

Minor Papillotomy for Treatment of Idiopathic Acute Pancreatitis With Pancreas Divisum

A Randomized Clinical Trial

Gregory A. Coté, MD, MS; Valerie Durkalski-Mauldin, PhD; Evan L. Fogel, MD, MSc; Dana C. Moffatt, MD; Andrew Y. Wang, MD; Luis F. Lara, MD; Paul R. Tarnasky, MD; James L. Buxbaum, MD; Sun-Chuan Dai, MD; Sreeni Jonnalagadda, MD; Field F. Willingham, MD; Andrew Ross, MD; Rajesh N. Keswani, MD; Sumant Inamdar, MD; Truptesh H. Kothari, MD; Timothy B. Gardner, MD, MS; Priya A. Jamidar, MD; Srinivas Gaddam, MD; Douglas K. Pleskow, MD; Jeffrey J. Easler, MD; B. Joseph Elmunzer, MD; John Gerard Coney, MD; J. Shawn Mallery, MD; Daniel S. Strand, MD; Georgios I. Papachristou, MD, PhD; Adam Slivka, MD, PhD; Prashant Kedia, MD; Ara B. Sahakian, MD; Abdul Kouanda, MD; Anh Phan, MS; April Williams, BS; Dana K. Andersen, MD; Jose Serrano, MD, PhD; Dhiraj Yadav, MD, MPH; for the SHARP Consortium

IMPORTANCE Pancreas divisum is implicated as an obstructive cause for acute pancreatitis. Observational data suggest endoscopic retrograde cholangiopancreatography (ERCP) with minor papillotomy reduces the risk of pancreatitis episodes. Even though this endoscopic procedure is widely used in practice, clinical trials are lacking.

OBJECTIVE To determine whether ERCP with minor papillotomy reduces the risk of acute pancreatitis among adults with unexplained acute recurrent pancreatitis and pancreas divisum.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, sham-controlled, double-blind randomized clinical trial enrolled adults with 2 or more episodes of acute pancreatitis and pancreas divisum. Adults with other etiologies for acute pancreatitis or concomitant chronic calcific pancreatitis were excluded. The trial was conducted between September 1, 2018, and August 30, 2024, at 21 referral centers in the US and Canada. Last follow-up occurred on February 15, 2025.

INTERVENTION Participants were randomized in a 1:1 ratio to ERCP with minor papillotomy or sham ERCP.

MAIN OUTCOMES AND MEASURES The primary outcome was development of acute pancreatitis more than 30 days after randomization as a time-to-event outcome. The secondary outcomes included acute pancreatitis episode frequency and development of chronic calcific pancreatitis, diabetes, and exocrine pancreatic dysfunction.

RESULTS A total of 148 participants were randomized (mean age, 54 [SD, 19.5] years; 68.2% female; 95.3% non-Hispanic or Latino and 87.2% White; mean lifetime acute pancreatitis episodes, 3 [SD, 2]; mean duct diameter, 2.2 [SD, 1.3] mm) and followed up for a median of 34 months (IQR, 21.7-45.7 months). Of the 75 participants in the ERCP with minor papillotomy group, 26 (34.7%) developed acute pancreatitis compared with 32 of 73 participants (43.8%) in the sham ERCP group (adjusted hazard ratio, 0.83 [95% CI, 0.49 to 1.41]). The incidence rate ratio for acute recurrent pancreatitis episode frequency was 0.25 (95% CI, 0.18 to 0.34) in the ERCP with minor papillotomy group vs 0.30 (95% CI, 0.23 to 0.41) in the sham ERCP group. There were no between-group differences in frequency and incidence of chronic calcific pancreatitis (4.0% in the ERCP with minor papillotomy group vs 2.7% in the sham ERCP group; risk difference [RD], 0.01 [95% CI, -0.05 to 0.07]), diabetes (15.8% vs 12.8%, respectively; RD, 0.03 [95% CI, -0.13 to 0.19]), and exocrine pancreatic dysfunction (7.7% vs 17.2%; RD, -0.10 [95% CI, -0.27 to 0.08]). The adverse event of acute pancreatitis within 30 days of randomization occurred more frequently in the ERCP with minor papillotomy group (14.7%) vs the sham ERCP group (8.2%) (RD, 0.06 [95% CI, -0.04 to 0.17]).

CONCLUSIONS AND RELEVANCE Among patients with unexplained acute recurrent pancreatitis and pancreas divisum, ERCP with minor papillotomy does not reduce the risk of another episode of acute pancreatitis or related sequelae.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT03609944](https://clinicaltrials.gov/ct2/show/study/NCT03609944)

JAMA. 2026;335(8):682-692. doi:[10.1001/jama.2025.23988](https://doi.org/10.1001/jama.2025.23988)
Published online January 14, 2026.

- [+ Visual Abstract](#)
- [+ Research Summary](#)
- [← Editorial page 671](#)
- [+ Supplemental content](#)

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the SHARP Consortium appear in Supplement 4.

Corresponding Author: Gregory A. Coté, MD, MS, Division of Gastroenterology and Hepatology, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239 (coteg@ohsu.edu).

Pancreatic duct obstruction can cause acute pancreatitis, which is an acute inflammatory syndrome that leads to more than 250 000 hospitalizations in the US annually and is increasing in incidence worldwide.^{1,2} Centuries ago, anatomists observed pancreas divisum as a congenital variant in which the dorsal and ventral pancreatic ducts have incomplete or nonexistent fusion during embryologic development.³ With the advent of endoscopic retrograde cholangiopancreatography (ERCP) in the 1970s, pancreas divisum was promulgated as an obstructive phenotype and minor papilla endoscopic sphincterotomy (or minor papillotomy) was considered the appropriate treatment.⁴ Expert consensus and cohort studies support this practice but are limited by their open-label and often retrospective design, subjective end points, and the absence of a natural history comparator.^{5,6}

Approximately 20% of patients who develop acute pancreatitis remain idiopathic after their initial workup and are at risk for recurrence.⁷ There is a critical need for treatments because acute recurrent pancreatitis significantly reduces quality of life and increases the risk of chronic pancreatitis and its sequelae.⁸ When pancreas divisum (**Figure 1**) is identified by cross-sectional imaging, many clinicians proceed to ERCP with minor papillotomy because of its suggested benefit in reducing future episodes. This practice has been disputed because pancreas divisum is present in 7% to 10% of asymptomatic individuals, ERCP connotes a significant risk of causing acute pancreatitis or other adverse events, and due to the paucity of comparative effectiveness studies.⁹ To address this controversy, the primary aim of the Sphincterotomy for Acute Recurrent Pancreatitis (SHARP) trial was to determine if ERCP with minor papillotomy reduces the risk of acute pancreatitis in patients with pancreas divisum and otherwise unexplained acute recurrent pancreatitis.

Methods

Trial Design and Oversight

The current study was a sham-controlled, double-blind (both the participants and outcome adjudicators), randomized clinical trial conducted at 21 referral centers in the US and Canada. The study protocol and rationale have been reported¹⁰ (the trial protocol appears in [Supplement 1](#)). Recruitment occurred between September 1, 2018, and August 30, 2024; last follow-up occurred on February 15, 2025. The statistical analysis plan appears in [Supplement 2](#).

The study was monitored by an independent data and safety monitoring board. Before commencement of recruitment, the trial protocol and each site's participation was approved by a central institutional review board at the Medical University of South Carolina. The trial was conducted in accordance with Good Clinical Practice, adhered to the Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guideline,¹¹ and respected the ethical principles outlined in the Declaration of Helsinki.¹²

Participants

We enrolled adults with 2 or more episodes of documented acute pancreatitis, evidence of pancreas divisum assessed by

Key Points

Question Does endoscopic retrograde cholangiopancreatography (ERCP) with minor papillotomy reduce the risk of acute pancreatitis in patients with unexplained acute recurrent pancreatitis and pancreas divisum anatomy?

Findings In this randomized trial including 148 individuals with unexplained acute recurrent pancreatitis and pancreas divisum followed up for a median of 34 months, ERCP with minor papillotomy did not significantly reduce the rate of acute pancreatitis during follow-up (34.7% vs 43.8% for sham ERCP; adjusted hazard ratio, 0.83 [95% CI, 0.49-1.41]). There was no between-group difference in acute pancreatitis episode frequency and development of chronic calcific pancreatitis, diabetes, or exocrine pancreatic dysfunction.

Meaning Among patients with unexplained acute recurrent pancreatitis and pancreas divisum, ERCP with minor papillotomy does not reduce the risk of another episode of acute pancreatitis or related sequelae.

magnetic resonance cholangiopancreatography and confirmed by a site radiologist, and no other definitive etiology for acute pancreatitis. Race and ethnicity were self-reported by participants using fixed categories.

We excluded individuals with chronic calcific pancreatitis, main pancreatic duct stricture, and prior ERCP with minor papillotomy (complete exclusionary and eligibility criteria appear in the [eMethods in Supplement 3](#)). Individuals were excluded if they reported opioid use on a regular basis for the past 3 months or had a high probability (defined by a score ≥ 4 on the 5-item TWEAK [Tolerance, Worried, Eye-opener, Amnesia, Kut down] screening tool¹³) of alcohol misuse.

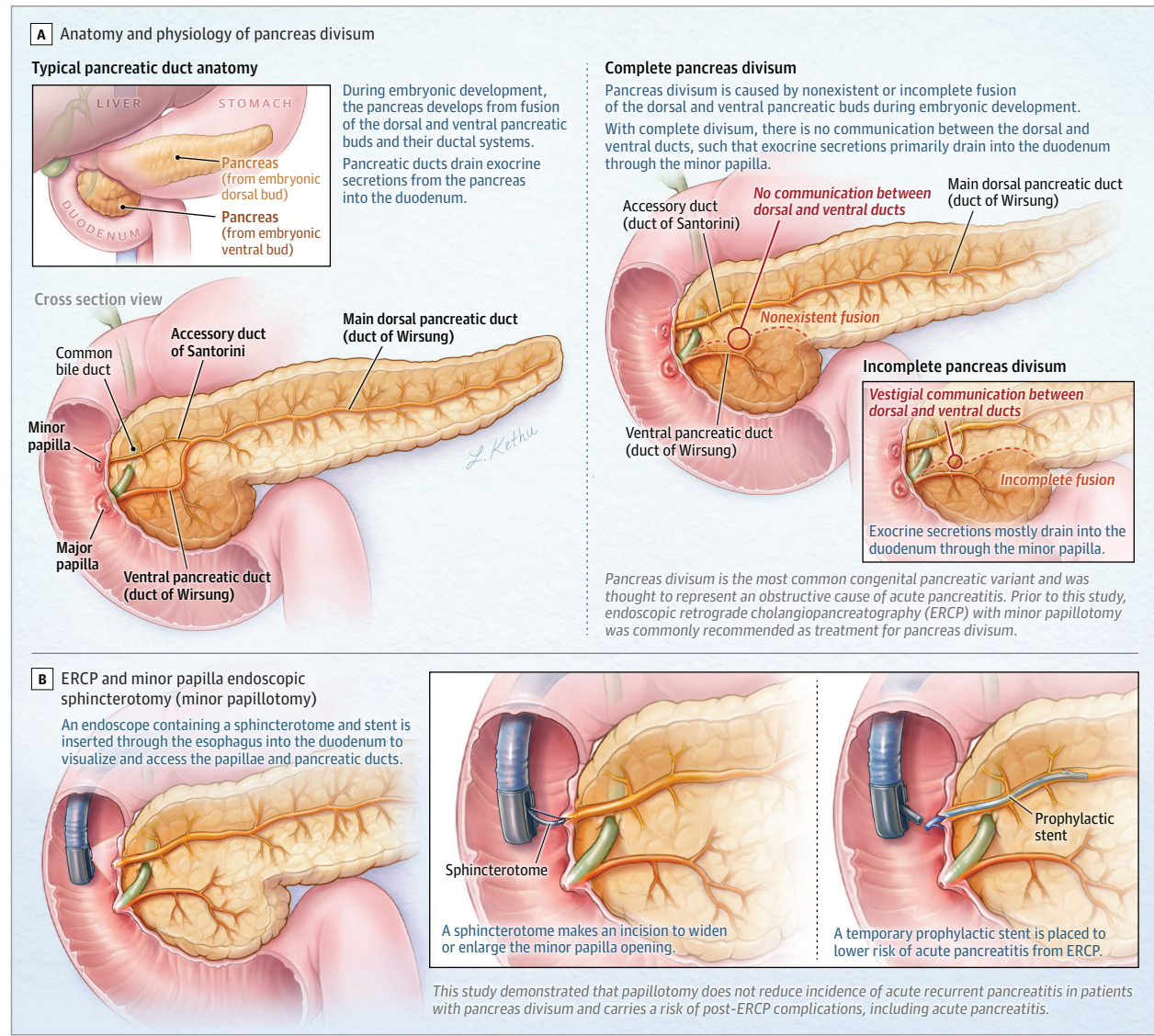
Acute pancreatitis was defined by the revised Atlanta classification¹⁴; each participant was required to have had 2 documented episodes before enrollment and at least 1 episode within 2 years of randomization. Participants who declined randomization were enrolled in an observational cohort and followed up in a similar manner ([eResults in Supplement 3](#)). All participants gave written informed consent before enrollment.

Randomization and Masking

Prior to randomization, all participants underwent endoscopic ultrasonography under anesthesia to rule out the presence of an occult pancreatic tumor or pancreatic duct calcification. After a physician confirmed final eligibility, participants were randomized using a centralized web-based system in a 1:1 ratio to ERCP with minor papillotomy or sham ERCP.

Based on our hypothesis that a higher number of acute pancreatitis episodes and a dilated main pancreatic duct may be associated with the primary outcome, the randomization algorithm was balanced on the number of acute pancreatitis episodes in the preceding 2 years, the pancreatic duct diameter measured by endoscopic ultrasonography, and the study site. Sealed and opaque envelopes were used in the procedure suite to conceal allocation. To preserve masking, the procedure notes in each patient's electronic health record did not provide written or photographic details of the ERCP procedure (if performed). The randomization sequence was generated by the

Figure 1. Anatomy and Physiology of Pancreas Divisum and Endoscopic Retrograde Cholangiopancreatography With Minor Papillotomy



statistical principal investigator (V.D.M.) who was not otherwise involved in the management of participants.

Procedures

For those randomized to the intervention group, ERCP with cannulation and minor papillotomy was performed using standard techniques, including placement of a prophylactic pancreatic duct stent and use of rectal indomethacin to minimize the risk of post-ERCP pancreatitis. In the sham ERCP group, participants did not receive rectal indomethacin, the physician did not attempt cannulation but did photograph the minor papilla, and a pancreatic duct stent was deployed into the duodenal lumen.

The unblinded physician who performed the randomization procedures managed the participants for the next 30 days, including adjudication and treatment of adverse events. Participants completed a 30-day follow-up visit with a blinded

study coordinator. Participants were followed up for a minimum of 6 months (≤ 4 years) and there were semiannual research-related telephone visits.

Blinded central study coordinators directed the scheduled follow-up visits. If participants developed signs or symptoms suspicious for acute pancreatitis, blinded central and local study personnel (study coordinators and physicians) provided guidance to participants regarding the need to obtain further clinical evaluation from their local physician or hospital (such as additional laboratory assessments and possible cross-sectional imaging). After participants received care for suspected acute pancreatitis, a blinded physician reviewed the medical records to determine if the event met study criteria for acute pancreatitis. The unblinded physician who performed the randomization procedures did not participate in the evaluation or treatment of participants for more than 30 days after randomization.

Primary and Secondary Outcomes

The primary outcome was development of acute pancreatitis more than 30 days after randomization as a time-to-event outcome. We selected this time frame to avoid confounding from post-ERCP pancreatitis, other postprocedure symptoms, and the spontaneous or endoscopic removal of the prophylactic pancreatic stent in the ERCP with minor papillotomy group. We used the same definition of acute pancreatitis for eligibility and the primary outcome, requiring symptoms consistent with acute pancreatitis and documentation of a serum lipase level greater than $3 \times$ the upper limit of normal, radiographic changes consistent with acute pancreatitis, or both.¹⁴

A secondary outcome was the incidence rate ratio of acute pancreatitis episodes that was estimated for each treatment group based on the number of acute pancreatitis episodes over total person-time after randomization and divided by the number of acute pancreatitis episodes over total time before randomization, keeping person-time equal between periods.

Additional secondary outcomes included the development of chronic pancreatitis (defined similarly to the eligibility criteria), diabetes (defined using American Diabetes Association criteria¹⁵), and exocrine pancreatic dysfunction (defined by a stool sample fecal elastase level of $<100 \mu\text{g/g}$ or clinical history of steatorrhea¹⁶). Pancreas-related pain events were defined by the need for medical evaluation (eg, emergency department or inpatient hospitalization) for abdominal pain similar to previous acute pancreatitis episodes but not meeting the study definition for acute pancreatitis.

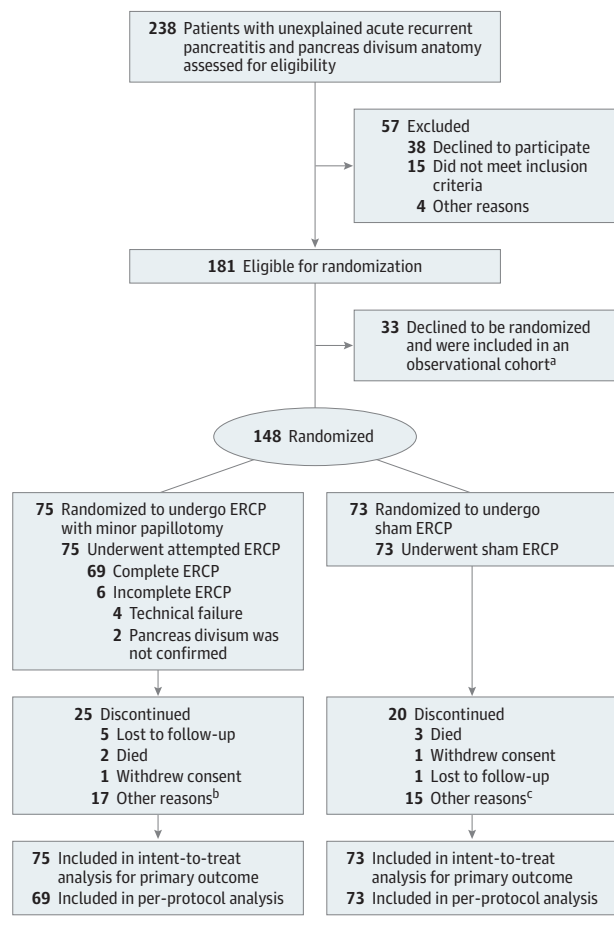
Statistical Analysis

At trial inception, we estimated a risk of 60% for recurrence within 12 months of randomization in the sham ERCP group. The chosen minimum effect size of clinical relevance was a relative risk reduction of 33% or an event rate of 40% in the ERCP with minor papillotomy group (hazard ratio [HR], 0.56). Setting the accrual period to 42 months, a minimum follow-up period of 6 months and maximum of 4 years, a 2-sided α error of .05, and power of 85%, the trial required a sample size of 150 randomized participants (105 outcome events).

The sample size was inflated to 234 to account for nonadherence to the study protocol. The trial plan included a pre-specified, blinded sample size reestimation based on the observed number of participants with acute pancreatitis recurrence that was conducted after 50% of participants were enrolled and prior to a planned interim analysis for futility using conditional power. At the time of the blinded sample size reestimation, there were 117 randomized participants with a minimum follow-up of 6 months and 45 outcome events. Based on the overall event rate, the estimated sham ERCP event rate was 44%, which was lower than the anticipated rate of 60%. The revised sample size was 195 (preinflation factor) at 85% power, keeping the HR at 0.56 for detection. The data and safety monitoring board was also provided the reestimated sample size at 80% power, which was 162 (180 postinflation factor).

In October 2023, based on the lower than expected event rate and a lower than anticipated nonadherence rate, the data and safety monitoring board recommended that the study continue at a revised maximum sample size of 180 participants.

Figure 2. Recruitment, Randomization, and Follow-Up in the SHARP Trial



ERCP indicates endoscopic retrograde cholangiopancreatography; SHARP, Sphincterotomy for Acute Recurrent Pancreatitis.

[†]There were 20 patients who underwent minor papillotomy and 13 were followed up conservatively. Additional information about this cohort appear in eResults, eFigure 3, and eTables 1 and 2 in Supplement 3.

^bFollow-up was terminated early due to site closure ($n = 15$), patient was unable to participate in subsequent follow-up visits because of declining mental status ($n = 1$), and patient had competing medical issues and was withdrawn from the study after 2 years ($n = 1$).

^cFollow-up was terminated early due to site closure ($n = 15$).

In August 2024, the trial was stopped due to financial constraints (trial was entering final year of funding) and was not stopped early for futility.

The primary intent-to-treat population included all randomized participants and the analysis used a Cox proportional hazards model to assess time to first recurrence of acute pancreatitis more than 30 days after randomization. Two variables included in the randomization scheme (duct diameter and number of acute pancreatitis episodes within 2 years of enrollment) were included as covariates in the primary analysis. A sensitivity analysis was conducted in a per-protocol population; this population excluded randomized participants who did not receive the assigned study treatment, those who had an identified eligibility violation, and those who withdrew their consent within 30 days from randomization.

Table 1. Baseline Characteristics of the Intention-to-Treat Population (N = 148)^a

	ERCP with minor papillotomy (n = 75)	Sham ERCP (n = 73)
Age, median (IQR), y	56 (44-65)	52 (46-64)
Acute pancreatitis		
Age at first episode, median (IQR), y	55 (34-61)	50 (43-58)
No. of documented episodes during lifetime, median (IQR)	3 (2-4)	3 (2-4)
Had 1-2 episodes within 2 y of randomization, No. (%)	53 (70.7)	46 (63.0)
Sex at birth, No. (%)		
Female	49 (65.3)	52 (71.2)
Male	26 (34.7)	21 (28.8)
Race, No. (%)		
American Indian or Alaska Native	1 (1.3)	0
Asian	1 (1.3)	1 (1.4)
Black or African American	5 (6.7)	6 (8.2)
White	64 (85.3)	65 (89.0)
Unknown	4 (5.3)	1 (1.4)
Hispanic or Latino ethnicity, No./total (%)	3/74 (4.1)	4/70 (5.7)
Charlson Comorbidity Index, median (IQR) ^b	2 (1-3)	2 (1-3)
Tobacco exposure, No. (%)		
Never	42 (56.0)	32 (43.8)
Past	24 (32.0)	22 (30.1)
Current	9 (12.0)	17 (23.3)
Unknown	0	2 (2.7)
Alcohol exposure, No. (%) ^c		
Never	18 (24.0)	17 (23.3)
Past	34 (45.3)	38 (52.1)
Current	23 (30.7)	16 (21.9)
Unknown	0	2 (2.7)
Self-reported or based on laboratory test, No./total (%)		
Diabetes	12/62 (19.4)	12/56 (21.4)
Exocrine pancreatic dysfunction	10/52 (19.2)	6/55 (10.9)
Largest pancreatic duct diameter, median (IQR), mm	2.2 (1.7-2.7)	2.3 (1.9-3.1)
PROMIS Global Health t test score, median (IQR) ^d		
Physical	47.7 (37.4-54.1)	44.9 (39.8-50.8)
Mental	50.8 (43.5-6.0)	47.1 (41.1-54.7)
Presence of abdominal pain in the past 7 d		
No. (%)	53 (70.7)	61 (83.6)
Pain level, median (IQR) ^e	3 (0-6)	3 (1-6)
Current medication use, No. (%)		
Opioids	16 (21.3)	14 (19.2)
Pancreatic enzyme replacement therapy	11 (14.7)	7 (9.6)
Nonsteroidal anti-inflammatory drugs	9 (12.0)	8 (11.0)
Insulin	4 (5.3)	5 (6.9)
Neuromodulators	3 (4.0)	5 (6.9)
Length of follow-up, median (IQR), mo	33.4 (19.4-45.6)	34.0 (22.8-45.8)

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; PROMIS, Patient-Reported Outcomes Measurement Information System.

^a Includes all randomized patients.

^b Range, 0 to 15; higher scores indicate greater comorbidity burden and higher expected 1-year mortality.

^c Excluded from study if had a history of at-risk alcohol consumption.

^d The mean score is 50 (SD, 10); higher scores reflect better health. A difference of 2 to 3 points is generally considered the minimal clinically important difference.

^e Range, 0 to 10; higher scores indicate higher levels of pain.

Table 2. Primary, Secondary, and Safety Outcomes

	Intention-to-treat population (N = 148) ^a		
	ERCP with minor papillotomy (n = 75)	Sham ERCP (n = 73)	Treatment effect (95% CI)
Primary outcome			
Development of acute pancreatitis >30 d after randomization, No. (%) [95% CI]	26 (34.7) [24.0 to 45.6]	32 (43.8) [32.2 to 55.9]	Adjusted HR, 0.83 (0.49 to 1.41) ^b ; RD, -9.2 (-24.8 to 6.5)
Time to the first episode, mean (SD), mo	6 (7.0)	6 (7.5)	
Secondary outcomes			
Incident rate ratio for acute recurrent pancreatitis episode frequency (95% CI) ^c	0.25 (0.18 to 0.34)	0.30 (0.23 to 0.41)	
Chronic calcific pancreatitis, No. (%)	3 (4.0)	2 (2.7)	RD, 0.01 (-0.05 to 0.07)
Diabetes, No./total (%)	6/38 (15.8)	5/39 (12.8)	RD, 0.03 (-0.13 to 0.19)
Exocrine pancreatic dysfunction, No./total (%)	2/26 (7.7)	5/29 (17.2)	RD, -0.10 (-0.27 to 0.08)
Safety outcomes			
Within 30 d of randomization, No. (%)			
Acute pancreatitis	11 (14.7)	6 (8.2)	RD, 0.06 (-0.04 to 0.17)
Gastrointestinal bleeding	1 (1.3)	0	RD, 0.01 (-0.04 to 0.07)
Bowel perforation	0	1 (1.4)	RD, -0.01 (-0.07 to 0.04)
More than 30 d after randomization or at a follow-up ERCP			
Severe acute pancreatitis, No. (%)	2 (2.7)	4 (5.5)	RD, -0.03 (-0.09 to 0.04)
Hospitalized adverse event, No. (%)	37 (49.3)	39 (53.4)	RD, -0.04 (-0.20 to 0.12)
Adverse events requiring hospitalization/patient, mean (SD)	0 (2)	1 (2)	
Pancreas-related pain events			
Within 30 d of randomization, No. (%)			
Within 30 d of follow-up ERCP, No./total (%)	10 (13.3)	10 (13.7)	RD, 0 (-0.11 to 0.11)
More than 30 d after randomization or at a follow-up ERCP, No. (%)	4/15 (26.7)	3/20 (15)	RD, 0.12 (-0.16 to 0.39)
More than 30 d after randomization or at a follow-up ERCP, No. (%)	25 (33.3)	23 (31.5)	RD, 0.02 (-0.13 to 0.17)

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; HR, hazard ratio; RD, risk difference.

^a Includes all randomized patients.

^b From a Cox proportional hazards model adjusting for the number of acute pancreatitis episodes and pancreatic duct size.

^c Estimated from the number of acute pancreatitis episodes over total person-time after randomization (excludes any events occurring within 30 days of randomization) divided by the number of acute pancreatitis episodes over total time before randomization, keeping person-time equal between periods.

The summary measures (with 95% CIs) were calculated for the secondary outcomes and the safety outcomes. All analyses were 2-sided with an α level of .05 and were performed using SAS version 9.4 (SAS Institute Inc).

Results

Participant Characteristics

Between September 1, 2018, and August 30, 2024, there were 238 individuals screened for eligibility and 148 randomized to ERCP with minor papillotomy (n = 75) or sham ERCP (n = 73) (Figure 2). Most participants were assigned female at birth (68.2%) and had a mean of 3 (SD, 2) documented acute pancreatitis episodes before enrollment; 49 of 148 participants (33.1%) had 3 or more episodes within 2 years of randomization (Table 1).

The baseline prevalence of diabetes (22 of 146 participants [14.9%] determined with testing) approximated the US national average.¹⁷ Exocrine pancreatic dysfunction was present in 13 of 105 participants (8.8%) who completed fecal elastase testing prior to randomization. The current, self-reported use of

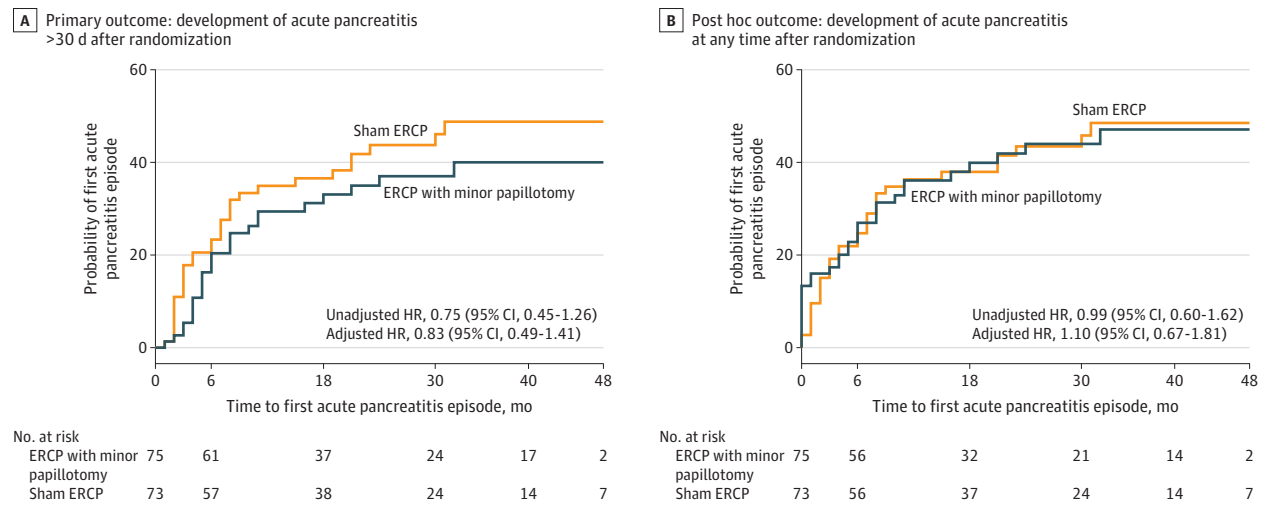
tobacco and alcohol was similar between groups; we excluded individuals with at-risk drinking (TWEAK score ≥ 4).¹³ Alcohol consumption was low: 141 of 148 participants (95.3%) had a TWEAK score of 0; 4 of 148 participants (2.7%) had a TWEAK score of 2; and 0 participants had a TWEAK score of 3.

Opioid use was reported by 30 of 148 participants (20.3%) at the time of enrollment compared with approximately 12% of the overall US adult population, but was lower than an estimated 29% of US adults with chronic pain disorders.¹⁸ Individuals who reported regular use of opioids for abdominal pain within the past 90 days were excluded from the trial. During the prerandomization endoscopic ultrasonography, 21 of 148 individuals (14.2%) had a dilated pancreatic duct measuring 4 mm or greater. The baseline characteristics were balanced between treatment groups.

Technical Outcomes

All participants completed endoscopic ultrasonography followed immediately by randomization. Of the 75 participants randomized to ERCP with minor papillotomy, 2 (2.7%) did not have pancreas divisum and a technical failure occurred during cannulation of the minor papilla in 4 (5.3%). These 6

Figure 3. Primary Outcome and Post Hoc Outcome of Development of Acute Pancreatitis After Randomization



A and B, Kaplan-Meier estimates for primary outcome and post hoc outcome. ERCP indicates endoscopic retrograde cholangiopancreatography; HR, hazard ratio. The median follow-up duration was 33.4 months (IQR, 19.4-45.6 months) after ERCP with minor papillotomy and was 34.0 months (IQR, 22.8-45.8 months) after the sham ERCP.

participants were excluded from the per-protocol analysis. Minor papilla cannulation and placement of a prophylactic pancreatic duct stent were completed in 69 of 75 participants (92.0%) in the ERCP with minor papillotomy group. Acute pancreatitis developed within 30 days of randomization in 11 of 75 participants (14.7%) in the ERCP with minor papillotomy group (in 10 participants within 4 days of randomization; 13.3%) at a median of 2 days (IQR, 1-22 days) compared with 6 of 73 participants (8.2%) in the sham ERCP group (in 0 participants within 4 days of randomization; 0%) at a median of 16 days (IQR, 5-18 days).

There were no episodes of severe acute pancreatitis within 30 days of randomization and 1 episode within 30 days of a follow-up ERCP that was performed for a participant in the sham ERCP group (eResults in Supplement 3). There was 1 episode of gastrointestinal bleeding in the ERCP with minor papillotomy group and 1 episode of bowel perforation in the sham ERCP group.

Primary Outcome

Of the 75 participants in the ERCP with minor papillotomy group, 26 (34.7%) developed acute pancreatitis compared with 32 of 73 participants (43.8%) in the sham ERCP group (risk difference [RD], -9.2% [95% CI, -24.8% to 6.5%]; HR, 0.75 [95% CI, 0.45 to 1.26]; adjusted HR, 0.83 [95% CI, 0.49 to 1.41]; *P* = .27 using the log-rank test) (Table 2 and Figure 3). This finding was unchanged in a sensitivity analysis limited to the per-protocol population (eFigure 1 in Supplement 3) and in a post hoc analysis including cases of acute pancreatitis occurring at any time after randomization (Figure 3). An exploratory subgroup analysis did not identify factors associated with response to ERCP with minor papillotomy (Figure 4).

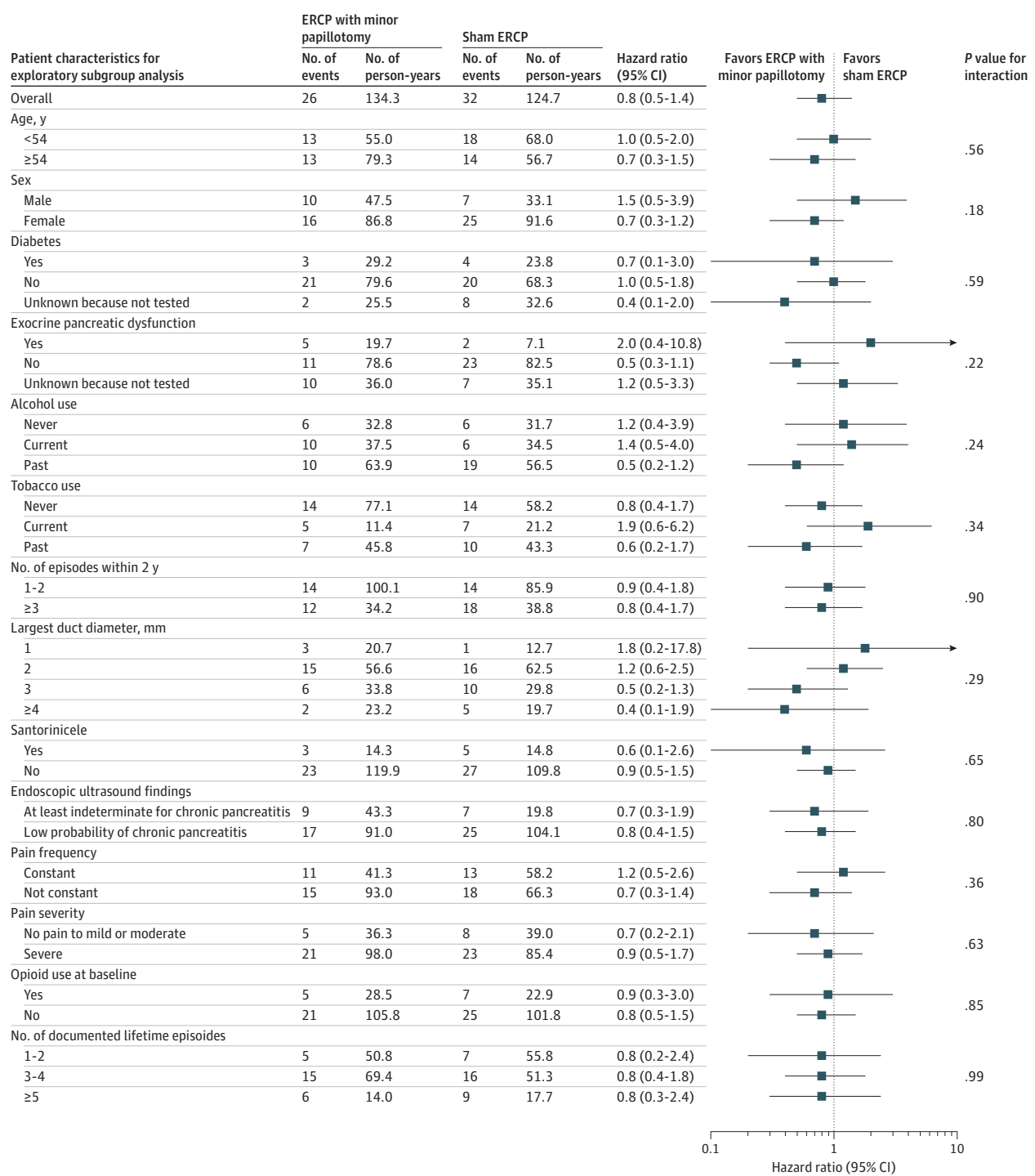
Secondary Outcomes

There were 187 acute pancreatitis episodes reported before randomization in the ERCP with minor papillotomy group and 46 episodes reported after randomization (total person-time follow-up, 1600.6 months; estimated incidence rate ratio, 0.25 [95% CI, 0.18 to 0.34]) compared with 184 acute pancreatitis episodes reported before randomization in the sham ERCP group and 56 episodes reported after randomization (total person-time follow-up, 1497.2 months; estimated incidence rate ratio, 0.30 [95% CI, 0.23 to 0.41]). There were no between-group differences in frequency and incidence of chronic calcific pancreatitis (3 [4.0%] in the ERCP with minor papillotomy group vs 2 [2.7%] in the sham ERCP group; RD, 0.01 [95% CI, -0.05 to 0.07]), diabetes (6 [15.8%] vs 5 [12.8%], respectively; RD, 0.03 [95% CI, -0.13 to 0.19]), and exocrine pancreatic dysfunction (2 [7.7%] vs 5 [17.2%]; RD, 0.10 [95% CI, -0.27 to 0.08]).

There were no between-group differences in the development of a pancreas-related pain event within 30 days of randomization (10 of 75 participants [13.3%] in the ERCP with minor papillotomy group vs 10 of 73 participants [13.7%] in the sham ERCP group; RD, 0 [95% CI, -0.11 to 0.11]) or in the development of a pain event more than 30 days from randomization or at any follow-up ERCP (25 [33.3%] vs 23 [31.5%], respectively; RD, 0.02 [95% CI, -0.13 to 0.17]). Other severe adverse events reported within 30 days of randomization, within 30 days of a follow-up ERCP, or at any other time are reported in eFigures 2A-2C in Supplement 3.

Post-ERCP pancreatitis occurred in 13% (10/75) of participants in the ERCP with minor papillotomy group vs 0% (0/73) of participants in the sham ERCP group. Development of acute pancreatitis at any time after randomization occurred in 49.3% (37/75) of participants in the ERCP with minor papillotomy group vs 52.1% (38/73) of participants in the sham ERCP group.

Figure 4. Subgroup Analysis of Factors Potentially Associated With Response to Minor Papillotomy



ERCP indicates endoscopic retrograde cholangiopancreatography. The forest plot evaluates the relationship between baseline patient factors (age, sex, diabetes, exocrine pancreatic dysfunction, alcohol or tobacco use), disease characteristics (pain frequency, pain severity, and episode frequency), and morphological features (presence of a focal, cystic dilatation of the duct of

Santorini at its insertion into the duodenum [santorinicele])^{19,20} on magnetic resonance cholangiopancreatography or ERCP, duct diameter, and endoscopic ultrasound findings of at least indeterminate for chronic pancreatitis by Rosemont criteria.^{21,22} No factor was associated significantly with ERCP with minor papillotomy.

Observational Cohort

An additional 33 participants were enrolled in an observational cohort (eResults in Supplement 3). The baseline char-

acteristics of participants in the observational cohort appear in eTable 1 in Supplement 3 and the outcomes appear in eTable 2 and eFigure 3 in Supplement 3.

Discussion

In a cohort of patients with unexplained acute recurrent pancreatitis and pancreas divisum, the current trial showed that patients who underwent ERCP with minor papillotomy did not have a lower risk of developing another episode compared with those managed conservatively (sham ERCP). The added risk of post-ERCP pancreatitis (occurred in 13.3% of ERCP with minor papillotomy group vs 0% with sham ERCP) furthers the argument to avoid minor papillotomy for pancreas divisum alone and controverts years of teaching that had been grounded in data from cohort studies suggesting a benefit. We observed a recurrence rate of acute pancreatitis in the ERCP with minor papillotomy group that was similar to the recurrence rates reported in previous cohorts⁵ for 20% to 40% of patients, indicating the current study population represents a comparable population. However, the recurrence rate in the sham ERCP group in the current study negated the implied benefit. The fundamental problem of the earlier studies⁵ was lack of a natural history comparator and rigorous long-term follow-up.

In the current study, participants had high-intensity disease. The eligibility criteria intentionally limited enrollment because patients with very low-frequency episodes (eg, 1 prior episode) would have been less likely to develop acute pancreatitis during the study's follow-up period and thus increase the chance of type II statistical error.²³ Despite focusing on a population with high-intensity disease, the current study failed to demonstrate a significant benefit with the use of ERCP with minor papillotomy. This lack of significance was also seen in the observational cohort.

We hypothesized that independent of its effect on incident acute pancreatitis, a meaningful benefit of ERCP with minor papillotomy would be a reduction in the frequency of acute pancreatitis episodes during follow-up. Both groups experienced similar and substantial reductions in the frequency of acute pancreatitis episodes after randomization. Similar to the patients enrolled in the current study, the patients seen in practice with acute recurrent pancreatitis are often found to have pancreas divisum shortly after a crescendo in episodes of acute pancreatitis and they are promptly referred for ERCP with minor papillotomy. Like episode frequency, ERCP with minor papillotomy did not seem to reduce the risk of declining exocrine or endocrine pancreatic function and incident chronic pancreatitis.

Limitations

There were study limitations. First, only 82% of the targeted sample size (n = 180) was reached due to funding constraints

and a lower enrollment rate during the COVID-19 pandemic.²⁴ Although the target sample size was not met, the RD of 9.2% for the primary outcome was well below the hypothesized RD of 20%. Assuming the observed treatment effect, the likelihood that statistical significance would be detected after reaching a sample size of 180 was 4%. The hypothesized RD was also the least acceptable risk reduction for the steering committee at the time of study planning because ERCP with minor papillotomy incurs a risk of post-ERCP pancreatitis. When including acute pancreatitis at any time after randomization (post hoc outcome), the RD was only 2.5%.

In addition, similar patterns of recurrence were detected in an observational cohort that included patients followed up and managed conservatively (no minor papillotomy). An offer of ERCP with minor papillotomy may introduce a clinical dilemma because patients who develop acute pancreatitis or pancreas-related pain after the intervention may be at risk to undergo repeated ERCPs. The benefit of these repeat procedures to examine the minor papillary orifice for postpapillotomy stenosis is unclear, potentially leading to a cycle of intervention, symptoms, and further interventions.²⁵

Second, the screening to enrollment ratio was high because individuals who previously received interventions, those with other causes of acute pancreatitis found during workup, and those with pancreas divisum ruled out by imaging reviews were excluded. Third, few participants had a dilated pancreatic duct that was 4 mm or larger (n = 21) or a santorinicele¹⁹ (n = 18), which are morphological characteristics suggestive of a stenotic papillary orifice but are also observed in asymptomatic individuals. A subgroup analysis did not show a statistically significant difference for ERCP with minor papillotomy, but the study lacked power for these comparisons.

Fourth, the reported incidence of chronic pancreatitis (3%-4%) is lower than previous studies,^{23,26-28} but this may be due to our more stringent definition of new pancreatic duct calcifications or strictures to match the study's enrollment criteria. Fifth, the study population predominantly included White, non-Hispanic individuals, which is consistent with prior studies and suggests a higher prevalence of pancreas divisum in White individuals. These results are most generalizable to White, non-Hispanic individuals.²⁹

Conclusions

Among patients with unexplained acute recurrent pancreatitis and pancreas divisum, ERCP with minor papillotomy does not reduce the risk of another episode of acute pancreatitis or related sequelae.

ARTICLE INFORMATION

Accepted for Publication: November 16, 2025.

Published Online: January 14, 2026.
doi:10.1001/jama.2025.23988

Author Affiliations: Department of Medicine, Oregon Health & Science University, Portland (Coté); Department of Public Health, Medical University of South Carolina, Charleston

(Durkalski-Mauldin, Phan, Williams); Department of Medicine, School of Medicine, Indiana University, Indianapolis (Fogel, Easler); Department of Medicine, University of Manitoba, Winnipeg, Canada (Moffatt, Coney); Department of Medicine, University of Virginia, Charlottesville (Wang, Strand); Department of Medicine, School of Medicine, Ohio State University, Columbus (Lara, Papachristou); Methodist Dallas Medical Center,

Dallas, Texas (Tarnasky, Kedia); Department of Medicine, University of Southern California, Los Angeles (Buxbaum, Sahakian); Department of Medicine, University of California, San Francisco (Dai, Kouanda); Saint Luke's GI Specialists, St Luke's Hospital of Kansas City, Kansas City, Missouri (Jonnalagadda); Department of Medicine, Emory University, Atlanta, Georgia (Willingham); Department of Medicine, Virginia Mason Medical

Center, Seattle, Washington (Ross); Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Keswani); Department of Medicine, School of Medicine, University of Arkansas, Little Rock (Inamdar); Department of Medicine, University of Rochester Medical Center, Rochester, New York (Kothari); Department of Medicine, Geisel School of Medicine, Dartmouth College, Lebanon, New Hampshire (Gardner); Department of Medicine, School of Medicine, Yale University, New Haven, Connecticut (Jamidar); Department of Medicine, Cedars Sinai Medical Center, Los Angeles, California (Gaddam); Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts (Pleskow); Department of Medicine, Medical University of South Carolina, Charleston (Elmunzer); Department of Medicine, University of Minnesota Medical School, Minneapolis (Mallery); Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Slivka, Yadav); National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland (Andersen, Serrano).

Author Contributions: Drs Coté and Durkalski-Mauldin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Coté, Durkalski-Mauldin, Fogel, Moffatt, Buxbaum, Ross, Gardner, Serrano, Yadav.
Acquisition, analysis, or interpretation of data: Coté, Durkalski-Mauldin, Fogel, Moffatt, Wang, Lara, Tarnasky, Buxbaum, Dai, Jonnalagadda, Willingham, Ross, Keswani, Inamdar, Kothari, Jamidar, Gaddam, Pleskow, Easler, Elmunzer, Coneys, Mallery, Strand, Papachristou, Slivka, Kedia, Sahakian, Kouanda, Phan, Williams, Serrano, Yadav.
Drafting of the manuscript: Coté, Durkalski-Mauldin, Lara, Buxbaum, Jonnalagadda, Gardner, Easler, Phan, Yadav.
Critical review of the manuscript for important intellectual content: Coté, Durkalski-Mauldin, Fogel, Moffatt, Wang, Lara, Tarnasky, Buxbaum, Dai, Jonnalagadda, Willingham, Ross, Keswani, Inamdar, Kothari, Jamidar, Gaddam, Pleskow, Easler, Elmunzer, Coneys, Mallery, Strand, Papachristou, Slivka, Kedia, Sahakian, Kouanda, Williams, Serrano, Yadav.
Statistical analysis: Durkalski-Mauldin, Kothari, Phan.
Obtained funding: Coté, Durkalski-Mauldin, Fogel, Buxbaum, Yadav.
Administrative, technical, or material support: Coté, Fogel, Moffatt, Wang, Lara, Tarnasky, Buxbaum, Jonnalagadda, Willingham, Inamdar, Kothari, Gardner, Gaddam, Easler, Strand, Williams, Serrano.
Supervision: Durkalski-Mauldin, Fogel, Moffatt, Wang, Dai, Inamdar, Jamidar, Pleskow, Serrano, Yadav.

Conflict of Interest Disclosures: Dr Wang reported receiving personal fees from Cook Medical and owning stock in GE HealthCare Technologies and Pfizer. Dr Lara reported receiving grants from AbbVie. Dr Dai reported receiving personal fees from Boston Scientific. Dr Ross reported receiving personal fees from Boston Scientific and Olympus. Dr Keswani reported receiving personal fees from Boston Scientific, Cook Medical, Olympus, and Neptune Medical and receiving grants from Medtronic. Dr Gaddam reported receiving personal fees from Boston Scientific and receiving grants from Cook Medical. Dr Pleskow reported receiving personal fees from Boston Scientific, Olympus, and

Medtronic. Dr Easler reported receiving personal fees from Boston Scientific. Dr Yadav reported receiving personal fees from Pfizer. No other disclosures were reported.

Funding/Support: This research was supported by awards U34DK112673 (planning phase) and U01DK116743 (trial phase) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Role of the Funder/Sponsor: The NIDDK had a role in the design and conduct of the study; management and interpretation of the data; and review of the manuscript. The NIDDK had no role in the collection and analysis of the data; preparation or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The members of the SHARP Consortium appear in [Supplement 4](#).

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Sharing Statement: See [Supplement 5](#).

Additional Contributions: We thank the study teams at the participating sites for their efforts to conduct this trial; this study would not have been possible without the commitment of the study's central and site research coordinators. Most importantly, we acknowledge and thank all of the study participants and their families. We also thank Martin Freeman, MD (Department of Medicine, University of Minnesota Medical School), for screening and enrolling participants. Dr Freeman was not compensated for his contribution. We thank the members of the data and safety monitoring board for their dedication and expertise: Pankaj J. Pasricha, MBBS, MD (chair; Department of Medicine, Mayo Clinic in Arizona, Scottsdale), Linda Lee, MD (Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts), and Marie Ganz, PhD (RTI International, Research Triangle Park, North Carolina). We thank the medical safety monitor (Vinay Chandrasekhara, MD, Department of Medicine, Mayo Clinic Rochester, Minnesota). Drs Pasricha, Lee, Ganz, and Chandrasekhara were compensated for their contributions.

Additional Information: Coauthor Dana K. Andersen, MD, died July 17, 2025, after the initial manuscript was submitted to *JAMA* for peer review. Dr Andersen contributed to project administration, supervision, and review and editing of the initial manuscript draft.

REFERENCES

- Iannuzzi JP, King JA, Leong JH, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. *Gastroenterology*. 2022;162(1):122-134. doi:10.1053/j.gastro.2021.09.043
- Peery AF, Murphy CC, Anderson C, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2024. *Gastroenterology*. 2025;168(5):1000-1024. doi:10.1053/j.gastro.2024.12.029
- Stern CD. A historical perspective on the discovery of the accessory duct of the pancreas, the ampulla 'of Vater' and pancreas divisum. *Gut*. 1986; 27(2):203-212. doi:10.1136/gut.27.2.203

4. Cotton PB. Congenital anomaly of pancreas divisum as cause of obstructive pain and pancreatitis. *Gut*. 1980;21(2):105-114. doi:10.1136/gut.21.2.105

5. Schepis T, Pafundi PC, Tringali A, et al. Endoscopic minor papilla sphincterotomy in patients with complete pancreas divisum and acute recurrent pancreatitis: a meta-analysis. *Scand J Gastroenterol*. 2024;59(2):225-231. doi:10.1080/00365521.2023.2266079

6. Strand DS, Law RJ, Yang D, Elmunzer BJ. AGA clinical practice update on the endoscopic approach to recurrent acute and chronic pancreatitis: expert review. *Gastroenterology*. 2022;163(4):1107-1114. doi:10.1053/j.gastro.2022.07.079

7. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. *Am J Gastroenterol*. 2012;107(7):1096-1103. doi:10.1038/ajg.2012.126

8. Coté GA, Yadav D, Abberbock JA, et al. Recurrent acute pancreatitis significantly reduces quality of life even in the absence of overt chronic pancreatitis. *Am J Gastroenterol*. 2018;113(6):906-912. doi:10.1038/s41395-018-0087-7

9. Guda NM, Muddana V, Whitcomb DC, et al. Recurrent acute pancreatitis: international state-of-the-science conference with recommendations. *Pancreas*. 2018;47(6):653-666. doi:10.1097/MPA.0000000000001053

10. Coté GA, Durkalski-Mauldin VL, Serrano J, et al; SHARP Consortium. SpHincterotomy for Acute Recurrent Pancreatitis randomized trial: rationale, methodology, and potential implications. *Pancreas*. 2019;48(8):1061-1067. doi:10.1097/MPA.0000000000001370

11. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomized trials. *JAMA*. 2025;333(22):1998-2005. doi:10.1001/jama.2025.4347

12. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human participants. *JAMA*. 2025;333(1):71-74. doi:10.1001/jama.2024.21972

13. Moe J, Koh J, Ma JA, et al. Screening for harmful substance use in emergency departments: a systematic review. *Int J Emerg Med*. 2024;17(1):52. doi:10.1186/s12245-024-00616-2

14. Banks PA, Bollen TL, Dervenis C, et al; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111. doi:10.1136/gutjnl-2012-302779

15. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes—2024. *Diabetes Care*. 2024;47(suppl 1):S20-S42. doi:10.2337/dc24-5002

16. Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG clinical guideline: chronic pancreatitis. *Am J Gastroenterol*. 2020;115(3):322-339. doi:10.14309/ajg.0000000000000535

17. US Centers for Disease Control and Prevention. National Diabetes Statistics Report. Published May 15, 2024. Accessed April 1, 2025. <https://www.cdc.gov/diabetes/php/data-research/index.html>

18. Zajacova A, Grol-Prokopczyk H, Limani M, Schwarz C, Gilron I. Prevalence and correlates of prescription opioid use among US adults, 2019-2020. *PLoS One*. 2023;18(3):e0282536. doi:10.1371/journal.pone.0282536
19. Crinò SF, Bernardoni L, Conti Bellocchi MC, et al. Efficacy of endoscopic minor papilla sphincterotomy for symptomatic santorinicele. *Clin Gastroenterol Hepatol*. 2017;15(2):303-306. doi:10.1016/j.cgh.2016.08.004
20. Manfredi R, Costamagna G, Brizi MG, et al. Pancreas divisum and "santorinicele": diagnosis with dynamic MR cholangiopancreatography with secretin stimulation. *Radiology*. 2000;217(2):403-408. doi:10.1148/radiology.217.2.r00nv29403
21. Trikudanathan G, Munigala S, Barlass U, et al. Evaluation of Rosemont criteria for non-calcific chronic pancreatitis (NCCP) based on histopathology—a retrospective study. *Pancreatol*. 2017;17(1):63-69. doi:10.1016/j.pan.2016.10.010
22. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc*. 2009;69(7):1251-1261. doi:10.1016/j.gie.2008.07.043
23. Li S, Gao L, Gong H, et al. Recurrence rates and risk factors for recurrence after first episode of acute pancreatitis: a systematic review and meta-analysis. *Eur J Intern Med*. 2023;116:72-81. doi:10.1016/j.ejim.2023.06.006
24. McDonald K, Seltzer E, Lu M, et al. Quantifying the impact of the COVID-19 pandemic on clinical trial screening rates over time in 37 countries. *Trials*. 2023;24(1):254. doi:10.1186/s13063-023-07277-1
25. Dufault DL, Elmunzer BJ, Cotton PB, Williams A, Cote GA. Adverse events and reinterventions following pancreatic endoscopic sphincterotomy. *Pancreas*. 2018;47(7):880-883. doi:10.1097/MPA.0000000000001084
26. Das R, Clarke B, Tang G, et al. Endoscopic sphincterotomy (ES) may not alter the natural history of idiopathic recurrent acute pancreatitis (IRAP). *Pancreatol*. 2016;16(5):770-777. doi:10.1016/j.pan.2016.07.009
27. Ahmed Ali U, Issa Y, Hagenaaers JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol*. 2016;14(5):738-746. doi:10.1016/j.cgh.2015.12.040
28. Coté GA, Imperiale TF, Schmidt SE, et al. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. *Gastroenterology*. 2012;143(6):1502-1509.e1. doi:10.1053/j.gastro.2012.09.006
29. Wilcox CM, Sandhu BS, Singh V, et al. Racial differences in the clinical profile, causes, and outcome of chronic pancreatitis. *Am J Gastroenterol*. 2016;111(10):1488-1496. doi:10.1038/ajg.2016.316