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Factors Predicting Loss of Remission in Crohn's Disease Patients in Endoscopic Remission in the Real World

Results From TARGET-IBD

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Background: There is limited evidence that histologic remission improves outcomes in Crohn's disease (CD). We aimed to characterize a cohort of patients with CD in endoscopic remission and explore factors associated with subsequent loss of remission (LOR).

Methods: In total, 4474 patients were enrolled in TARGET-IBD, a longitudinal, observational cohort study. Patients with a normal steroid-free colonoscopy (index) were defined as "in endoscopic remission" and were followed for LOR, defined as presence of inflammation, erosion, ulceration, or stricturing on a subsequent colonoscopy or commencement of steroids. Histologic activity was dichotomized using standard of care reports for active inflammation. Unadjusted and multivariable-adjusted Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of LOR in relation to independent variables.

Results: Of 658 patients with CD with steroid-free endoscopic remission, the majority were female (57%), white (83%), non-Hispanic (93%); 20% had ileal and 20% isolated colonic disease. Inflammatory (B1) disease was the most common phenotype (43%). Of these 658 patients, 257 (39%) had histologic inflammation on index colonoscopy. Histologic inflammation at index colonoscopy was associated with nearly twice the LOR risk (HR 1.96, 95% CI: 1.50-2.57) with median time to relapse of 1.20 years. Biologic use at index was associated with lower LOR risk (monotherapy, HR 0.61, 95% CI: 0.45-0.82; combination therapy, HR 0.43, 95% CI: 0.28-0.66).

Conclusions: Active histologic inflammation despite endoscopic remission, and lack of biologic use were independently associated with risk of subsequent LOR, providing evidence that histologic remission may impart improved outcomes in patients with CD.

Key Words: Crohn's disease, inflammatory bowel disease, histologic remission, treat-to-target, real-world data

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Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that is characterized by segmental, transmural, granulomatous inflammation that most commonly affects the terminal ileum or colon, and a relapsing and remitting disease course.[1] Treatment goals in adult CD include early symptomatic improvement leading to clinical response, and medium-term clinical remission and normalization of inflammatory biomarkers, and longer-term goals of endoscopic healing, normalized health-related quality of life and reduction in long-term disability.[2] Histologic remission is increasingly studied as a potential treatment target in CD but is not yet a treatment target in clinical practice.[2]

Understanding associations between treatment targets in CD and longer-term patient outcomes informs decisions on prognosis, treatment modification and escalation. Endoscopic healing (absence of ulcerations) has emerged as an adjunct treatment target in CD because achieving endoscopic healing at first endoscopic assessment on treatment is associated with improved rates of longer-term clinical remission and endoscopic healing, and reduced risk of CD-related hospitalization and surgery.[3] Achieving endoscopic healing in addition to symptom resolution after 48 weeks of treatment in early CD is associated with a decreased risk of disease progression for a 3-year follow-up period.[4] However, there is limited evidence to support a hypothesis that histologic remission may be an independent predictor of improved outcomes in CD.[5,6] Studies have been limited by a lack of agreement on biopsy numbers and locations, and standardized, validated definitions of histologic remission.[7,8] However, 2 small, retrospective cohort studies suggest that, in patients with CD with endoscopic healing, the presence of persistent histologic inflammation may be associated with an increased risk of flare,

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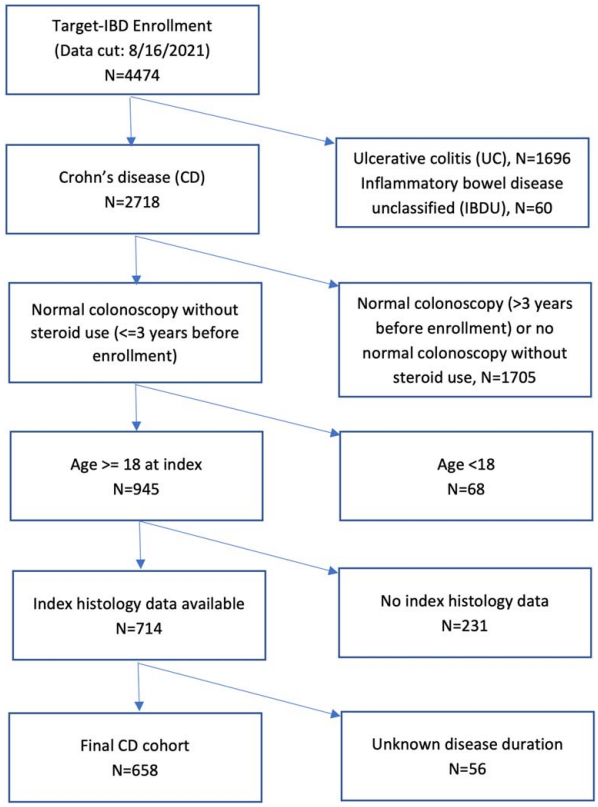

FIGURE 1. Consort diagram for adult CD participants with colonoscopies and histology. The boxes on the right show patients excluded during selection process. After all exclusions, 658 participants with steroid-free endoscopic remission were eligible for analysis. Note: normal colonoscopy was defined as no evidence of endoscopic inflammation, erosion, ulceration, or stricturing.

corticosteroid use and hospitalization over ~2 years of follow-up.[9,10] However, these studies were limited by sample size (n = 62 and n = 101), were performed at a Veteran's Affairs hospital or academic IBD center, and used expert GI pathologist review to score biopsies, all limiting the generalizability and external validity.

TARGET-IBD is a large, prospective, longitudinal, multicenter observational cohort study at both community and academic centers that is designed to generate real-world evidence on treatment patterns and outcomes in patients with IBD. This study aims to characterize a cohort of CD patients in endoscopic remission within the TARGET-IBD database, and to explore whether demographic, clinical, therapeutic or histologic characteristics are associated with subsequent loss of remission for a 3-year follow-up period.

MATERIALS AND METHODS

Study Population

TARGET-IBD is a longitudinal, observational cohort study of adult and pediatric patients with IBD receiving care at academic and community sites in the United States. Enrolled participants consent to the collection of up to 3 years of retrospective, redacted medical records including clinician notes, laboratory data, prior imaging reports, and other diagnostic procedures. Prospective medical record collection occurs every 6 months following study enrollment. All data are processed, transmitted, and stored via the central electronic data capture system as described in detail elsewhere.[11]

Inclusion and Exclusion Criteria

This analysis included adults with CD enrolled between July 2017 and August 2021 and in remission as of the first normal steroid-free colonoscopy (no evidence of endoscopic inflammation, erosion, ulceration, or stricturing and no steroid use), occurring no more than 3 years before study enrollment (hereafter referred to as "index" colonoscopy). Participants were also required to have histologic assessment at index colonoscopy and known duration of disease. Patients diagnosed with ulcerative colitis or IBD-unclassified colitis were excluded along with those who were not in steroid-free endoscopic remission within the 3-year retrospective period before enrollment or later. Patients with no available histologic data, with unknown disease duration, or those younger than 18 years of age were also excluded. The procedures of patients' selection were illustrated in Figure 1.

Statistical Analysis

Patients were followed from the time of the index colonoscopy for loss of remission (LOR), the outcome of interest, which was defined as the presence of inflammation, erosion, ulceration, or stricturing on a follow-up colonoscopy, or the commencement of steroids. The predictive variables included age at index (years), age at diagnosis (years), sex (male, female), race (white, black or African American, Native Hawaiian or Pacific Islander, Asian, other, not reported), ethnicity (Hispanic or Latino, not Hispanic or Latino), body mass index (BMI, kg/m^2), insurance type (private, Medicare, Medicaid, supplemental, unknown, other, uninsured), site type (academic, community), presence of histologic inflammation assessed via biopsy at index (no, yes), disease duration at index (years), disease location (ileum, colonic, ileocolonic, not reported), and disease phenotype, which was categorized as inflammatory (B1), stricturing (B2), or fistulizing (B3). Detailed treatment history was also assessed including steroid use in 6 months before index (no, yes), current use of 5-ASA derivatives at index (no, yes), biologics (anti-TNF, anti-integrin, anti-IL-12/23, JAK inhibitors) taken before index (0, 1, > 1 unique biologics), at index (no, yes), and duration of biologics (≤ 1, > 1 y). Histologic inflammation was determined by biopsy reports and/or related documentation from patient medical records. Inflammation was recorded as yes or no for each location biopsied. If inflammation was noted in any location, it was counted "yes" for histologic inflammation. Specific biologics included adalimumab, certolizumab, golimumab, infliximab, natalizumab, ustekinumab, and vedolizumab.

Unadjusted and multivariable-adjusted Cox proportional hazards regression[12] was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of LOR in relation to the independent variables. Follow-up time was calculated as person-years from index colonoscopy until the earliest of: LOR (event), death, discontinuation from the study, IBD surgery, lost to follow up, or end of available data. The final adjusted model included age at index colonoscopy, duration of disease, disease location, phenotype, number of unique biologics used (and discontinued) before index colonoscopy, current biologic use at index, and histologic inflammation. Variables that were not

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TABLE 1. Characteristics of Adult TARGET-IBD Participants With Crohn's Disease

Category	Characteristics	All participants (N = 658)
Demographics	Age at index (y)*	
	Median (IQR)	40 (25)
	Min–max	18–86
	Age at diagnosis (y)	
	Median (IQR)	26 (24)
	Min–max	3–81
	Duration of disease at index (y)†	
	Median (IQR)	10 (14)
	Min–Max	0–60
	Sex, N (%)	
	Female	378 (57.4)
	Male	280 (42.6)
	Race, N (%)	
	White	546 (83)
	Black or African American	65 (9.9)
	Asian, Native Hawaiian, Pacific Islander	14 (2.2)
	Other/not reported	33 (5)
	Ethnicity, N (%)	
	Hispanic or Latino	17 (2.6)
	Not Hispanic or Latino	614 (93.3)
	Other/not reported	27 (4.2)
Disease characteristics	Location of Crohn's disease, N (%)‖	
	Colon	132 (20.1)
	Ileocolon	286 (43.5)
	Ileum	132 (20.1)
	Not reported	108 (16.4)
	Crohn's disease phenotype, N (%)¶	
	Inflammatory (B1)	284 (43.2)
	Stricturing (B2)	56 (8.5)
	Fistulizing (B3)	191 (29)
	Prior CD surgery (non-B1 phenotype)#	127 (19.3)
Treatment history	Number of unique biologics discontinued before index, N (%)**	
	0	394 (59.9)
	1	157 (23.9)
	> 1	107 (16.3)
	Biologic use ongoing at index, N (%)	
	No	231 (35.1)
	Yes—combination therapy††	118 (17.9)
	Yes—monotherapy	309 (47.0)
	Duration on biologic at index, N (%)	
	≤ 1y	148 (34.7)
	> 1y	279 (65.3)
	Missing	231
	Anti-TNF use ongoing at index, N (%)	
	No	344 (52.3)
	Yes—combination therapy††	94 (14.3)
	Yes—monotherapy	220 (33.4)
	Anti-integrin use ongoing at index, N (%)	
	No	597 (90.7)
	Yes	61 (9.3)
	Anti IL-12/23 use ongoing at index, N (%)	
	No	605 (91.9)
	Yes	53 (8.1)
	5-ASA derivative use ongoing at index, N (%)	
	No	529 (80.4)
	Yes	129 (19.6)
	Steroid use within 6mo before index, N (%)	
	No	593 (90.1)
	Yes	65 (9.9)
Index biopsy	Inflammation on biopsy, N (%)	
	No	401 (60.9)
	Yes	257 (39.1)

*Age at Index calculated as year of index colonoscopy minus year of birth.
†Duration of disease at index calculated as year of index colonoscopy minus year of diagnosis.
‡Based on most recent BMI at or before the index colonoscopy.
§If index colonoscopy is after enrollment, then most recent insurance information from at/before the colonoscopy date is used. If colonoscopy date is before enrollment, then earliest available insurance information (from enrollment) is used.
‖Based on most recent IBD Status assessment at or before the index colonoscopy.
¶Crohn's disease phenotype derived using data up through the index colonoscopy.
#Individuals who underwent prior CD surgery (ie, intestinal resection) who therefore are non-B1 phenotype, but not known whether B2 or B3.
**Biologics include adalimumab, certolizumab, golimumab, infliximab, natalizumab, ustekinumab, and vedolizumab.
††Combination therapy includes concurrent use of methotrexate, azathioprine, or mercaptopurine.

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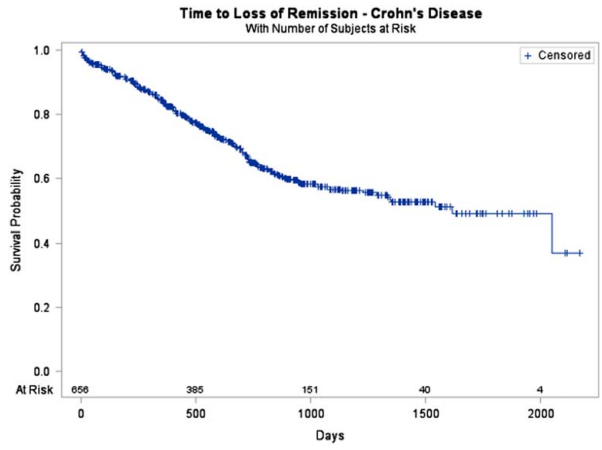

FIGURE 2. This Kaplan–Meier curve estimates the survival probability by the time of loss of remission for Crohn's disease.

informative were dropped from the model. A sensitivity analysis was conducted by using alternative LOR calculation method (Figure S1, Supplemental Digital Content 1, http://links.lww.com/JCG/B93). In the alternative method, steroid use was not considered. SAS version 9.4 was used for all statistical analyses.

RESULTS

Study Population

A total of 4474 patients (2718 of them with CD) were enrolled in TARGET-IBD from July 2017 to August 2021. After all exclusions, 658 participants with steroid-free endoscopic remission were eligible for analysis (Fig. 1). The majority of the cohort were female (57%), white (83%), non-Hispanic (93%), had private insurance (76%), and were being seen for IBD at academic sites (78%) (Table 1). The median age at index colonoscopy was 40 years (IQR = 25), and median disease duration was 10 years (IQR = 14). Twenty percent of patients had ileal disease and 20% isolated colonic, while both locations were affected in 43% of patients. Inflammatory (B1) disease was the most common phenotype (43%) followed by fistulizing (B3) (29%). Although, most patients had no previous biologic use (60%), the majority (65%) were receiving their first biologic at index (47% monotherapy, 18% concurrent immunomodulator). For most of these (65%), time on the current biologic exceeded 1 year. Anti-TNF was the most common biologic class among the cohort with 33% of users on monotherapy and 14% on combination therapy. Anti-integrins and anti-IL-12/23 therapies were less common (9% and 8%, respectively). Twenty percent of patients were using 5-ASA derivatives, and 10% had used steroids within 6 months preceding index. Histologic inflammation was detected via biopsy in 39% of the cohort despite endoscopic remission. At day 0, there were 656 participants at risk; after 500 and 1000 days, the numbers of participants at risk were 385 and 151, respectively (Figure 2).

Factors Associated With Loss of Remission

On multivariable modeling, the presence of histologic inflammation at index was associated with nearly twice the risk of LOR relative to no histologic inflammation (HR 1.96, 95% CI: 1.50-2.57) after adjustment for age at index, duration of disease, location, phenotype, and use of biologics (Table 2). Current biologic use at index was associated with lower risk compared with no use (monotherapy, HR 0.61, 95% CI: 0.45-0.82; combination therapy, HR 0.43, 95% CI: 0.28-0.66). Participants with stricturing or

TABLE 2. Factors at the Time of a Steroid-free Endoscopic Remission Colonoscopy Associated With Subsequent Loss of Remission Represented as Unadjusted and Multivariable-adjusted Cox Models

Variables	LOR N	Person-years	Unadjusted HR (95% CI)	Multivariable-adjusted* HR (95% CI)
Age at index colonoscopy (y)†	221	1210.5	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Duration of disease at index (y)‡	221	1210.5	1.00 (0.99-1.01)	0.99 (0.98-1.01)
Location of Crohn's disease				
Colon	44	273.9	Ref	Ref
Ileocolon	101	500.7	1.23 (0.86-1.75)	1.13 (0.79-1.62)
Ileum	40	225.4	1.07 (0.70-1.64)	0.98 (0.63-1.53)
Not reported	36	210.5	1.06 (0.68-1.65)	0.89 (0.57-1.40)
Crohn's disease phenotype				
Inflammatory	90	549.0	Ref	Ref
Stricturing or fistulizing	131	661.5	1.21 (0.93-1.59)	1.31 (0.99-1.74)
Number of unique biologics discontinued before index colonoscopy§				
0	129	769.2	Ref	Ref
1	54	279.3	1.16 (0.84-1.59)	1.24 (0.89-1.72)
>1	38	162.0	1.36 (0.95-1.96)	1.42 (0.97-2.07)
Biologic use ongoing at index colonoscopy				
No	104	426.6	Ref	Ref
Yes—combination therapy‖	29	228.0	0.52 (0.34-0.78)	0.43 (0.28-0.66)
Yes—monotherapy	88	555.9	0.64 (0.48-0.85)	0.61 (0.45-0.82)
Inflammation on index biopsy				
No	105	771.2	Ref	Ref
Yes	116	439.3	1.93 (1.48-2.51)	1.96 (1.50-2.57)

*Mutually adjusted for all other variables.
†Calculated as year of index colonoscopy minus year of birth.
‡Calculated as year of index colonoscopy minus year of diagnosis.
§Adalimumab, certolizumab, golimumab, infliximab, natalizumab, ustekinumab, and vedolizumab.
‖Concurrent use of methotrexate, azathioprine, or mercaptopurine.

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TABLE 3. The Number of Patients with Histologic Inflammation at Index and Follow-up Biopsy

	Follow-up inflammation (biopsy)*				
Index inflammation (biopsy)	**Ileal**	**Ileocolonic**	**Colonic**	**No ileal or colonic inflammation**	**Total**
Ileal	3	2	3	8	16
Ileocolonic	1	3	3	5	12
Colonic	5	3	29	13	50
No ileal or colonic inflammation	7	9	29	73	118
Total	16	17	64	99	196

Ileal: Inflammation noted in ileum but not colon/rectum.
Ileocolonic: Inflammation noted in both ileum and colon/rectum.
Colonic: Inflammation noted in colon/rectum but not ileum.
*Based on biopsy from the same date as first colonoscopy within 3 to 30 months after index.

fistulizing disease had approximately 30% higher risk of LOR than those with inflammatory disease, although this finding was of marginal statistical significance (HR 1.31, 95% CI: 0.99-1.74).

In the sensitivity analysis excluding steroid commencement from loss of response definition, the associations between LOR and biologic use, complicated disease behavior, and active histologic inflammation remained significant (Table S1, Supplemental Digital Content 1, http://links.lww.com/JCG/B93).

Among the 78 patients who also had a follow-up biopsy, 52 (67%) had histologic inflammation at follow-up: 35 (45%) experienced recurrent inflammation at the same location, whereas 17 (22%) had inflammation at a different location (Table 3).

DISCUSSION

In this large real-world study among 658 patients with CD in steroid-free endoscopic remission undergoing biopsy, histologic evidence of inflammation was a significant independent predictor of subsequent LOR with a median time to LOR of 1.20 years. Conversely, current biologic use was associated with lower relative risk of LOR. These associations were robust on sensitivity analysis.

These findings extend what is available in the current literature; as mentioned above, there has been little to support that histologic remission may be an independent predictor of improved CD outcomes.[5,6] Our findings corroborate prior studies,[9,10] in that histologic inflammation was associated with increased risk of flare, corticosteroid use and hospitalization for a 2-year follow-up. The current study, while applicable only to patients with ileal/colonic disease, adds significant external validity to the previous findings based on the inclusion of nonacademic centers and using standard of care pathology reports with binary definition of inflammation. Based on these combined findings, potential incorporation of routine biopsy assessment for histologic activity even in endoscopic remission may help risk stratify patients. However, studies have not yet demonstrated clear benefit of altering therapy based on histologic activity in absence of endoscopic activity.

Furthermore, our study found that marginal suggestive evidence that complicated disease phenotype may play a role in predicting subsequent loss of remission because participants with stricturing or fistulizing disease had about 30% higher risk of LOR than those with only inflammatory disease. These findings support a body of evidence which establishes lesser response to anti-TNF therapy in such groups and increased disease severity.[13–17] Thus, it is critical to also consider an individual's disease history and phenotype in addition to current activity when establishing a clinical risk monitoring strategy.

Finally, this study showed the current biologic use, most often the initial biologic, was associated with significant reduction in risk of subsequent loss of response compared with individuals not receiving biologic. This risk reduction was modestly different between those receiving biologic monotherapy (39%) and those receiving concurrent immunomodulator (57%, Δ18%). This further supports the mounting evidence that biologics are the most effective medical therapy for CD. Given that the most common biologic class utilized was anti-TNFs, the risk reduction seen with combination therapy supports existing prospective trial data.

This was an observational study conducted among patients seen in real-world usual practice across a geographically diverse area in the United States. There are many strengths to this study. It provides a large collection of patients with the appropriate characteristics for analysis and follows them longitudinally. There is a large number of these patients who are cared for in a community setting, which strengthens the external validity of these findings. Furthermore, the management of these patients was clinician-directed, and not mandated by the study, so it captures standard of care practice, data, and outcomes.

Limitations of this study include that the decision to have an endoscopy was not standardized and thus could be influenced by clinical disease activity. Similarly, the decision to biopsy and the location of biopsies relative to the known disease location was not standardized, and there may be differences in those who underwent biopsy and those who did not. In addition, laboratory results were not integrated into this analysis. Although tracking fecal calprotectin may have been an interesting addition, only 31 of the patients in this study (4.7%) had an available fecal calprotectin in the appropriate time window; this is a limitation in the capturing of standard of care data. In addition, electronic medical records may be incomplete for some variables. As this is a real-world noninterventional study, the potential for bias and unmeasured confounding factors are unable to be ruled out as participants are not randomized. Furthermore, despite a diverse sampling of academic and community gastroenterology sites across the United States, patients were predominantly non-Hispanic white participants seen at academic sites with private insurance. And yet, this sample provides a greater sampling size and increases the generalizability previously limited in prior studies. For endoscopy

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reports, objective scales such as the SES-CD was not universally recorded, and endoscopic reports varied in their level of detail to assign such scores. In addition, our definition of remission on index and follow-up is not clinically based, but rather based on endoscopic results. The correlation between clinical experience and endoscopy is not strong, but the more objective and complete results provided by endoscopy were chosen for this analysis. At present, NSAID use and smoking were not evaluated in this study as it was limited to specific biologics. Future analyses would benefit from the inclusion of these variables. Finally, a prespecified definition of endoscopic assessment, which required a "normal" description of the colon and ileum, was used to define endoscopic remission and while not utilized in clinical trial programs, similar definitions have been used in other large, real-world studies.[18,19]

CONCLUSIONS

This study shows that, in patients with CD in corticosteroid-free endoscopic remission, persistent active histologic inflammation is associated with an almost two-fold increased risk of subsequent LOR, compared with patients without persistent histologic inflammation. In addition, current use of biologic therapy may be protective for subsequent LOR. These data support the use of histologic remission as a treatment target in CD recognizing that achieving such a stringent endpoint can take an extended amount of time and is an area for future exploration. However, prospective studies are needed to confirm these findings and to further delineate if closer disease monitoring or treatment modification is effective at preventing LOR in patients with known risk factors. Importantly, it is unknown whether such optimization to a goal of histologic healing is feasible or cost effective in IBD management. Furthermore, patients with ongoing histological activity, even though they show endoscopic healing, should not electively undergo treatment withdrawal. Clinicians should consider implementing routine biopsies for histologic activity assessment in individuals with Crohn's disease in endoscopic remissi.

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