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Abstract

Purpose: Histopathological abnormalities may be detected despite normal endoscopic findings in pediatric upper gastrointestinal (GI) endoscopy. However, the clinical value of routine biopsies from macroscopically normal mucosa remains uncertain. We aimed to evaluate the impact of such biopsies on diagnosis, treatment, and follow-up.

Methods: We conducted a retrospective study of children undergoing upper GI endoscopy at a tertiary care center over a one-year period. Biopsy specimens obtained from macroscopically normal esophageal, gastric, and duodenal mucosa were analyzed. Biopsy findings were assessed for their impact on clinical management, defined as any change in treatment or follow-up. Outcomes were evaluated at both the patient and biopsy-specimen levels.

Results: A total of 577 patients and 1,071 biopsy specimens were included. Biopsy findings altered clinical management in 60 patients (10.4%). After excluding patients with guideline-supported indications for biopsy despite normal endoscopic findings, biopsy findings altered clinical management in 44 of 516 patients (8.5%). At the biopsy-specimen level, 60 (5.6%) revealed clinically significant findings, 281 (26.2%) showed histopathological abnormalities without clinical impact, and 729 (68%) were histologically normal. *Helicobacter pylori* infection was the most frequent management-changing finding (26/60). Clinical impact varied according to presenting symptoms and biopsy site.

Conclusions: Biopsies from macroscopically normal mucosa remain important in selected clinical scenarios; however, their overall impact on clinical management appears limited outside established indications. These findings support an indication-based approach to biopsy sampling rather than routine tissue acquisition. Further multicenter prospective studies are warranted to validate these findings and support more standardized biopsy practices.

Introduction

Upper gastrointestinal (GI) endoscopy is a widely used, invasive diagnostic tool with high diagnostic yield in pediatric gastroenterology. It is performed in a range of clinical scenarios, including refractory abdominal pain, vomiting, dyspepsia, dysphagia, gastrointestinal bleeding, celiac disease, and chronic diarrhea. In addition to macroscopic evaluation, obtaining biopsies for histopathological analysis is a key step that enhances diagnostic accuracy [1, 2].

Although many gastrointestinal disorders in childhood may present with focal or microscopic abnormalities, routine acquisition of multiple biopsies during every endoscopic procedure can prolong procedure time and increase costs, as well as the workload of pathology laboratories [3]. Current guidelines suggest routine tissue sampling even in the absence of visible endoscopic abnormalities in all children undergoing upper GI endoscopy; however, this is a weak recommendation based on low-quality evidence[1]**.** Although disease-specific guidelines provide biopsy recommendations for selected conditions such as celiac disease and eosinophilic esophagitis, no practical guidance is available regarding which macroscopically normal sites should be routinely sampled, how many biopsy specimens should be obtained, or whether biopsy strategies should vary according to clinical presentation[4, 5]. Consequently, biopsy practices largely depend on individual endoscopists and institutional preferences rather than standardized evidence-based protocols. In pediatric practice, where procedures are commonly performed under general anesthesia, the threshold for obtaining biopsies from normal-appearing mucosa may be even lower, further contributing to practice variability. This discrepancy between a guideline recommending routine biopsies and the limited evidence supporting that recommendation highlights an important evidence gap in pediatric endoscopy.

Although previous pediatric studies have investigated the histopathological yield of upper GI biopsies and the concordance between endoscopic and histological findings, none has specifically evaluated whether biopsies obtained exclusively from macroscopically normal mucosa result in clinically meaningful changes in diagnosis, treatment, or follow-up [6, 7]. Therefore, the actual clinical value of this widely adopted practice remains uncertain, and evidence is lacking to support a more standardized, indication-based biopsy strategy.

We conducted this study to evaluate the clinical impact of biopsies obtained from macroscopically normal mucosa during pediatric upper GI endoscopy. Specifically, we aimed to determine how frequently these biopsies influenced diagnosis, treatment, or follow-up and whether their value differed according to presenting symptoms, thereby providing evidence to help refine current practice and support a more rational, standardized approach to biopsy sampling in children.

Methods

The study was approved by the local Institutional Review Board (AEŞH-BADEK2-2026-193, Date:17.02.2026), and written informed consent was obtained from the patients and/or their legal guardians prior to the procedures.

This retrospective observational study included pediatric patients (0–18 years) who underwent upper gastrointestinal (GI) endoscopy between March 2025 and March 2026 at a tertiary care center. Patients with incomplete data, those undergoing interventional procedures (e.g., foreign body removal, percutaneous endoscopic gastrostomy), and follow-up endoscopies were excluded. When both upper GI endoscopy and colonoscopy were performed in the same patient, only upper GI findings were analyzed.

Data were collected by a single investigator from endoscopy records and electronic medical files, including demographic, clinical, endoscopic, and histopathological variables. Procedures were performed by four endoscopists, and histological evaluations by eleven pathologists. Because this was a retrospective study reflecting routine clinical practice, biopsy decisions outside established guideline-based indications were left to the discretion of the attending pediatric gastroenterologist. Nevertheless, esophageal biopsies in cases of dysphagia and duodenal biopsies in suspected celiac disease are obtained routinely.

Histopathological diagnoses were established according to routine pathology practice. *Helicobacter pylori* gastritis was assessed using the Updated Sydney System, celiac disease according to the modified Marsh classification, and eosinophilic esophagitis was diagnosed in the presence of ≥15 eosinophils per high-power field together with compatible clinicopathological findings.

The primary outcome was the proportion of patients in whom biopsy findings from macroscopically normal mucosa resulted in a change in clinical management, defined as any modification in treatment or follow-up. Macroscopically normal mucosa was defined as the absence of visible inflammatory, erosive, ulcerative, nodular, or other abnormal endoscopic findings in the relevant anatomical segment according to the endoscopy report. Normality was assessed on a site-specific basis; therefore, biopsy specimens from a macroscopically normal segment were included even if endoscopic abnormalities were present elsewhere in the upper gastrointestinal tract. Histopathological findings were categorized as (1) clinically significant findings resulting in a change in clinical management, (2) abnormalities without clinical consequences, and (3) normal histology. Associations between the clinical impact of biopsy findings and presenting symptoms, age, sex, and biopsy site were analyzed using appropriate statistical tests.

Each biopsy specimen was also evaluated independently for its contribution to clinical decision-making. For biopsy-level analyses, multiple tissue fragments obtained from the same anatomical site and submitted in a single specimen container were considered a single histopathological specimen.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [8], and the completed STROBE checklist is provided as Supplementary Material 2.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0. Categorical variables were expressed as number and percentage, and continuous variables as mean ± standard deviation or median (min–max). Normality was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Comparisons were made using the independent samples t-test or Mann–Whitney U test for continuous variables, and the chi-square test for categorical variables. A two-sided p value < 0.05 was considered statistically significant. Only complete-case data were included in the analyses.

3.Results

A total of 696 pediatric endoscopies were initially reviewed; after excluding repeat procedures (n=22), interventional endoscopies (n=86), and cases with incomplete data (n=11), 577 procedures were included in the final analysis. The distribution of demographic characteristics and indications is summarized in Table 1. In brief, most patients were adolescents, and abdominal pain was the most common indication, followed by nausea–vomiting and positive celiac serology.

Among 577 patients, 517 (89.6%) had no clinically significant histopathological findings that affected management, whereas 60 patients (10.4%) had findings that altered treatment or follow-up. After excluding patients with established clinical indications for biopsy despite normal endoscopic findings (suspected celiac disease, dysphagia and chronic diarrhea), 516 patients remained for secondary analysis and biopsy findings altered clinical management in 44 patients (8.5%) in this group.

The clinical impact and underlying causes of management changes are summarized in Supplementary Table 1. Among the 60 patients whose clinical management was altered based on biopsy findings from macroscopically normal mucosa, *Helicobacter pylori* infection was the most frequent finding (26/60, 43.3%), followed by foveolar cell metaplasia (8/60, 13.3%), esophagitis (7/60, 11.7%), eosinophilic esophagitis (6/60, 10.0%), intestinal metaplasia (4/60, 6.7%), and *Giardia lamblia* infection (4/60, 6.7%). Less frequent findings included gastric atrophy (2/60, 3.3%), gastritis requiring treatment (2/60, 3.3%), and celiac disease (1/60, 1.7%).

The comparison of the clinical impact of biopsies from normal-appearing mucosa according to presenting symptoms is shown in Table 2. The diagnostic yield of biopsies obtained from normal-appearing mucosa differed significantly according to presenting symptoms ($p = 0.015$). Management-changing findings were most frequently observed in patients presenting with dysphagia (33.3%) and chronic diarrhea (25.0%), while biopsies rarely altered management in patients evaluated for reflux symptoms (2.9%), dyspepsia (4.2%), or abdominal pain (9.6%). There was no statistically significant association between clinical impact and patient age or sex.

At the biopsy-specimen level, histopathological outcomes according to anatomical site are summarized in Table 3. A total of 1,071 biopsy specimens were analyzed. Of these, 1,005 (93.7%) contained multiple biopsy fragments obtained from the same anatomical site. No discordant histopathological findings were identified among fragments submitted within the same specimen

container. Overall, 60 specimens (5.6%) revealed findings that altered treatment or follow-up, 281 (26.2%) showed abnormalities without clinical impact, and 730 (68%) were histologically normal, consistent with the macroscopic appearance. Clinically significant findings were most frequently identified in antral specimens (15.6%), followed by duodenal bulb specimens (6.5%).

4.Discussion

Obtaining biopsies from macroscopically normal mucosa during upper gastrointestinal endoscopy remains a common practice in pediatric gastroenterology. Although routine biopsy is recommended in selected clinical scenarios, current recommendations regarding biopsies from normal-appearing mucosa outside these established indications remain limited and are based on relatively low-quality evidence[5, 9]. As a result, there is no standardized approach regarding whether routine biopsies should be obtained, from which anatomical sites, or in what number, and biopsy practices vary considerably among clinicians and institutions. This variability largely reflects the limited pediatric evidence addressing the clinical utility of routine biopsies from macroscopically normal mucosa. Therefore, we conducted this study to evaluate the real-world clinical impact of this practice. In a large pediatric cohort, we evaluated not only the histopathological yield of these biopsies but also, more importantly, their impact on clinical management, specifically whether biopsy findings influenced treatment or follow-up decisions. To our knowledge, this is the first study to assess the clinical utility of biopsies from macroscopically normal mucosa at both the patient and biopsy-specimen levels in pediatric upper gastrointestinal endoscopy to inform a more standardized, evidence-based approach to biopsy practice in children.

Our findings demonstrate that the clinical contribution of biopsies obtained from macroscopically normal mucosa is generally limited and varies according to biopsy site and presenting symptoms. Biopsy findings altered clinical management in only 60 of 577 patients (10.4%). After excluding patients with guideline-supported indications for biopsy despite normal endoscopic findings (suspected celiac disease, dysphagia, and chronic diarrhea), 516 patients remained for secondary analysis, and biopsy findings altered clinical management in only 44 patients (8.5%). These findings further support the limited overall clinical yield of routine biopsies from macroscopically normal mucosa, particularly outside established indications. Consequently, the low frequency of management-changing findings raises questions regarding the clinical utility of routinely detecting minor histopathological abnormalities that do not influence patient management. Moreover, biopsy sampling may prolong procedure and anesthesia time and rarely, lead to complications such as bleeding or perforation [10, 11].

Taken together, these results suggest that a selective, patient-centered biopsy approach may be more appropriate than routine sampling from all sites in pediatric patients. While no comparable studies are available for upper GI endoscopy, Glass et al. demonstrated in pediatric colonoscopy that routine

biopsy of normal-appearing mucosa may be unnecessary, particularly in cases of abdominal pain, with an 81% concordance between macroscopic and histological findings[12]. In pediatric upper GI endoscopy, Sheiko et al. reported a 69.9% concordance between endoscopic and histological findings, and Anafy et al. showed low sensitivity but high specificity of endoscopic findings, suggesting that histopathological abnormalities may be present despite normal endoscopic appearance [6, 13]. However, neither study assessed the clinical impact. Similarly, Scomparin et al. reported that histological findings altered clinical management in more than half of the cases, a markedly higher rate than in our study [7]. This difference may be explained by their inclusion of biopsies from both normal and abnormal mucosa, whereas our analysis was restricted to macroscopically normal mucosa.

Overall, although endoscopic–histological discordance is well documented, our findings suggest that it does not consistently translate into clinically significant outcomes. While comparable pediatric data are lacking, an adult study [14] similarly demonstrated that non-targeted biopsies rarely influence clinical management, supporting our results. Consistent with this, a review of routine upper gastrointestinal biopsy practice emphasized that biopsy decisions should be guided by specific clinical indications rather than routine sampling of normal-appearing mucosa [15].

In our study, only a limited number of patients had clinical management changes based on biopsies from macroscopically normal mucosa. Most of these cases were related to *H. pylori* (43.3% of this subgroup; 4.5% overall). However, indications for eradication therapy and treatment strategies may vary among clinicians and institutions, which should be considered when interpreting its contribution to the overall clinical impact. Another notable finding was intestinal metaplasia. Although potentially more clinically relevant, its frequency was quite low (6.6% of the subgroup; 0.7% overall). Follow-up endoscopies in these patients showed no progression, suggesting limited clinical impact despite its theoretical relevance. While random sampling for premalignant lesions is recommended during initial endoscopy in adults [16], no such recommendation exists in pediatric practice. Moreover, intestinal metaplasia in children is reported to be self-limited [17], and our findings did not demonstrate a frequency that would justify additional biopsies from normal mucosa for the detection of premalignant lesions.

Notably, eosinophilic esophagitis was identified in six patients despite a macroscopically normal esophagus, underscoring the importance of esophageal biopsies when clinically suspected. However, as this is already a well-established indication for routine biopsy regardless of endoscopic appearance, this finding primarily supports current recommendations [4]. In contrast, no cases of non-esophageal eosinophilic gastrointestinal disorders or lymphocytic gastritis were identified in our cohort, likely reflecting the absence of clinical suspicion for these conditions. Therefore, our findings should not be interpreted as discouraging biopsies when these disorders are clinically suspected, even in the presence of macroscopically normal mucosa.

Management-changing findings from biopsies of macroscopically normal mucosa varied by anatomical site, being highest in the antrum (15.6%). Esophageal biopsies appear most useful in the presence of dysphagia, while duodenal biopsies may better be reserved for specific indications such as suspected celiac disease or chronic diarrhea. Although clinically relevant findings were identified, their overall yield of duodenal biopsies was low (2%), supporting selective rather than routine sampling. The clinical relevance of antral and corpus biopsies largely depends on institutional approaches to *H. pylori* management, as eradication decisions are often clinician-dependent in the absence of ulcer disease [18, 19].

Our findings suggest that biopsy decisions should be individualized based on presenting symptoms and clinical context. In practice, biopsies from normal mucosa may be particularly valuable in selected scenarios such as dysphagia, suspected celiac disease, or *H. pylori* evaluation in the presence of peptic ulcer disease. Beyond these indications, our findings support a selective biopsy strategy guided by clinical and endoscopic findings rather than routine random sampling.

Limitations

This study has several limitations. First, its retrospective, single-center design may limit the generalizability of the findings. Second, biopsy decisions reflected routine clinical practice and were left to the discretion of the attending endoscopist outside established indications, which may have introduced selection bias. Third, clinical impact was determined retrospectively from medical records and treating physicians' management decisions, which may have introduced some subjectivity. Finally, the retrospective evaluation of pathology reports prevented complete standardization of biopsy sampling and may have been affected by interobserver variability among pathologists. Similarly, the classification of mucosa as macroscopically normal may have been influenced by differences in endoscopic assessment and reporting practices.

Conclusion

This study provides real-world evidence on the clinical impact of biopsies obtained from macroscopically normal mucosa during pediatric upper gastrointestinal endoscopy. Although biopsies from normal-appearing mucosa remain essential in selected clinical scenarios, our findings suggest that their overall impact on clinical management is limited outside established indications. These findings support an individualized, indication-based approach to biopsy sampling rather than routine tissue acquisition from every anatomical site. Further multicenter prospective studies are warranted to validate these findings and support more standardized biopsy practices.

Declarations

Ethics Committee Approval

Ethical approval was obtained from the local ethics committee (AEŞH-BADEK2-2026-193, Date:17.02.2026). All procedures performed in this study involving human participants were conducted

in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to Participate

Written informed consent was obtained from all individual participants included in this study.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by the authors. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic Characteristics and Indications for Upper GI Endoscopy

Variable	**n (%)**
Total patients	577 (100)
Age (years), mean ± SD	13.76 ± 3.46
Sex	
Female	387 (67.1)
Male	190 (32.9)
Indications	
Abdominal pain	282 (48.9)
Nausea–vomiting	112 (19.4)
Positive celiac serology	14 (2.4)
Upper GI bleeding	23 (4.0)
Lower GI bleeding	24 (4.2)
Reflux symptoms	34 (5.9)
Dysphagia	27 (4.7)
Dyspepsia	24 (4.2)
Chronic diarrhea	20 (3.5)
Portal hypertension	2 (0.3)
Iron deficiency anemia	6 (1.0)
Malignancy screening	5 (0.9)
Halitosis	3 (0.5)
Anal complaints	1 (0.2)

Abbreviations: GI, gastrointestinal; SD, standard deviation.

Table 2. Clinical Impact of Biopsies from Normal Mucosa According to Presenting Symptoms

Indication	**Clinical Impact n (%)**	**No Clinical Impact n (%)**	**Total n (%)**	**p value***
Abdominal pain	27 (9.6)	255 (90.4)	282 (100)	0.015
Nausea–vomiting	8 (7.1)	104 (92.9)	112 (100)	
Positive celiac serology	2 (14.3)	12 (85.7)	14 (100)	
Upper GI bleeding	3 (13.0)	20 (87.0)	23 (100)	
Lower GI bleeding	3 (12.5)	21 (87.5)	24 (100)	
Reflux symptoms	1 (2.9)	33 (97.1)	34 (100)	
Dysphagia	9 (33.3)	18 (66.7)	27 (100)	
Dyspepsia	1 (4.2)	23 (95.8)	24 (100)	
Chronic diarrhea	5 (25.0)	15 (75.0)	20 (100)	
Portal hypertension	0 (0)	2 (100)	2 (100)	
Iron deficiency anemia	1 (16.7)	5 (83.3)	6 (100)	
Malignancy screening	0 (0)	5 (100)	5 (100)	
Halitosis	0 (0)	3 (100)	3 (100)	
Anal complaints	0 (0)	1 (100)	1 (100)	
Total	60	517	577 (100)	

*Global chi-square test.

Table 3. Histopathological Outcomes of Biopsies Obtained From Macroscopically Normal Mucosa by Anatomical Site

Site	Total biopsy specimens (n)	Outcome	n (%)
Esophagus	260	Clinical impact	13 (5.0)
		No clinical impact	60 (23.1)
		Normal histology	187 (71.9)
Corpus	64	Clinical impact	2 (3.1)
		No clinical impact	26 (40.6)
		Normal histology	36 (56.3)
Antrum	205	Clinical impact	32 (15.6)
		No clinical impact	89 (43.4)
		Normal histology	84 (41.0)
Bulb	46	Clinical impact	3 (6.5)
		No clinical impact	10 (21.7)
		Normal histology	33 (71.7)
Duodenum	498	Clinical impact	10 (2.0)
		No clinical impact	98 (19.7)
		Normal histology	390 (78.3)
Total	1071	Clinical impact	60 (5.6)
		No clinical impact	281 (26.2)
		Normal histology	730 (68.0)

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Figures

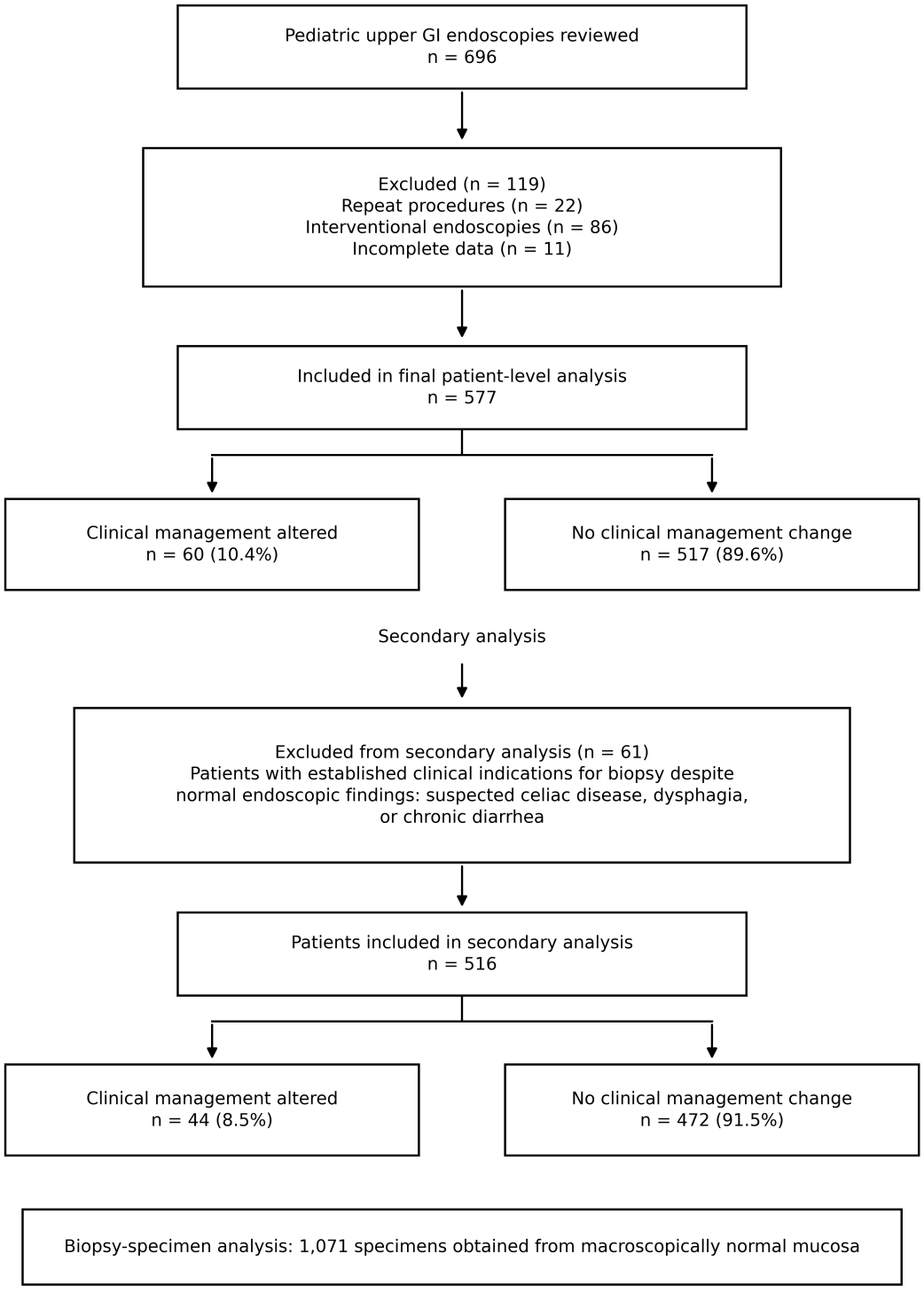


Figure 1

Figure 1. Study Flow Diagram

Supplementary Files

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- SupplementaryTable1revised.docx