

# Yield of upper gastrointestinal screening in colonic adenomatous polyposis of unknown etiology: a multicenter study



## Authors

Filsan Farah<sup>1</sup>, Swati G. Patel<sup>2,3</sup>, Jeannine M. Espinoza<sup>2,3</sup>, Nicholas Jensen<sup>4</sup>, Bryson W. Katona<sup>4</sup>, Charles Muller<sup>5</sup>, Sonia S. Kupfer<sup>5</sup>, Jennifer M. Weiss<sup>6</sup>, Alice Hinton<sup>7,8</sup>, Peter P. Stanich<sup>8</sup>

## Institutions

- 1 Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, United States
- 2 Division of Gastroenterology, University of Colorado Anschutz Medical Center, Aurora, Colorado, United States
- 3 Division of Gastroenterology, Rocky Mountain Regional Veterans Affairs Medical Center, Denver, Colorado, United States
- 4 Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States
- 5 Section of Gastroenterology, Hepatology and Nutrition, University of Chicago, Chicago, Illinois, United States
- 6 Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States
- 7 Division of Biostatistics, The Ohio State University, Columbus, Ohio, United States
- 8 Division of Gastroenterology, Hepatology & Nutrition, The Ohio State University Wexner Medical Center, Columbus, Ohio, United States

Medical Center, Columbus, Ohio, United States, 395 W 12th Ave, Suite 200, Columbus, OH 43210, United States  
 Fax: +1-614-293-8518  
 Peter.Stanich@osumc.edu

## ABSTRACT

**Background and study aims** The majority of patients with 10 or more cumulative colorectal adenomas have uninformative genetic testing and meet criteria for colonic adenomatous polyposis of unknown etiology (CPUE). The yield of upper gastrointestinal screening in patients with CPUE after multi-gene panel testing is unknown and our objective was to characterize this.

**Patient and methods** A multicenter, retrospective analysis of screening upper endoscopies in adults with CPUE after multi-gene panel testing was performed. Those with a history of gastroduodenal neoplasia prior to CPUE diagnosis were excluded. Demographic and clinical variables were collected and compared.

**Results** One hundred and twenty-eight patients with CPUE were included from five participating centers. Nine (7.0%) had gastroduodenal neoplasia on initial screening upper endoscopy. Those with over 100 colorectal adenomas had a significantly higher rate of gastroduodenal neoplasia than those with 20–99 or 10–19 colorectal adenomas (44.4% vs 4.1% vs 4.4%,  $P=0.002$ ). Similar results were seen when the analysis was restricted to only duodenal or ampullary adenomas. The only malignancy was a gastric cancer in a patient with 20 to 99 colorectal adenomas. When comparing patients with gastroduodenal neoplasia to those without, the only significantly different characteristic was the cumulative number of colorectal adenomas.

**Conclusions** We found a 7% rate of gastroduodenal neoplasia in patients with CPUE after multi-gene panel testing. Although patients with  $\geq 100$  colorectal adenomas had a significantly higher risk, over 4% of patients with 10 to 99 colorectal adenomas had gastroduodenal neoplasia. Given this, we recommend a screening upper endoscopy at the time of a colonoscopy after CPUE diagnosis.

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## Bibliography

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Georg Thieme Verlag KG, Rüdigerstraße 14,  
70469 Stuttgart, Germany

## Corresponding author

Peter P. Stanich, MD, Division of Gastroenterology,  
Hepatology & Nutrition, The Ohio State University Wexner

## Introduction

Colonic adenomatous polyposis of unknown etiology (CPUE), also referred to as multiple colorectal adenomas or colon polyposis of unknown etiology in previous literature, has generally been defined as 10 or more cumulative adenomatous colorectal polyps with negative germline genetic testing for familial adenomatous polyposis (*APC*) and *MUTYH*-associated polyposis (*MUTYH*) [1, 2]. The National Comprehensive Cancer Network (NCCN) recommends colonoscopy every 1 to 2 years for individuals with 20 or more colorectal adenomas and consideration of these intervals for those with 10 to 19 adenomas [3]. A recommendation to consider upper endoscopic screening for those individuals with 20 or more adenomas was more recently added to their guidelines. International guidelines have similar recommendations for colonoscopy interval but do not recommend upper endoscopic screening [4].

The risk of gastroduodenal neoplasia is well known in polyposis patients with *APC* and biallelic *MUTYH* pathogenic variants [5]. Only a few studies have reported the prevalence in those with CPUE. In an initial small study of 19 patients from a single center in the United States, upper endoscopy revealed duodenal neoplasia in 31.6% of patients [1]. A more recent study of 83 participants from the United Kingdom and the Netherlands reported duodenal adenomas in 9.6% [2]. The generalizability of these case series with limited genetic testing is unclear in the era of multi-gene panel testing (MGPT). Recent discoveries have shown that pathogenic/likely pathogenic variants in multiple other genes, including *AXIN2*, *GREM1*, *NTHL1*, *POLE*, *POLD1*, and *MSH3*, result in a colonic adenomatous polyposis phenotype [6]. MGPT that includes simultaneous analysis of genes associated with polyposis and non-polyposis colorectal cancer phenotypes has been shown to have a higher diagnostic yield [7]. Given this, MGPT is now the standard of care for genetic evaluation of patients with a colonic adenomatous polyposis phenotype [3, 8].

At this time, there is minimal available information on the risk for gastric and duodenal neoplasia in CPUE patients after MGPT. There is a clear need to clarify this risk to help guide screening recommendations. The aim of our study was to assess the results of upper endoscopic screening in a multicenter cohort of CPUE patients after uninformative MGPT.

## Patients and methods

This was a retrospective study assessing patients with CPUE that completed genetic testing and were followed at specialized hereditary and high-risk gastroenterology clinics at the participating centers. Institutional Review Board approval was obtained at Ohio State University on April 29, 2020 and a reliance agreement was reached with the other centers. A waiver of informed consent was approved, given the minimal risk nature of the study.

Participants were considered for inclusion in the study if they had 10 or more cumulative colorectal adenomas, uninformative MGPT, and received a screening upper endoscopy after being diagnosed with colonic adenomatous polyposis from Au-

gust 2014 through January 2020. Patients were excluded if they were under age 18, did not have *APC* and *MUTYH* included in their genetic panel testing, had a known pathogenic/likely pathogenic genetic variant in any hereditary cancer gene (including those not traditionally associated with colorectal cancer), had a history of gastric or duodenal neoplasia (such as adenomatous polyps or adenocarcinoma), had a diagnosis of serrated polyposis syndrome or had a history of abdominal radiation or chemotherapy for a childhood cancer (given reports of therapy-associated polyposis) [9, 10].

If the participants met study criteria, demographic and clinical details were obtained from medical records including endoscopy and pathology reports. This included data on age, race, sex, past medical history, social history, family history (including pedigrees obtained during genetic counseling sessions), genetic testing results, cumulative colorectal adenoma counts, and findings on upper endoscopy after polyposis diagnosis including whether the ampulla was visualized (utilizing either a side-viewing duodenoscope or with a clear cap distal attachment). Standard clinical practice at all participating centers during the study period was to resect or at least biopsy any lesions concerning for neoplasia. As such, pathology results were assessed to confirm the presence of gastric adenoma, gastric adenoma with high-grade dysplasia, gastric cancer, duodenal adenoma, duodenal adenoma with high-grade dysplasia, duodenal cancer, ampullary adenoma, ampullary adenoma with high-grade dysplasia, and ampullary cancer. The comprehensive category of “any gastroduodenal neoplasia” was considered positive if any of these were present.

The deidentified data were then collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the Ohio State University. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [11, 12].

Data are presented as mean and standard deviation or frequency and percentage. Comparisons were done with *t*-tests for continuous variables and Fisher exact tests for categorical variables.  $P < .05$  was considered statistically significant. SAS software (version 9.4; SAS Institute, Cary, North Carolina, United States) was used to perform all analyses.

## Results

Across the five participating centers, 128 patients with CPUE met study criteria and were further analyzed. The median number of participants per center was 19 (range 3–68). The colorectal phenotypes of the patients were 46 (35.9%) with 10 to 19 colorectal adenomas, 73 (57.0%) with 20 to 99 colorectal adenomas and nine (7.0%) with 100 or more colorectal adenomas. Twenty-six patients (20.3%) had a personal history of cancer, including colorectal cancer in 13 (10.2%) and thyroid cancer in four (3.1%). Family history of colorectal cancer in a first-

► **Table 1** Demographics and clinical history.

	n = 128	
Age at index endoscopy (mean, SD)	58.1	13.0
Women	51	39.8%
Body mass index (mean, SD)	29.3	6.4
Race		
▪ White (non-Hispanic)	115	89.8%
▪ Black	12	9.4%
▪ Unknown	1	0.8%
Alcohol use		
▪ Light	47	36.7%
▪ Heavy	8	6.3%
▪ None or unknown	73	57%
Tobacco history		
▪ Former smoker	32	25%
▪ Current smoker	33	25.8%
▪ Never smoker	63	49.2%
Aspirin use (daily)	41	32.0%
History of <i>Helicobacter pylori</i>	14	10.9%
Cumulative number of colorectal adenomas		
▪ 10–19 adenomas	46	35.9%
▪ 20–99 adenomas	73	57.0%
▪ ≥ 100 adenomas	9	7.0%
History of colectomy	19	14.8%
History of cancer <sup>1</sup>	26	20.3%
History of colorectal cancer	13	10.2%
History of thyroid cancer	4	3.1%
Family history of colon cancer in first degree relative	33	25.8%
Family history of polyposis in first degree relative	11	8.6%
Variant of uncertain significance in a gene of interest	24	18.8%
Single variant in a biallelic condition <sup>2</sup>	4	3.1%

<sup>1</sup> Excluding non-melanoma skin cancers  
<sup>2</sup> *MSH3*, *MUTYH*, *NTHL1*

degree relative was present for 33 (25.8%) subjects and 11 (8.6%) reported a first-degree relative with colon polyposis. Further demographic and clinical details are available in ► **Table 1**. Genetic counseling and MGPT was completed in all patients and ► **Table 2** includes the list of genes of interest that were assessed and for which no pathogenic/likely pathogenic variants were identified.

There were nine patients (7.0%) with gastroduodenal neoplasia identified on the index upper endoscopy. The cohort

► **Table 2** Genes of interest included in multi-gene panel testing

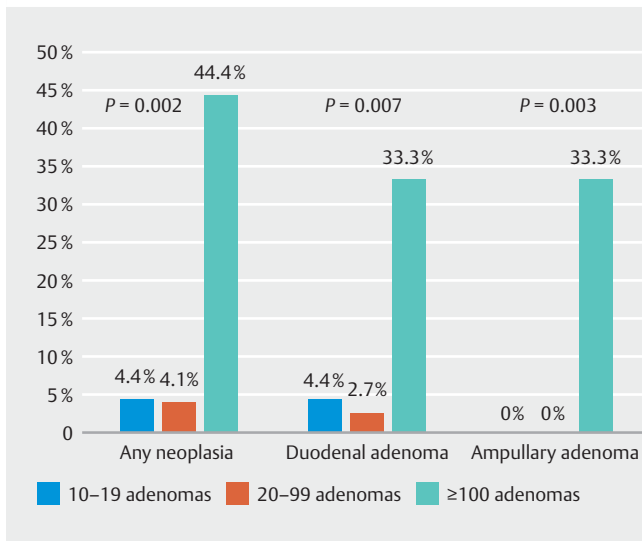
	n = 128	
<i>APC</i>	128	100%
<i>MUTYH</i>	128	100%
<i>MLH1</i>	121	94.5%
<i>MSH2</i>	121	94.5%
<i>MSH6</i>	121	94.5%
<i>PMS2</i>	121	94.5%
<i>EPCAM</i>	120	93.8%
<i>POLD1</i>	119	93.0%
<i>POLE</i>	119	93.0%
<i>GREM1</i>	115	89.8%
<i>TP53</i>	115	89.8%
<i>CHEK2</i>	113	88.3%
<i>AXIN2</i>	98	76.6%
<i>NTHL1</i>	53	41.4%
<i>MSH3</i>	52	40.6%
<i>GALNT12</i>	10	7.8%
<i>RPS20</i>	6	4.7%

with 100 or more colorectal adenomas had a significantly higher rate of any gastroduodenal neoplasia than those with 20 to 99 colorectal adenomas or 10 to 19 colorectal adenomas (44.4% vs 4.1% vs 4.4%,  $P=0.002$ ) (► **Fig. 1**). Similar results were seen when the analysis was restricted to only duodenal adenomas (33% vs 2.7% vs 4.4%,  $P=0.007$ ) (► **Fig. 1**). Interestingly, none of the 17 patients with 50 to 99 colorectal adenomas were found to have gastroduodenal neoplasia. The only malignancy found on screening upper endoscopy was gastric cancer in the setting of a concomitant *Helicobacter pylori* infection in a patient with 20 to 99 colorectal adenomas. For those with duodenal adenomas, one subject had four duodenal adenomas, one subject had two duodenal adenomas, and otherwise, a single adenomatous polyp was found per subject. The polyps ranged in size from 2 mm to 2.5 cm and were all able to be resected endoscopically by snare polypectomy or endoscopic mucosal resection.

Documentation of ampullary visualization was present for 91 patients (71.1%) with similar rates across the three cohorts ( $P=0.3$ ). For those with an assessment performed, ampullary adenomas were only identified in the cohort with 100 or more adenomas (33.3% vs 0% vs 0%,  $P=0.003$ ) (► **Fig. 1**).

The cumulative number of colorectal adenomas was the only significantly different demographic or clinical feature between the cohort with gastroduodenal neoplasia on index upper endoscopy and those without (► **Table 3**). There was no difference across the participating medical centers ( $P=0.604$ ).

Additional upper endoscopies were performed on 28 patients without baseline neoplasia. From this group, gastroduo-



► **Fig. 1** Results of index screening upper endoscopy in colonic adenomatous polyposis of unknown etiology cohorts grouped by cumulative number of colorectal adenomas.

denal neoplasia was noted in two patients (7.1%), including one with gastric adenoma 7 years after index upper endoscopy and one with duodenal adenoma 2 years after index procedure.

## Discussion

In this multicenter analysis of CPUE patients after negative MGPT, we found a 7.0% rate of gastroduodenal neoplasia at initial screening upper endoscopy. This was primarily duodenal adenomas, although two ampullary adenomas and a gastric cancer were also identified. These results are noteworthy as this is the largest cohort of CPUE patients receiving upper endoscopic screening to be reported to date and is the first to have inclusion criteria requiring broad multi-gene genetic testing.

The prevalence of gastroduodenal neoplasia in our cohort is lower than in previous reports focused on upper gastrointestinal findings in CPUE patients. One potential cause for this is the different genetic testing criterion between the studies. Tieu et al. reported on upper endoscopic findings on 19 patients with CPUE after genetic testing for only *APC* and *MUTYH* [1]. They reported six patients (31.6%) with duodenal adenomas and did not find any malignancies. Kallenberg et al. included 83 patients that were also primarily patients with CPUE after genetic testing for only *APC* and *MUTYH*, although their cohort did include two with MGPT and 23 with small genetic testing panels [2]. They found eight patients (9.6%) with duodenal adenomas and did not report any malignancies. Although pathogenic/likely pathogenic variants in the additional genes tested are rare individually, recent evaluation of colonic adenomatous polyposis patients has found an increased yield when MGPT is performed, especially in patients with less than 100 colorectal adenomas [7]. As such, it seems likely that some patients included in previous series would be found to have identifiable

hereditary cancer syndromes with currently available MGPT, and thus, not be eligible for our study and, more importantly, not be managed as CPUE clinically.

Given its nature as a diagnosis of exclusion based on a fairly common clinical phenotype, CPUE represents a heterogeneous mixture of patients. We need to ensure the use of optimal available testing to identify those that may no longer have an unknown etiology. As such, the current definition of CPUE, both clinically and in research efforts, needs to be updated to include unremarkable MGPT that includes available polyposis and non-polyposis colorectal cancer genes rather than only the classic polyposis genes *APC* and *MUTYH*.

In our cohort, the cumulative number of colorectal adenomas was significantly different between subjects with gastroduodenal neoplasia and those without. Those with over 100 colorectal adenomas had a significantly higher risk of having gastroduodenal neoplasia when compared to the other cohorts and seem to be a clearly different phenotype. This lends credence to recommendations to manage those with over 100 colorectal adenomas according to familial adenomatous polyposis guidelines independently of an identified genetic pathogenic variant [3].

Although the risk of duodenal neoplasia was lower in those with 10 to 19 and 20 to 99 colorectal adenomas, these cohorts still had a rate of gastroduodenal neoplasia over 4%. For comparison, the prevalence of sporadic duodenal adenomas in the general population is estimated at 0.1% to 0.3% while *MUTYH*-associated polyposis and familial adenomatous polyposis have prevalence rates of 21.1% and 65%, respectively [13–15]. We were unable to otherwise identify any demographic or clinical features to help guide decision-making regarding upper endoscopic screening. This is similar to previous studies, as Kallenberg et al. also reported a lack of significant differences in their neoplasia and non-neoplasia cohorts while Tieu et al. only found that their neoplasia patients were younger at diagnosis [1,2]. With these factors taken into account, we feel the current evidence supports the recommendation to perform at least a baseline screening upper endoscopy for all CPUE patients. To limit risk of multiple sedation events, we favor performing this at the time of a surveillance colonoscopy. Future work should continue to attempt to identify the most appropriate age to initiate screening and if there are clinical features that can be used to optimize screening guidelines.

Similarly, optimal screening and surveillance intervals are unknown. For those with identified neoplasia, we would favor following the guidelines in place for familial adenomatous polyposis-related neoplasia. The necessity and appropriate interval for repeat screening after a negative initial screening event remains to be elucidated, although our experience suggests this should at least be considered, given the rate of neoplasia identified in those undergoing more than one upper endoscopy in our cohort. To clarify this, the effectiveness of ongoing screening programs should also be a focus of future research.

There are limitations to this study that need to be considered. This includes that this is a retrospective analysis relying on review of medical records for documentation of clinical and endoscopic findings and the inherent potential of inaccuracy.

► **Table 3** Comparison of participants grouped by gastroduodenal neoplasia

	With gastroduodenal neoplasia		Without gastroduodenal neoplasia		P value
	n=9		n=119		
Age at index endoscopy (mean, SD)	52.3	13.9	58.5	12.8	0.168
Women (sex)	5	55.6%	46	38.6%	0.482
Body mass index (mean, SD)	28.7	10.3	29.3	6.1	0.794
Race					1.000
▪ White (non-Hispanic)	8	88.9%	107	89.9%	
▪ Black	1	11.1%	11	9.2%	
▪ Unknown	0	0%	1	0.8%	
Alcohol use					1.000
▪ Light	3	33.3%	44	37.0%	
▪ Heavy	0	0%	8	6.7%	
▪ None or unknown	6	66.7%	67	56.3%	
Tobacco history					0.437
▪ Former smoker	2	22.2%	30	25.2%	
▪ Current smoker	4	44.4%	29	24.4%	
▪ Never smoker	3	33.3%	60	50.4%	
Aspirin use (daily)	3	33.3%	38	31.9%	1.000
History of <i>Helicobacter pylori</i>	1	11.1%	13	10.9%	1.000
Cumulative number of colorectal adenomas					0.002
▪ 10–19 adenomas	2	22.2%	44	37.0%	
▪ 20–99 adenomas	3	33.3%	70	58.8%	
▪ ≥100 adenomas	4	44.4%	5	4.2%	
History of colectomy	3	33.3%	16	13.5%	0.130
History of cancer <sup>1</sup>	1	11.1%	25	21.0%	0.685
History of colon cancer	0	0%	13	10.9%	0.597
Family history of colorectal cancer in first degree relative	3	33.3%	30	25.2%	0.694
Family history of polyposis in first degree relative	1	11.1%	10	8.4%	0.567
Variant of uncertain significance in a gene of interest	1	12.5%	23	22.3%	1.000
Single variant in a biallelic condition <sup>2</sup>	1	12.5%	3	3.0%	0.266

<sup>1</sup> Excluding non-melanoma skin cancers.

<sup>2</sup> *MSH3, MUTYH, NTLH1*

Similarly, the endoscopies were performed according to standard practice at each institution rather than a strict study protocol. In addition, this cohort may not be truly representative of all oligopolyposis patients given the use of genetic testing as an inclusion criterion and the lack of racial diversity. However, we feel that the size and multicenter nature of the reported cohort outweigh these concerns.

## Conclusions

In summary, we found a 7% rate of gastroduodenal neoplasia in patients with CPUE after MGPT. Although patients with over 100 colorectal adenomas had a significantly higher risk, 4% of those with 10 to 99 adenomas had gastroduodenal neoplasia. Given this, we favor performing screening upper endoscopy at the time of a colonoscopy after CPUE diagnosis.

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## Competing interests

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