# LESSONS LEARNT FROM THE IMPLEMENTATION OF A COLORECTAL CANCER SCREENING PROGRAMME FOR LYNCH SYNDROME IN A TERTIARY PUBLIC HOSPITAL

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## Abstract

**Background:** Lynch syndrome (LS) is the first cause of inherited colorectal cancer (CRC), being responsible for 2-4% of all diagnoses. Identification of affected individuals is important as they have an increased lifetime risk of multiple CRC and other neoplasms. However, LS is consistently underdiagnosed at the population level. We aimed to evaluate the yield of LS screening in CRC in a single-referral centre and provide tools for its effective implementation.

**Methods:** LS screening programme included individuals with CRC <70 years, multiple CRC, or CRC after endometrial cancer at any age. Mismatch repair (MMR) protein immunohistochemistry (IHC) analysis was performed in routine practice on the surgical specimen and, if MLH1 IHC was altered, *MLH1* gene promoter methylation was analysed. Results were collected in the CRC multidisciplinary board database. LS suspected individuals (altered MMR IHC without *MLH1* promoter methylation) were referred to the Cancer Genetic Counselling Unit (CGCU). If accepted, a genetic study was performed. Two checkpoints were included: periodic review of the pathology data and verification of patient referral by a genetic counsellor.

**Results:** Between 2016 and 2019, 381 individuals were included. MMR IHC analysis was performed in 374/381 (98.2%) CRC cases and *MLH1* promoter methylation in 18/21 (85.7%). Seventeen of the 20 LS suspected individuals were invited for referral at the CGCU. Two cases were not invited and the remaining patient died of cancer before completion of tumour screening. Fifteen individuals attended and a genetic analysis was performed in 15/20 (75%) LS suspected individuals. Ten individuals were diagnosed with LS, in concordance with the IHC profile (2.7% of the total cohort). This led to cascade testing in 58/75 (77.3%) of the available adult relatives at risk, identifying 26 individuals with LS. The inclusion of checkpoints in the workflow has proven effective in limiting the loss of candidate individuals.

**Conclusions:** Establishing a standardized institutional LS screening programme with checkpoints in the workflow is key to increasing the yield of LS identification.

**Keywords:** Colorectal cancer, Effectiveness, Programme evaluation, Lynch syndrome, screening programme

## List of abbreviations

LS: Lynch syndrome

CRC: Colorectal cancer

MMR: Mismatch repair

IHC: Immunohistochemistry

CRC MDB: Colorectal cancer multidisciplinary board

MSI: microsatellite instability

MMRd: Mismatch repair deficient

MMRp: Mismatch repair proficient

MS-MLPA: methylation-specific Multiplex Ligation-dependent Probe Amplification

CGCU: Cancer Genetic Counselling Unit

DNA: deoxyribonucleic acid

NGS: Next generation sequencing

PCR: Polymerase chain reaction

## 1. Introduction

Colorectal cancer (CRC) is the most common cause of cancer when considering both genders, and the second cause of cancer in men and women separately, representing 15% of all tumours diagnosed in Spain in 2020 [1]. Lynch syndrome (LS) is an autosomal dominant disorder caused by germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2,* or *EPCAM* gene deletions, silencing the *MSH2* gene in epithelial tissues). It is the main cause of inherited CRC, being responsible for approximately 2-4% of all diagnoses [2–4]. CRC cumulative incidences at 75 years are 48.3-57.1%, 46.6-51.4%, 18.2-20.3% and 10.4% for *MLH1*, *MSH2*, *MSH6,* and *PMS2* mutation carriers, respectively. However, the risk of cancer for *PMS2* mutation carriers is not evident before 50 years of age. LS individuals also have an increased incidence of metachronous CRC and other LS spectrum tumours (mainly endometrial, ovarian, extracolonic gastrointestinal, urinary tract, and biliary tract) [5,6]. Risk-reducing surgeries can be offered to modify their cancer risk as well as family planning processes [7,8]. Therefore, it is important to identify LS individuals as early as possible, along with their at-risk relatives.

Microsatellite instability (MSI) analysis or immunohistochemistry (IHC) staining of MMR proteins in CRC samples can be performed to identify individual candidates for genetic testing for LS [9]. MSI is a molecular hallmark of mismatch repair deficiency (MMRd) CRC [10]. IHC staining of two (PMS2, MSH6) or four (MLH1, MSH2, MSH6, PMS2) MMR proteins suggests mutations in MMR genes when proteins are not expressed in tumour tissue [11].

MSI/MMRd can also be identified in 4-5% of metastatic sporadic CRC and 12-20% of non-metastatic sporadic CRC due to somatic *MLH1* promoter methylation. *MLH1* promoter methylation or the *BRAF* V600E mutation (associated with *MLH1* promoter methylation in CRC) should be initially tested in these cases [10,12,13]. While both strategies are accepted, the analysis of *MLH1* promoter methylation when MLH1 protein expression is absent seems to be more cost-effective [14]. MSI testing sensitivity, as a

106 screening test for LS in CRC, ranges from 66.7% to 100% and the specificity ranges
107 from 61.1% to 92.5%. IHC staining sensitivity ranges from 80.0% to 100% and the
108 specificity ranges from 80.5% to 91.9% [15].
109 The selection of suitable individuals for LS screening can be made based on clinical
110 criteria, considering age at CRC onset or family history (Amsterdam or Bethesda criteria).
111 These criteria, however, fail to identify up to 50% of LS individuals, especially in
112 unselected CRC patients [2,16–22]. In consequence, other screening strategies have
113 been proposed such as universal screening, screening by Bethesda criteria, age-related
114 (Jerusalem recommendations), or combined strategies [2,3].
115 Despite the emerging consensus that LS screening programmes should be established,
116 most centres and healthcare systems still rely on informal networks between
117 professionals to identify these individuals. Networks for cancer care aim to formally
118 organise cooperation and intend to facilitate equity of access to cancer care and
119 implementation of clinical guidelines [23–26]. While reports emphasize the importance
120 of establishing a standardised protocol, to date, no publication has described its
121 implementation in detail [3,27–33].
122 In 2016, in our institution (a tertiary hospital of the Spanish National Health System), we
123 set up a LS CRC screening programme based on the selection of patients fulfilling
124 Jerusalem criteria (age under 70) and/or at least fulfilling one Bethesda criteria. This
125 study aimed to describe the established protocol, identify the difficulties that arose during
126 its implementation, and evaluate the yield after four years of operation.

## 127 2. Material and methods

### 128 2.1 Study population

129 This was a prospective study from the Catalan Institute of Oncology Hereditary Cancer
130 Program and Bellvitge University Hospital analysing the established screening
131 programme for LS identification between 01/2016 and 12/2019. Individuals included in
132 the programme were those diagnosed with CRC before or at the age of 70 years,

individuals diagnosed with synchronous or metachronous CRC, or individuals diagnosed with CRC after having developed endometrial cancer, at any age.

The two centres (Catalan Institute of Oncology and Bellvitge University Hospital) act together as a highly complex tertiary hospital within the Spanish national health system, which offers free universal health coverage to all individuals of the geographical area as well as the genetic counselling, testing and follow-up if required of their relatives at risk. All the specialties required for the diagnosis, treatment and follow-up of the individuals diagnosed of CRC and Lynch syndrome are found in both centres.

**2.2 LS CRC screening interventions**

The LS CRC screening programme consisted of the following steps and timelines (Fig. 1 and supplementary Fig. 2):

A) An IHC study of the MSH6 and PMS2 proteins in the CRC surgical specimen of all individuals included. If MSH6 and PMS2 protein expression was conserved the tumour was considered MMR proficient (MMRp). If staining of any protein was absent in the tissue, MLH1 and MSH2 IHC staining was then performed. When any of the MMR proteins were absent the tumour was considered MMRd. The complete MMR protein IHC analysis was performed in 1-2 weeks

B) When loss of MLH1 staining occurred, DNA was extracted from the formalin-fixed, paraffin-embedded tissue and the *MLH1* promoter methylation status was assessed by MS-MLPA (2016-2017) analysed in 2-3 weeks or pyrosequencing (2018-2019) analysed in 1-2 weeks. If *MLH1* promoter methylation was identified in the tumour but absent in paired normal tissue, the tumour was considered a probably sporadic MMRd CRC.

C) Results of IHC and *MLH1* promoter methylation were reported by the pathologists during the following week's meeting of the Colorectal Cancer MultiDisciplinary Board (CRC MDB) where the upcoming information was collected: histology, age of onset of CRC, tumour localisation, synchronicity or metachronicity, results of MMR protein IHC and *MLH1* promoter methylation analyses.

D) LS suspected individuals (altered MMR IHC without *MLH1* promoter methylation) were offered genetic counselling during the subsequent week by the navigator nurse of the CRC MDB and, if they accepted, were referred to the Cancer Genetic Counselling Unit (CGCU).

Two checkpoints were introduced to ensure the proper performance of the programme: 1) Every three months, the completeness of the information regarding MMR protein IHC and *MLH1* promoter methylation was reviewed by the genetic counsellor. Discrepancies were discussed with the corresponding pathologist or in the MDB meeting. The corrected information was updated in the programme database; 2) Every three months, the CGCU genetic counsellor updated attendance to the genetic counselling unit, acceptance of testing, and the result of the genetic study.

**2.3 Genetic testing and counselling**

Time to first visit in the CGCU was 1-60 days. During that visit, information regarding demographic, personal characteristics, genogram, and personal history of cancer were collected and stored in the clinical database of the Hereditary Cancer Program. After appropriate counselling, a genetic study was offered. Genetic testing was performed in peripheral blood DNA using our *ad hoc* NGS custom panel I2HCP, which comprises 122-135 HC-associated genes, depending on the version used. Library preparation methods and bioinformatics pipeline were previously described [34,35]. The analysis of the panel for diagnostics was phenotype-driven and time to result was 11-14 weeks [36]. In LS suspected individuals, the clinically valid and actionable genes analysed included: *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *POLD1*, *POLE*, as well as *BRCA1*, *BRCA2* as opportunistic screening. When a mutation in the *PMS2* gene was suspected by exclusive PMS2 expression loss in the tumour, genetic analysis of the *PMS2* gene was performed via long-range PCR. Time to result of this study was 11-14 weeks. If family history was consistent with other syndromes, additional genes were analysed. If a pathogenic variant was identified in the panel testing, a confirmation study was performed in an independent blood sample. Variant classification was performed according to ACMG/AMP guidelines

[37]. When a pathogenic variant was identified, a predictive study of the pathogenic variant was offered to at-risk relatives of 18 years of age or older (cascade testing) and time to result of this study was 3-4 weeks.

At the time of the study, follow-up recommendations on LS individuals in our institution were colonoscopies every 1-2 years starting at the age of 25 years [38]. Recommendations for lynch-like syndrome (LLS) individuals were done based on on the knowledge that LLS individuals and their first-degree relatives (FDR) were at a risk of developing CRC between that of the general population and individuals with LS [39–43]. In that context, we recommended colonoscopies every 2 years starting at 25 years of age, unless family history suggested a more intense follow-up. These recommendations were later supported by the British guidelines published in 2019 which stated that LLS individuals (if no double somatic mutations were identified) should be followed as LS individuals [44]. Nowadays in the absence of MMR somatic analysis, recommendations should be done based on family history of CRC, following the clinical practice guideline of the European Society of Gastrointestinal Endoscopy (ESGE) [45]

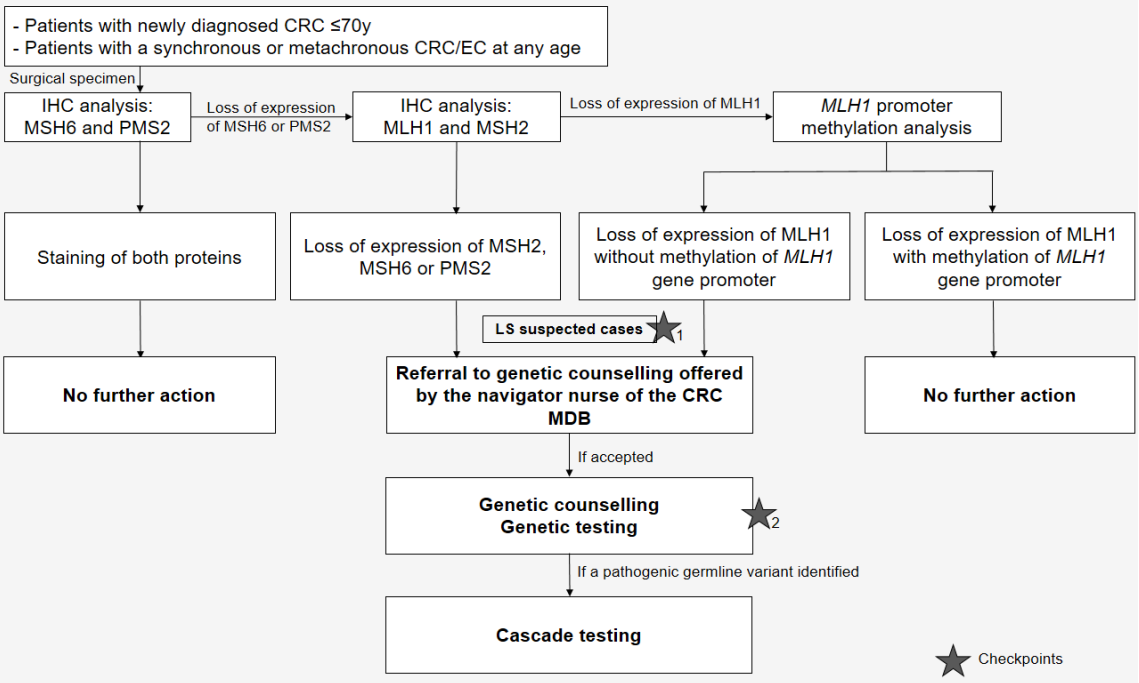


**Fig. 1** Workflow of the Lynch syndrome colorectal cancer screening programme. CRC: colorectal cancer; y: years; EC: endometrial cancer; IHC: immunohistochemistry; LS: Lynch syndrome; CRC MDB: Colorectal cancer multidisciplinary board.
Checkpoint 1: Every three months, the completeness of information regarding MMR protein IHC and *MLH1* gene promoter methylation was reviewed by the genetic counsellor. Discrepancies were discussed during the CRC MDB meeting. The corrected information was updated in the programme database; Checkpoint 2: Every three months, the genetic counsellor updated attendance to the cancer genetic counselling unit, acceptance of genetic testing and result of genetic testing

## 3. Results

### 3.1 Yield of the LS CRC screening programme

***3.1.1 Immunohistochemistry results***. Of the 381 individuals included in the screening programme, 362 were diagnosed with one or more CRC (adenocarcinoma) before the age of 70 years and 19 were diagnosed with synchronous or metachronous CRC, or CRC after having developed endometrial cancer after 70 years of age (Table 1).

**Table 1**. CRC cohort description

| | ALL INDIVIDUALS | | ≤70y | | >70y | |
|---|---|---|---|---|---|---|
| | **381** | 100.0% | **362** | 95.0% | **19** | 5.0% |
| Age at CRC (range) | **61.5 (16.6-85.8)** | | 60.7 (16.6-70.9) | | 78.2 (71-85.8) | |
| Individuals with one CRC | **346** | 90.8% | 344 | 95.0% | 2 | 10.5% |
| Individuals with multiple CRC | **35** | 9.2% | 18 | 5.0% | 17 | 89.5% |

Individuals included in the LS screening programme between 01/2016 and 12/2019 separated by age and number of CRC. Multiple CRC refers to both synchronous and metachronous CRC. Individuals are counted only once regardless of the number of CRC they had during the screening programme period. *CRC: colorectal cancer; *y: years

MMR IHC analysis (MSH6 and PMS2 staining in all cases, MLH1 and MSH2 when required) was completed in 374/381 cases (98.2%). In seven out of 381 (1.8%) CRC, MMR IHC was not performed. Four of them died due to postoperative complications during the first 2 weeks after surgery and three were referred to their designated hospital. None of these cases were followed-up.

MMR expression was altered in 32 out of 374 cases (8.6%): 19 tumours showed loss of expression in MLH1/PMS2, two in MLH1/PMS2/MSH6, four in MSH2/MSH6, and exclusive loss of MSH6 or PMS2 were observed in five and two tumours, respectively. Twelve of the 21 tumours with MLH1 loss, showed *MLH1* promoter methylation and six

did not. Three cases were not tested (14.3%): two were directly referred by their medical specialists to the CGCU as they met Amsterdam criteria. The remaining patient died due to non-oncological reasons 5 weeks after surgery.

In all, 20 of the 374 (5.4%) CRC individuals having completed IHC analysis and *MLH1* promoter methylation analysis, if indicated, were identified as LS suspected individuals and, therefore, candidates for genetic counselling (Fig 1). The remaining 12 cases with MMR loss and *MLH1* methylation were considered probably sporadic MMRd tumours (3.2%). Information regarding the whole series, as well as information divided by age at diagnosis (≤70 years vs. >70 years), is described in figure 2 and supplementary figure 1.

***3.1.2 Genetic testing results.*** Seventeen of the 20 LS suspected individuals were invited for referral at the CGCU. Two of the remaining three cases were not invited despite being listed in the database as ongoing referrals. The remaining patient died of cancer before completion of tumour screening. Sixteen accepted referral and 15 finally attended the clinic appointment and consented to genetic testing after appropriate genetic counselling. Ten individuals were diagnosed with LS, accounting for 2.7% of the individuals with complete LS screening: four harbouring mutations in *MLH1* (1.1%), one in *MSH2* (0.3%), four in *MSH6* (1.1%), and one in *PMS2* (0.3%). The germline MMR gene mutations identified were concordant with the tumour MMR staining pattern (Fig. 2 and supplementary Fig.1). Of the 10 LS individuals, nine met clinical criteria: six met Amsterdam criteria (four *MLH1*, one *MSH2*, and one *MSH6*), and three met Bethesda criteria (all *MSH6*). The individual with a *PMS2* mutation did not fulfil any clinical criteria. The identification of LS in these individuals led to cascade testing with predictive studies in 58 out of 75 at-risk adult individuals, who were then contacted (77.3%) and 26 individuals were diagnosed with LS (Fig. 2).

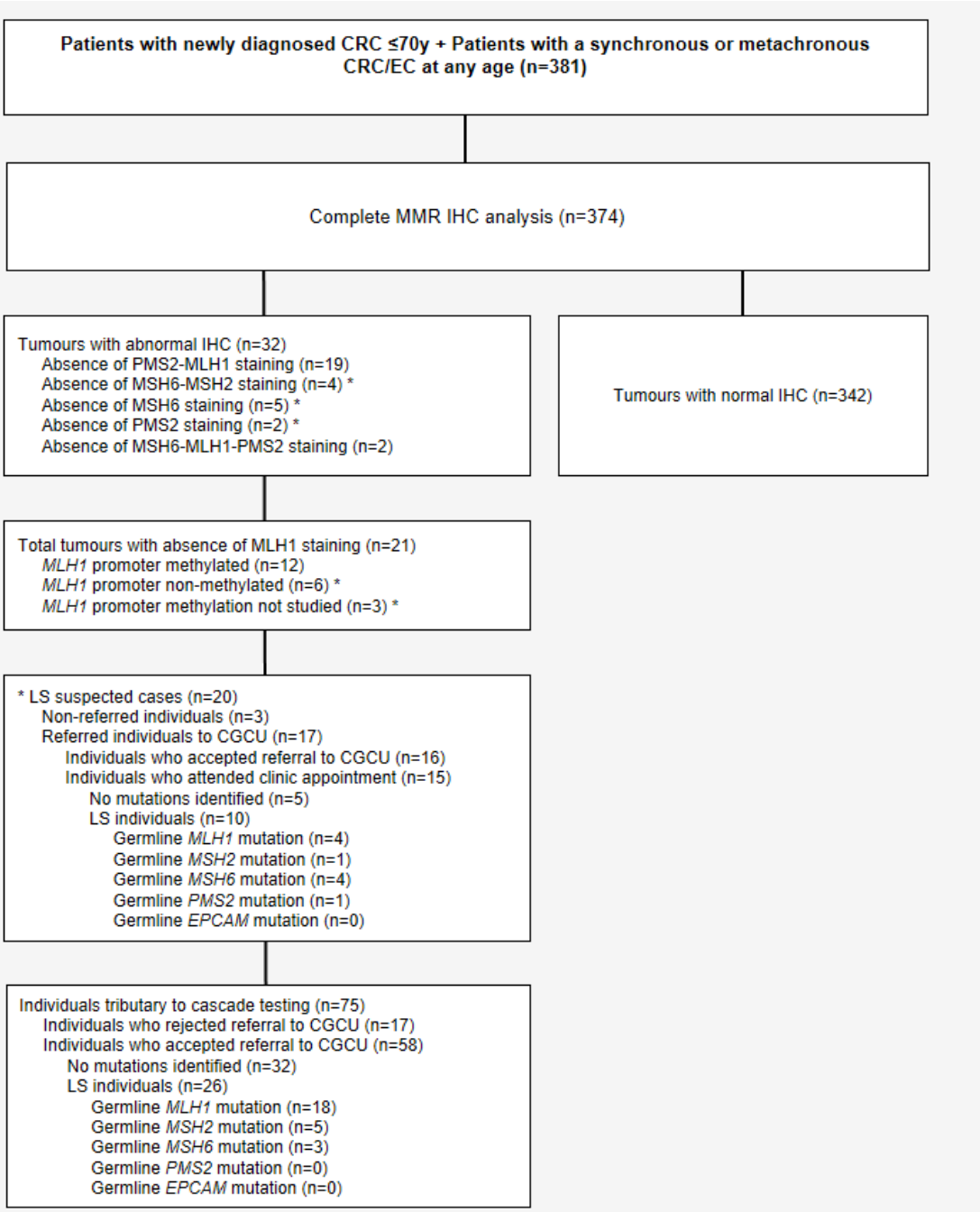


**Fig. 2** Outcomes of the Lynch syndrome colorectal cancer screening programme. CRC: colorectal cancer; y: years; EC: endometrial cancer; MMR: mismatch repair; IHC: immunohistochemistry; LS: Lynch syndrome; CGCU: cancer genetic counselling unit

## 4. Discussion

This paper shows that establishing a systematic institutional LS CRC screening programme in patients diagnosed with CRC is key to adequate LS identification. Ten individuals (2.7%) were diagnosed with LS, nine of them meeting clinical criteria in line

with the expected frequency [2–4]. The identification of LS in these individuals led to cascade testing with predictive studies in 58 out of 75 at-risk adult individuals.

Compliance with the LS screening programme in our institution was good and checkpoints worked correctly. IHC analysis was completed in 98.2% of the tumours and *MLH1* promoter methylation was tested in 85.7% of the tumours where the study was indicated. These results are in line with those reported in literature [4,31]. In a recent meta-analysis, complete IHC in the whole group was performed in 81.7% (47850/58580) of newly diagnosed CRC, while the percentage of complete IHC achieved in those under 70 years was 75% (1497/1998). No information regarding the compliance of *MLH1* promoter methylation was provided [4]. Moreover, in a multicentric Dutch study including 3602 newly diagnosed CRCs below age 70, complete IHC was performed in 84% of cases and *MLH1* promoter methylation in 88% of the candidate tumours [31].

In our centre, referral for genetic testing occurred in 85% of LS suspected individuals, being higher than the 69% of cases referred in the aforementioned Dutch study [31]. It is likely that the inclusion of two checkpoints in the workflow (periodic review of pathology data and referral for genetic testing) has proven effective in limiting the loss of candidate individuals. We want to highlight the impact of human error associated with the manual revision of data that accounted for all non-referred cases.

Our results show that only one of the 17 LS suspected individuals did not agree to be referred to the CGCU (5.9%), similar to those of the Dutch study where only one out of 53 individuals refused to be referred (1.9%) [31]. In a survey conducted in the Canadian population, 77% of participants agreed that LS screening could be useful and 94% wanted to discuss the screening results with their doctors and other healthcare professionals [46]. This was not always the case. Only 45% of the 245 MMRd CRC patients constituting an Australian cohort consented to germline testing [47]. At Ohio State University, uptake for genetic counselling and genetic study was lower, only seven out of 34 (20.6%) candidates completed the genetic testing process [30]. The impact of

private healthcare policies and/or the need to travel long distances may account for the differences observed.

It is widely accepted that the identification of individuals with LS is beneficial not only to the patients themselves but also to their at-risk relatives and to the healthcare system. We have obtained remarkable success in effectively testing 58 at-risk adults, averaging a ratio of six relatives per proband. All carriers can benefit from cancer surveillance programmes and females with LS can be offered risk-reducing gynaecological surgeries [7,48,49]. The cost-effectiveness of any LS identification strategy improves as the number of at-risk relatives contacted increases.

Our programme has several strengths. It is offered in an NHS-funded specialized comprehensive cancer centre that effectively offers multidisciplinary healthcare, encompassing genetic diagnosis, surveillance programmes, and family planning. The embedding of the program with the CRC multidisciplinary board is a plus since communication has greatly improved among professionals. The proactive role of the navigator nurses of the CRC MDB is key, together with the participation of the CGCU, and has likely led to a better referral. Among the limitations of the study is the caution required to extrapolate our model to other health centres or health systems without universal healthcare coverage.

We have identified several opportunities to improve LS detection including (a) ensuring rapid communication of the screening result, that has included change of the *MLH1* gene promoter methylation analysis technique from MS-MLPA to pyrosequencing and inclusion of a fast-track circuit (10 days maximum until the visit in the CGCU and 3-4 weeks days until the result of the analysis) when germline analysis result should be urgent for treatment decisions, (b) pre-scheduled verification of the completion of molecular pathology testing, (c) inclusion of detailed information on referral to the CGCU, and (d) the transition to universal screening in all newly diagnosed CRC and EC patients, irrespective of age of onset. Moreover, we are currently working to refine the workflow

by implementing in clinical practice the MMR mutation analysis in tumors when no germline mutation was found in LS-suspected individuals [50]

## 5. Conclusions

In conclusion, the LS CRC screening programme implemented in our centre presents a good outcome in identifying individuals with LS, the workflow of the programme is easy to follow by the specialists involved, and the checkpoints limit patient loss. These results provide further evidence of the utility of population-based LS CRC screening programmes and provide tools for their implementation in other settings.

## 6. Declarations


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### 6.3 Ethics approval and consent to participate

All patients underwent appropriate genetic counselling prior to all genetic tests and gave informed consent for genetic analysis and the internal Ethics Committee approved this study (code PR225/11). This study was performed in accordance with the Declaration of Helsinki.

### 6.4 Availability of data and materials

Data supporting the results are stored in the clinical database of the Hereditary Cancer Program and the database of Bellvitge University Hospital and Catalan Institute of Oncology. The datasets

generated and/or analysed during the current study are not publicly available due to the Spanish Royal Decree 1720/2007, 21st December, regulation for development of the Organic Law 15/1999 for Personal Data Protection, but are available from the corresponding author on reasonable request.

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