator of adherence to a health-care system that enables a continuing discussion between the carrier and an endoscopist about the disclosure and testing situation of the offspring. Conversely, non-adherence to a surveillance programme, which is quite rare, is an indicator that the family may not even know about the parental function-affecting variant, which may increase the probability of the offspring not being tested. Male carriers appeared to perform worse with regards to their children becoming tested, although the effect of sex did not reach significance in the multivariate model ($P = 0.051$).

To our knowledge, this is the first report to analyse the uptake of PT by direct offspring across three generations of LS families. The apparent strengths of the study are the high number of subjects, exact family structures, the status of LSRFi as the only registry provider, and limiting this analysis only to genetically tested probands. There were also some limitations to address. Parenthood has been identified to associate with genetic testing uptake in a previous study[22]; however, we did not obtain the information on the number of children of those who did not undergo PT or tested negative. We also did not have access to educational background information, precluding characterization of this factor.[24] Although LSRFi receives information from all health-care providers in the country, it is possible that some individuals may have undergone PT but refused to inform the registry. However, carriers and at-risk individuals generally respond well to information requests by LSRFi and usually do not decline, which is also reflected by the 97.8% adherence rate to endoscopic surveillance.[17,28,29] Therefore, we consider that there is low risk of compromised data quality.

Considerable effort has been put into recognizing new LS families through tumour testing but much less has been applied to discussing the importance of counselling, testing, and surveillance of at-risk FDRs. In comparison, the number of PTs for *BRCA1/2* is constantly increasing, whereas that for LS it is not, probably owing to poor uptake of relatives at risk. In both predisposing syndromes, approximately a third of eligible relatives have been reported to undergo PT but the worse overall performance of PT in LS is believed to reflect lower level of information of patients and relatives.[13] Unfortunately, the cost-effectiveness of universal tumour screening strategies are based on the successful PT uptake of high-risk relatives of individuals identified.[30] High numbers of remaining untested adult individuals among LS families, even in a well-established nationally operated registry, therefore represent a clinical challenge for the endoscopists who meet with the tested carriers on a regular basis. A direct approach to untested at-risk individuals and the development of new technologies should be considered within the limits of legislation and ethics to improve the uptake of genetic testing in LS. Towards this goal, we have launched a new DCA study to contact approximately 540 untested persons at risk to improve our testing uptake.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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