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COVID-19 disruptions to endoscopic surveillance in Lynch syndrome

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Abstract

Disruptions in cancer screening due to the COVID-19 pandemic may disproportionately affect patients with inherited cancer predisposition syndromes, including Lynch syndrome. Herein we study the effect of the COVID-19 pandemic on endoscopic surveillance in Lynch syndrome through a prospective study of Lynch syndrome patients at a tertiary referral center who were scheduled for endoscopic surveillance during the COVID-19 pandemic shutdown between 3/16/2020 and 6/4/2020. Of our cohort of 302 individuals with Lynch syndrome, 34 (11%) had endoscopic procedures scheduled during the COVID-19 pandemic shutdown. Of the 27 patients whose endoscopic surveillance was canceled during this period, 85% rescheduled procedures within six months with a median delay of 72 days (IQR 55–84 days), with identification of an advanced adenoma or gastrointestinal cancer in 13%. Individuals who did not have a rescheduled endoscopic procedure were significantly younger than those with a rescheduled procedure (age 35 [IQR 26–43] vs. age 55 [IQR 43–63], $p = 0.018$). Male sex was also suggestive of increasing likelihood of not having a rescheduled procedure. Taken together, our study demonstrates that the COVID-19 pandemic shutdown led to delayed endoscopic surveillance in Lynch syndrome, with potentially impactful delays among young patients. This data also emphasizes the importance of timely surveillance in Lynch syndrome during this current, as well as potential future, global pandemics.

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Introduction:

The COVID-19 pandemic has led to unprecedented disruptions in medical care, including cancer screening. While it will take years to realize the true consequences of these disruptions, the immediate effects are increasingly apparent with an estimated 86% reduction in colonoscopy screenings during the height of the COVID-19 pandemic; with the diagnostic delay following the pandemic resulting in an estimated 16% increase in colorectal cancer (CRC)-related deaths (1,2). These disruptions may disproportionately affect individuals at increased cancer risk, including those with Lynch syndrome, the most common inherited CRC risk syndrome with a prevalence of 1 in 279 (3). Lynch syndrome confers a significantly increased lifetime risk of CRC, with accelerated carcinogenesis, emphasizing the importance of frequent endoscopic surveillance in this population (4,5). Current guidelines recommend that individuals with Lynch syndrome have colonoscopies every 1–2 years, which has been demonstrated to significantly reduce CRC risk (6,7). While *MLH1*, *MSH2*, and *EPCAM* carriers are generally recommended to start surveillance at age 20–25, recent guidelines have recommended starting surveillance in *MSH6* and *PMS2* carriers at an older age of 30–35 given the lower CRC risk associated with pathogenic variants in these genes (6).

Given increased CRC risk and need for frequent endoscopic surveillance in Lynch syndrome, it is critical that these individuals undergo regular and timely surveillance. However, how COVID-19 pandemic-related disruptions will affect cancer surveillance in Lynch syndrome remains uncertain. Herein we examine endoscopic surveillance disruptions in individuals with Lynch syndrome caused by the COVID-19 pandemic, the efficiency of rescheduling these important procedures, surveillance findings, and factors associated with decreased likelihood of rescheduling in this high-risk group.

Materials and Methods:

This was a prospective cohort study of individuals with Lynch syndrome followed at our tertiary care center. This study was conducted after approval by the University of Pennsylvania Institutional Review Board and was conducted in accordance with the U.S. Common Rule. A waiver of informed consent was granted by the Institutional Review Board. We identified and collected data on those individuals who had an endoscopic procedure canceled, scheduled, or performed during the COVID-19 pandemic shutdown. This shutdown was defined as the time from initial implementation of procedural restrictions on 3/16/2020 through 6/4/2020, which was the beginning of the yellow phase of re-opening in our region. Data was subsequently collected through 12/4/2020, 6 months after our region's yellow phase of re-opening. At our institution, all individuals with endoscopic procedures canceled during the COVID-19 pandemic shutdown were added to an administrative rescheduling list. Once routine surveillance procedures began to be scheduled again, attempts to contact and reschedule individuals on this list were made by administrative staff via either phone call and/or communication through the electronic medical record. Individuals not rescheduled during the study period were contacted by phone by a single staff member who inquired via similar open-ended questioning as to the reason why the endoscopic procedure was not rescheduled, and offered assistance in

rescheduling if desired by the patient. Descriptive statistics were presented as medians and interquartile ranges (IQR) or as percentages. We compared characteristics between those who rescheduled endoscopic procedures and those who did not. Continuous and categorical variables were compared using Wilcoxon rank-sum and Fisher's exact tests, respectively. Logistic regression was used to estimate the odds of rescheduling as a function of variables retained with a p-value <0.05.

Results:

Of the 302 individuals with Lynch Syndrome followed by our center, 34 (11%) had an endoscopic procedure scheduled during the COVID-19 pandemic shutdown between 3/16/2020 and 6/4/2020. Of these 34, 7 (21%) had procedures performed as scheduled whereas 27 (79%) had procedures canceled. Six months after entering the yellow phase, of those who had canceled procedures, 4 (15%) had not yet rescheduled their procedures whereas 23 (85%) had procedures rescheduled and completed. Of those who completed their rescheduled procedures, the median delay in procedure completion was 72 days (IQR 55–84) (Table 1). Three individuals (11%) with canceled procedures were outside of a 2-year surveillance window, which is often considered the upper surveillance interval limit for Lynch syndrome in the United States (6). Conversely, amongst individuals who completed their rescheduled procedure and were within a 2-year surveillance window, the median time remaining prior to reaching a 2-year surveillance interval was 246 days (IQR 230–287 days).

Individuals without a rescheduled endoscopic procedure were significantly younger than those with a rescheduled procedure (age 35 [IQR 26–43] vs. age 55 [IQR 43–63], $p = 0.018$) (Table 1). Of note, there were no individuals in this cohort under age 35 with pathogenic variants in *MSH6* or *PMS2*, and therefore none whose age of surveillance initiation may have been affected by recent guideline changes (6). Apart from age there were no other statistically significant differences between the groups, however male sex was also suggestive of increased likelihood of not having a procedure rescheduled (75% of those not rescheduled were male vs. 26% of those rescheduled, $p = 0.093$) (Table 1). In logistic regression, the odds of rescheduling increased by 92% per 5-year increase in age (95% confidence interval 1.02–3.59, $p = 0.04$). Predicted probabilities of rescheduling as a function of age are shown in Figure 1. The four individuals who did not have rescheduled endoscopic procedures were contacted by phone, with two of them not feeling comfortable about coming in for a procedure during the pandemic given COVID-19-related concerns, one being unaware that a procedure needed to be rescheduled, and one who was delaying the procedure until completion of recently initiated chemotherapy.

Of the 23 individuals with rescheduled and completed procedures, clinically significant endoscopic findings were identified in 8 (35%) individuals. Increased age was associated with increased likelihood of identifying a clinically significant endoscopic finding (Table 2). The identified clinically significant findings included colonic tubular adenomas/sessile serrated lesions in 7 individuals, including 2 individuals with advanced adenomas, and identification of a previously unknown gastric cancer recurrence. Of those individuals with advanced adenomas, neither had a history of CRC, however both had prior advanced adenomas. Specifically, a 14 mm tubular adenoma was identified in a 61-year-old female

with a pathogenic variant in *MSH2*, 400 days after her previous surveillance colonoscopy. This individual had a history of 11 prior tubular adenomas including one prior 15 mm tubular adenoma. Additionally, a 12 mm tubular adenoma was identified in a 48-year-old male with a pathogenic variant in *MSH2*, whose previous surveillance colonoscopy 185 days prior had identified a 30 mm tubular adenoma with high grade dysplasia.

Discussion:

Lynch syndrome is a high-risk cancer predisposition syndrome, and therefore it is critical to identify the magnitude of the delays in preventive care ensued during the COVID-19 pandemic and identify sub-groups in this cohort who may be disproportionately affected. Our study demonstrates that the COVID-19 pandemic shutdown led to delayed endoscopic surveillance in Lynch syndrome, with potentially impactful delays among young patients.

While most individuals with Lynch syndrome in our cohort had endoscopic procedures successfully rescheduled in an expedited manner, 15% of those with canceled procedures had not yet rescheduled six months after movement of our region to the yellow phase of reopening. We found younger patients were less likely to have a rescheduled procedure, indicating that this demographic may benefit from dedicated outreach to ensure rescheduling is completed. This data is consistent other studies looking at uptake of cancer screening, which was lower in young people (8). Our data also demonstrated that men may be less likely to have rescheduled endoscopic surveillance, however this trend did not meet statistical significance, possibly on the basis of small sample size. Men have been shown to be less likely to undergo genetic testing for cancer susceptibility (9) as well as less likely to undergo cancer screening (10, 11), consistent with the results we observed in this Lynch syndrome cohort. Finally, we explored why individuals may not have a rescheduled procedure, finding that half of individuals without a rescheduled procedure were not comfortable coming in for an invasive procedure during the pandemic. Apart from COVID-19-related concerns, there are many other reasons that may factor into not rescheduling such as not knowing surveillance is due and higher priority medical treatments, both of which we also observed. Other potential reasons that may be related to the ongoing pandemic include financial hardship, loss of insurance, or change in child/family care responsibilities within one's family, which may also affect an individual's ability to undergo a rescheduled surveillance procedure (12).

It is also important to consider whether this delay in rescheduling procedures is of any consequence. Most current guidelines in the United States support up to at least a 2-year interval for colonoscopic surveillance in Lynch syndrome (6), while some studies have proposed that up to a 3-year interval is acceptable (13,14). We found only 11% of our cohort was outside of the 2-year surveillance interval, whereas the remainder of the cohort had a median of nearly eight months (246 days) prior to reaching their 2-year surveillance interval, indicating that some of these individuals may have been able to further delay their procedures and would still be within the recommended surveillance interval of current guidelines (6). However, given the rapid progression from polyp to malignancy in Lynch syndrome (5) the potential impacts of even relatively short delays in cancer screening may

be of larger consequence in individuals with Lynch syndrome compared to the general population.

We also show that of those who rescheduled and completed their procedures, 35% (8 of 23) demonstrated neoplastic endoscopic findings, including 13% (3 of 23) with either an advanced adenoma or gastrointestinal cancer identified. Of note, those individuals with advanced adenomas identified on their delayed surveillance procedures had a history of prior advanced adenomas, indicating they were at increased baseline risk. While the short procedural delay caused by COVID-19 likely did not play a significant role in the development of these neoplastic lesions, these findings underscore that high risk lesions are identified during Lynch syndrome surveillance, thus reaffirming the importance of timely endoscopic surveillance in this high-risk population, especially in individuals with a history of high-risk endoscopic lesions.

There are important limitations that we acknowledge. This is a single institutional cohort with limited racial diversity, and therefore the results may not be generalizable to all institutions. The small group size without a rescheduled procedure may have limited our ability to detect other statistical differences. Additionally, some individuals who follow with our program undergo endoscopic surveillance procedures outside of our institution, and therefore we are unable to capture their procedural cancellation and rescheduling data. However, despite these limitations, this study provides insight into a high-risk group of patients for whom no data are currently available about pandemic-related surveillance disruptions. Furthermore, given the unique nature of the current pandemic and its disruption to cancer screening, our findings underscoring the importance of ensuring endoscopic follow-up for patients with Lynch syndrome may be applicable across other high-risk groups as well. Future studies in this area will require analysis of larger, multi-institutional Lynch syndrome cohorts to determine other factors that may predict likelihood to reschedule, as well as longitudinal studies to determine the long-term outcomes of these surveillance delays.

With the possibility of additional shutdowns in the future, either related to resurgent COVID-19 or future global pandemics, it is important to recognize and actively target the groups at highest risk of cancer development resulting from postponed surveillance, including Lynch syndrome. In the event of canceled procedures due to COVID-19 or other future events, endoscopy practices should strive to maintain a record of all procedural cancellations, and work efficiently with administrative staff to reschedule these procedures once it is deemed safe to do so. Although this may require extensive administrative effort, it is also important to ensure that individuals who are not successfully rescheduled are provided additional outreach to facilitate this process. Lastly, those at the highest risk should be prioritized for rescheduling once rescheduling resumes. Among individuals with Lynch syndrome, endoscopy practices can consider prioritizing patients for surveillance rescheduling who have the highest risk of cancer, including those with a history of an advanced adenoma or prior gastrointestinal cancer, carriers of a pathogenic variant in *MLH1* or *MSH2/EPCAM*, and those overdue for surveillance at baseline; however, all patients with Lynch syndrome should be considered high-risk compared to the average-risk CRC screening population.

Much of the current literature has focused on persons at highest risk of COVID-19, as well as alternative methods of healthcare delivery during this pandemic (15,16). While individuals with Lynch syndrome are not considered “high-risk” for COVID-19, they are a group that requires frequent healthcare contacts for cancer surveillance, and illustrate the complex and far-reaching effects of the pandemic. Finally, the ongoing nature of the pandemic underscores the delays in care that high-risk patients are incurring and emphasizes the importance of ensuring that delays are minimized. As we continue to monitor COVID-19 related procedure delays worldwide, special attention should be paid to those with Lynch syndrome to ensure that these individuals have their endoscopic procedures rescheduled and performed in an efficient manner.

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References:

1. Mast C, Munoz del Rio A. Delayed Cancer Screenings. EPIC Health Research Network. Published online 4 May 2020. Accessed 8 August 2020.
2. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. *Lancet Oncol* 2020; 21(8):1023–1034. [PubMed: 32702310]
3. Win AK, Jenkins MA, Dowty JG, Antoniou AC, Lee A, Giles GG, et al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. *Cancer Epidemiol Biomarkers Prev* 2017;26:404. [PubMed: 27799157]
4. Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol* 2014;109(8):1159–1179. [PubMed: 25070057]
5. Edelstein DL, Axilbund J, Baxter M, Hyland LM, Romans K, Griffin CA, et al. Rapid development of colorectal neoplasia in patients with Lynch syndrome. *Clin Gastroenterol Hepatol* 2011; 9:340 – 3. [PubMed: 21070872]
6. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal (Version 1.2020). vol. 7 21, 2020
7. Vasen HF, Abdirahman M, Brohet R, Langers AM, Kleibeuker JH, Kouwen MV, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. *Gastroenterology* 2010;138: 2300–2306. [PubMed: 20206180]
8. Wong MC, Ching JY, Lam TY, Luk AK, Hirai HW, Griffiths SM, et al. Prospective cohort study of compliance with faecal immunochemical tests for colorectal cancer screening in Hong Kong. *Prev Med* 2013;57(3):227–31. [PubMed: 23732241]
9. Childers KK, Maggard-Gibbons M, Macinko J, Childers CP. National Distribution of Cancer Genetic Testing in the United States: Evidence for a Gender Disparity in Hereditary Breast and Ovarian Cancer. *JAMA Oncol* 2018;4(6):876–9. [PubMed: 29710084]
10. Davis JL, Buchanan KL, Katz RV, Green BL. Gender differences in cancer screening beliefs, behaviors, and willingness to participate: implications for health promotion. *Am J Mens Health* 2012;6(3):211–7. [PubMed: 22071507]
11. von Euler-Chelpin M, Brasso K, Lynge E. Determinants of participation in colorectal cancer screening with faecal occult blood testing. *J Public Health (Oxf)* 2010;32(3):395–405. [PubMed: 20015868]

12. Czeisler MÉ, Marynak K, Clarke KEN, Salah Z, Shakya I, Thierry JM, et al. Delay or Avoidance of Medical Care Because of COVID-19-Related Concerns - United States, June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69(36):1250–1257. [PubMed: 32915166]
13. Engel C, Vasen HF, Seppälä T, Aretz S, Bigirwamungu-Bargeman M, de Boer SY, et al. No Difference in Colorectal Cancer Incidence or Stage at Detection by Colonoscopy Among 3 Countries With Different Lynch Syndrome Surveillance Policies. *Gastroenterology* 2018;155(5):1400–1409. [PubMed: 30063918]
14. Dominguez-Valentin M, Seppälä TT, Sampson JR, Macrae F, Winship I, Evans DG, et al. Survival by colon cancer stage and screening interval in Lynch syndrome: a prospective Lynch syndrome database report. *Hered Cancer Clin Pract* 2019;17:28. [PubMed: 31636762]
15. Balzora S, Issaka RB, Anyane-Yeboah A, Gray DM 2nd, May FP. Impact of COVID-19 on colorectal cancer disparities and the way forward. *Gastrointest Endosc* 2020;92(4):946–950. [PubMed: 32574570]
16. Mann DM, Chen J, Chunara R, Testa PA, Nov O. COVID-19 transforms health care through telemedicine: Evidence from the field. *J Am Med Inform Assoc* 2020;27(7):1132–1135. [PubMed: 32324855]

Prevention Relevance Statement:

The COVID-19 pandemic has led to unprecedented disruptions in cancer screening, which may have disproportionate effects on individuals at increased cancer risk, including those with Lynch syndrome. Herein we show that the COVID-19 pandemic led to significant disruptions in Lynch syndrome surveillance with potentially impactful delays, thus highlighting the importance of ensuring timely surveillance amongst this high-risk cohort.

Figure 1 –.
Relationship between age and probability of rescheduling surveillance endoscopic procedures in Lynch syndrome

Table 1 –

Characteristics of individuals with Lynch syndrome who had endoscopic procedures canceled during the COVID-19 pandemic shutdown.

Variable	Had a rescheduled procedure N = 23	Did not have a rescheduled procedure N = 4	p-value
Days between canceled and rescheduled procedure, median (IQR)	72 (55, 84)	-	-
Outside of 2-year surveillance window	2 (9%)	1 (25%)	0.40
Age, median (IQR)	55 (43, 63)	35 (26, 43)	0.018 *
Male sex	6 (26%)	3 (75%)	0.093
Race			1.00
Asian	1 (4%)	0 (0%)	
White	22 (96%)	4 (100%)	
Personal history of any cancer	14 (61%)	2 (50%)	1.00
Personal history of colorectal cancer	8 (35%)	1 (25%)	1.00
Pathogenic gene variant			1.00
<i>EPCAM</i>	2 (9%)	0 (0%)	
<i>MLH1</i>	4 (17%)	1 (25%)	
<i>MSH2</i>	9 (39%)	2 (50%)	
<i>MSH6</i>	4 (17%)	0 (0%)	
<i>PMS2</i>	4 (17%)	1 (25%)	

* Statistically significant at the alpha = 0.05 level

Table 2 –

Characteristics of individuals with rescheduled endoscopic procedures.

Variable	No clinically significant endoscopic findings N = 15	Clinically significant endoscopic findings N = 8	p-value
Age, median (IQR)	51 (36, 59)	62 (57, 66)	0.02 *
Male sex	3 (20%)	3 (38%)	0.62
Race			0.35
Asian	0 (0%)	1 (13%)	
White	15 (100%)	7 (88%)	
Personal history of any cancer	9 (60%)	5 (62%)	1.00
Personal history of colorectal cancer	8 (53%)	1 (13%)	1.00
Pathogenic gene variant			0.87
<i>EPCAM</i>	2 (13%)	0 (0%)	
<i>MLH1</i>	3 (20%)	1 (13%)	
<i>MSH2</i>	5 (33%)	4 (50%)	
<i>MSH6</i>	3 (20%)	1 (13%)	
<i>PMS2</i>	2 (13%)	2 (25%)	

* Statistically significant at the alpha = 0.05 level