

# Increased Number of Colorectal Interval Cancers in Lynch Syndrome after the SARS-CoV-2 Pandemic: A Survey-Based Study

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## Keywords

Hereditary · Colorectal cancer · COVID-19 · Surveillance

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## Abstract

**Background:** Hereditary colorectal cancer syndromes require timely endoscopic surveillance. **Methods:** This study evaluated the approach of Italian gastroenterologists to the management of such patients. It then assessed the impact of SARS-CoV-2. All members affiliated with the leading Italian gastroenterology societies (AIGO, SIED, and SIGE) received an online questionnaire. **Results:** One hundred and twenty-one clinicians from 96 centers answered, not necessarily experts in the field (mean age  $50.26 \pm 11.22$  years). Many collected family history for genetic risk assessment (74.4%), but

only 14.0% used an online predictive software. 65.6% discussed cases in multidisciplinary units. Genetic analysis was available to most centers, but only a few hospitals offered dedicated endoscopy (19.0%), outpatient clinics (33.9%), or surgeries (23.1%). Since the start of the SARS-CoV-2 pandemic, the number of clinicians with a high volume of patients decreased (from 38.8% to 28.1%). Almost half of the responders (45.5%) reported a delay in the surveillance (median: 4–12 months). Ultimately, 30.6% detected one interval colorectal cancer in at least one of their patients. **Conclusion:** The SARS-CoV-2 pandemic directly affected the surveillance of hereditary colorectal cancer syndromes in Italy. Endo-

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scopic surveillance should resume in all centers to avoid the possible long-term consequences of its interruption, especially for inherited colorectal cancer syndromes.

## Introduction

The lifetime risk of colorectal cancer (CRC) increases with germline pathogenic variants in genes associated with CRC. A genetic predisposition exists in 2–8% of all CRCs and one in five CRCs is diagnosed before 50 years of age [1–3]. Lynch syndrome (LS) is the most common hereditary CRC syndrome with an estimated three million people aged between 45 and 70 years in Europe [2, 4]. Patients with LS can reduce their risk of CRC and other cancers (gastric, gynecological, and pancreatic cancers) with surveillance programs [5–10]. Familial adenomatous polyposis is rarer, but it confers a higher lifetime risk of CRC close to 100% [1]. As little as 11–26% of high-risk CRC patients receive genetic risk assessment [11] and, in some cases, the percentage of undiagnosed syndromes could be higher [9, 10, 12].

The SARS-CoV-2 pandemic had a rapid and dramatic effect on healthcare systems [13]. Many centers had to commit all their human resources to COVID-19 [14, 15]. Endoscopic activity in the UK dropped to 5% of normal at the pandemic peak, with a reduction of 85% in other countries [16, 17]. During the first pandemic wave in Italy (from March 1 to June 30, 2020), 10.7% of gastroenterology divisions were converted to COVID-19 units [18]. Outpatients' consultations, endoscopic, and ultrasound procedures were limited to urgencies in 85.1%, 96.2%, and 72.2% of units, respectively. 46.7% of Italian gastroenterology units suspended CRC screening. The primary aim of this survey study was to evaluate the burden of the SARS-CoV-2 pandemic on the surveillance of patients with hereditary CRC syndromes. As secondary outcomes, we evaluated (i) the awareness and (ii) the management of hereditary CRC syndromes in Italy.

## Materials and Methods

We designed an online, multiple-choice, and open-ended questionnaire with 38 items (10 optional) in 22 sections using Google Modules. It was then revised and approved by the AIGO (Italian Association of Hospital Gastroenterologists and Digestive Endoscopists), SIED (Italian Society of Digestive Endoscopy), and SIGE (Italian Society of Gastroenterology and Digestive Endoscopy) scientific board committees.

This online survey was administered through the AIGO, SIED, and SIGE newsletters to Italian gastroenterologists, not necessarily involved in the management of hereditary CRC syndromes. Data collection took place between March 8, 2021, and May 3, 2021. Ethics committee approval was waived. All participants provided written informed consent to anonymous use of data. The primary endpoints were the number of screening procedures in patients at risk before and during the pandemic, the number of consultations before and during the pandemic, changes to the surveillance processes, delays of surveillance intervals during the pandemic, and the number of interval cancers before and during the pandemic.

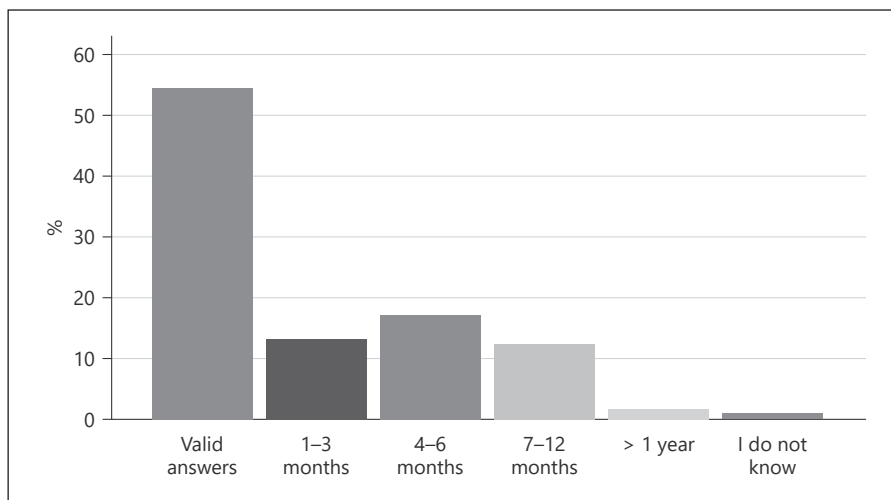
The questionnaire core assessed how many patients with hereditary CRC syndromes each gastroenterologist followed before and after March 1, 2020, per year (0, <10, 10–30, 31–50, >50 patients); how many patients they had for first visit and follow-up visits per year; and whether or not follow-up visits and prophylactic surgeries were delayed (if so, estimating by how much). For the secondary aims, we asked: whether patients' family history was collected; whether a genetic risk assessment tool was used (i.e., PREMM<sub>5</sub>) [19]; whether mismatch repair (MMR) immunohistochemistry (IHC) was performed on all surgical specimens; their management of MMR-deficient CRCs; whether there was a genetics laboratory, a multidisciplinary group, dedicated outpatient clinics, endoscopy units, and/or surgery. If not, participants were asked where the nearest dedicated facilities were.

We performed descriptive analyses using percentages for categorical variables. The distributions of answers were analyzed by plots (boxplots and bar charts), whereas summary statistics, across all centers, were reported as the minimum, maximum, average, standard deviation, and the total number of cases aggregated by type. Statistical analyses were performed using SPSS software.

## Results

A total of 121 gastroenterologists and endoscopists (males 60.3%; mean age  $50.26 \pm 11.22$  years; mean years of clinical activity:  $20.13 \pm 11.69$ ) from 96 Italian gastroenterology or endoscopy units completed the questionnaire (16.5% gastroenterologists, 31.4% endoscopists, 52.1% both) (online suppl. Table 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000524393](http://www.karger.com/doi/10.1159/000524393)). The survey included 18 regions and 64 cities (online suppl. Tables 2–3): 53 (55.2%) were in the North, 25 (26.0%) in the center, 19 (19.8%) in the South, and 2 (2.1%) in Sardinia (online suppl. Fig. 1).

Before the pandemic, 23.1% and 38.8% of participants had a high volume of patients (>10/year) at first or follow-up visits, respectively, while 52.1% and 38.0% had fewer than 10 patients per year at first examination or follow-up visit, respectively. After the pandemic, there was a decrease in the number of clinicians with a high volume of patients at first visit (from 23.1% to 18.2%) and at follow-up (from 38.8% to 28.1%). Similarly, there was an increase in the number of clinicians with no patients at first



**Fig. 1.** Mean periods of prolongation of surveillance timing due to the SARS-CoV-2 pandemic.

visit (from 24.8% to 25.6%) and at follow-up visits (from 23.1% to 25.6%). Clinicians confirmed the procrastination of control visits (45% of participants), with a delay of 4–12 months in 65.3% of cases (Fig. 1).

30.6% of clinicians diagnosed one or more interval cancers (CRC diagnosed in the time between two scheduled/delayed surveillance examinations) in at least one of their patients. Most diagnosed 1–3 interval cancers, but 8.1% reported up to five interval cancers. This result was likely not the consequence of endoscopy units shutting down because most units resumed endoscopy services shortly after the first wave [20]. Endoscopic emergencies were still performed (73.3% of cases). Prophylactic surgical procedures were discontinued in 27.3% of cases (mostly procrastinated by 4–6 months), even though 43.0% of participants could not answer this question. Therapeutic surgical procedures were performed in other centers (44.6% of cases), and in those centers, the presence of a dedicated surgery was confirmed in 27.8%.

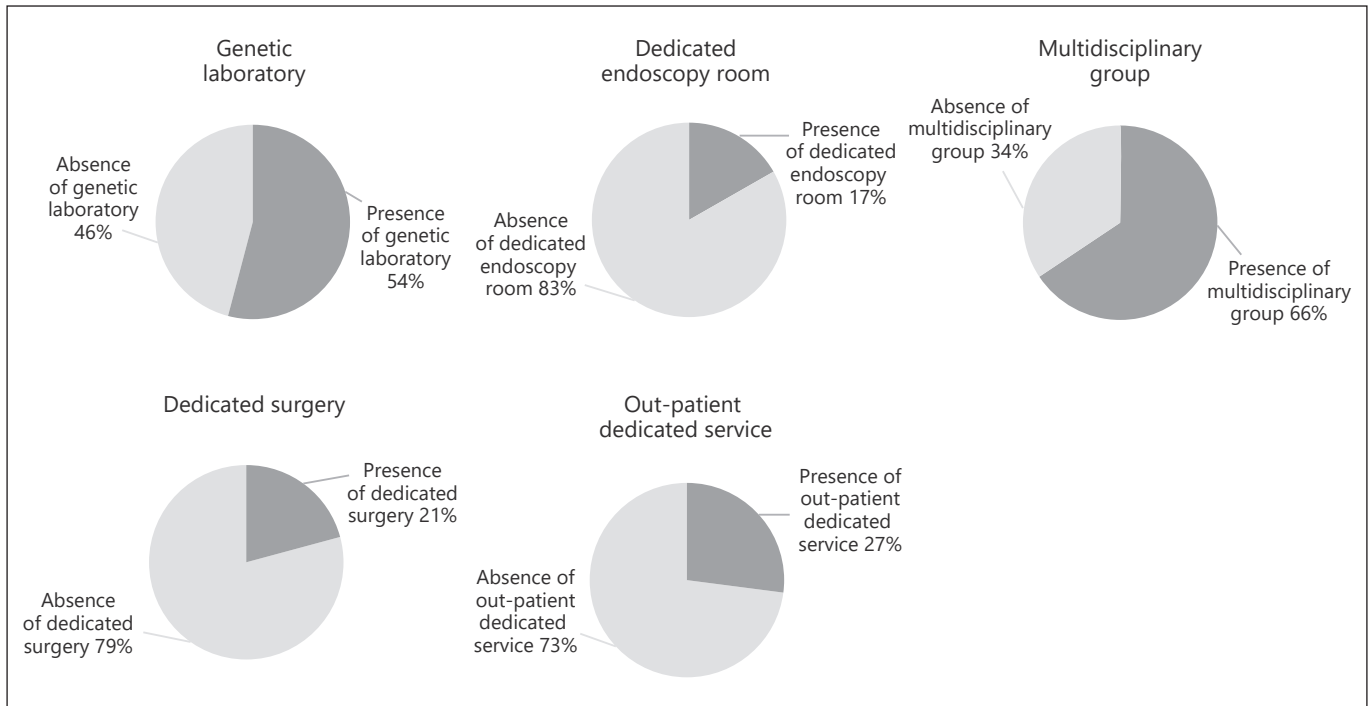
Most gastroenterologists and endoscopists (85.1%) referred to updated guidelines and scientific papers, while 6.6% received updates through congresses or symposia, 5.8% through the internet, and 2.5% admitted not being up-to-date. 74.4% collected family history, but only 14.0% used the PREMM<sub>5</sub> genetic risk assessment tool. 61.2% of clinicians used MMR-IHC on surgical specimens. When positive, 8.1% ordered genetic testing, 54.1% discussed the case in a multidisciplinary group, 32.4% referred to genetic counseling, and 5.4% did not perform further analysis or admitted not knowing what to do. When *MLH1* was not expressed, 24.4% evaluated *MLH1* promoter hyper-methylation or *BRAF* V600E; 9.5% tested

for MSI; and 20.3% requested germline tests, but the majority (45.9%) performed no further testing.

57.9% of clinicians reported having a genetic laboratory, while 2.5% did not know whether their center had one. Concerning participants without a genetic laboratory (39.7%), the nearest was in the same province (54.1%), same region (43.8%), or another region (2.1%). 33.1% of participants had access to somatic tests. However, 33.9% were not able to answer this question. Concerning those who declared not having this facility in their center (33.1%), the nearest dedicated laboratory was in their province (45.0%), their region (50.0%), or outside their region (2.5%), while 2.5% did not know. An endoscopic room, outpatient clinics, and surgical room for hereditary syndromes were not present in 81.0%, 66.1%, and 76.9% of participant centers, respectively. A multidisciplinary group was available in 63 out of 96 centers (65.6%) (Fig. 2).

## Discussion

This survey analyzed the Italian experience with hereditary CRC syndromes during the COVID-19 pandemic, covering 18 of 20 regions. 45.5% of the participants reported a delay in the surveillance endoscopic exams (median: 4–12 months). 30.6% of clinicians reported a diagnosis of interval CRC since the beginning of the pandemic. Participants were not exclusively specialists in hereditary CRC syndromes. They had, on average, over 20 years of clinical activity, and 52.1% of them practiced gastroenterology and endoscopy both.



**Fig. 2.** Distribution of dedicated facilities (genetic laboratory, endoscopy room, multidisciplinary group, dedicated surgery, and dedicated outpatient clinics) in the participating working centers.

Surveillance can reduce CRC risk in LS by up to 60%, but patient-specific risk factors and compliance can limit its effectiveness [21]. The benefit decreases with the procrastination of surveillance [20], much like what happened during the SARS-CoV-2 pandemic, as shown in this survey. Reduced surveillance, on one hand, and delays in colonoscopies, on the other, can contribute to later-stage CRC diagnoses [22]. 30.6% of clinicians from this survey witnessed at least one interval CRC during the pandemic (the prospective per-patient rate of interval cancer is estimated at 1.8% by Engel et al. [23]). SARS-CoV-2 caused immediate challenges to surveillance and screening services since March 2020 [24]. During the first pandemic wave in Italy, only 12.4% of endoscopy units were shut down. Of these, 66.7% were shut down only briefly, from March 1, 2020, to June 30, 2020. Although procedures continued, patients might not have attended endoscopic surveillance or visits. This discrepancy could be explained by the poor compliance of patients to follow-ups, maybe due to fear of SARS-CoV-2 infection. This survey did not investigate compliance directly, but 74.4% of responders reported a slight decrease in the number of patients followed per year after the pandemic. 45.5% of clinicians confirmed procrastination of follow-ups, with

an average delay time of 4–12 months, which supports this explanation. The impact of SARS-CoV-2 on the delays in cancer diagnosis and cancer death is concerning.

In the majority of Italian centers, there was neither an endoscopic room nor a dedicated surgery for hereditary CRC syndromes. 85.1% of clinicians relied on guidelines, and 74.4% collected family history [8]. Although clinical models (i.e., PREMM<sub>5</sub>) allow adequate genetic assessment for LS and other hereditary CRC syndromes [19, 25], only 14.0% used it. MSI and IHC were used in 9.5% and 61.2%, respectively, but the management of results seemed more challenging. 45.9% of participants did not know of *MLH1* promoter hypermethylation or *BRAF* V600E analysis. Genetic facilities are widely available (57.9% of centers), but only a few clinicians (32.4%) referred patients to genetic counseling, and even fewer (8.1%) requested genetic tests. This could be explained by the absence of a geneticist in the team (39.7% did not have a genetic counselor). This data highlights the need to use multidisciplinary team discussions [26–28] to improve diagnostic accuracy and adherence to guidelines, especially for complex patients [29].

One limitation of this study was the presence of discrepancies between clinicians from the same center. We

contacted all 11 centers to solve major inconsistencies. This pragmatic choice may have limited precision. Concerning the reported rate of interval cancers, another limitation of this study is that the survey assessed the number of clinicians diagnosing interval cancers, not the number of interval cancers [22, 23]. Besides limitations, the mean number of patients with interval cancers was reportedly high (up to three per hospital), and several centers reported a postponement of prophylactic surgical procedures.

In conclusion, the pandemic of SARS-CoV-2 had an impact on people with a hereditary risk of CRC in Italy. The worst repercussion was the reported increase in interval cancers during the pandemic. This probably resulted from poor compliance to surveillance, due to the fear of SARS-CoV-2. Therefore, CRC surveillance should resume and avoid the possible long-term consequences of its interruption, especially for hereditary CRC syndromes. In the meantime, all gastroenterology and endoscopic centers should carefully reorganize their activities to face the burden of delayed endoscopies. This represents a major challenge for the next year.

### Statement of Ethics

The paper is exempt from ethical committee approval because an ethics statement was not required for this study type where no human or animal subjects or materials were used.

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### Conflict of Interest Statement

Luigi Ricciardiello is a managing editor of the journal; Rocco Maurizio Zagari is an editorial board member of the journal; other authors have no conflicts of interest to declare.

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### Author Contributions

G.M.C.: conception and design; M.D.L. and G.L.: analysis and interpretation of the data; M.R., A.B., and G.M.C.: drafting of the article; G.M.C., A.M., M.P., R.A.Z., P.B., S.B., M.D.L., R.M.Z., E.G., L.P., R.C., F.M., and L.R.: critical revision of the article for important intellectual content and final approval of the article. All the authors have read and agreed to the published version of the manuscript.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author (G.M.C.) upon reasonable request.

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