Prevalence of *CFTR* Pathogenic Variants in Pancreatitis: A Systematic Review and Meta-Analysis

Joanna Jiang, MD[1,*], Gavisha Waidyaratne, MD[1,*], Shiab Mussad, MD[1], Spencer Harris, MS[1], Maegan E. Roberts, MS, CGC[2], Yevgeniya Gokun, MS[3], A. Jay Freeman, MD[4], Samuel Han, MD[1], Phil A. Hart, MD[1], Luis F. Lara, MD[1], Peter J. Lee, MBChB[1], Somashekar G. Krishna, MD, MPH, FACG[1], Georgios I. Papachristou, MD, PhD, FACG[1], Peter P. Stanich, MD[1] and Mitchell L. Ramsey, MD[1]

INTRODUCTION: **Pathogenic variants (PVs) in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene are commonly reported across the spectrum of pancreatitis, including acute (AP), recurrent acute (RAP), and chronic pancreatitis (CP). We aimed to define the pooled prevalence of *CFTR* PVs according to pancreatitis phenotype.**

Prevalence of *CFTR* Pathogenic Variants in Pancreatitis

What is the prevalence of *CFTR* pathogenic variants in acute (AP),

recurrent acute (RAP), and chronic pancreatitis (CP)?

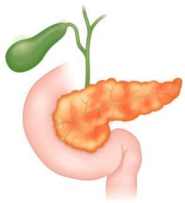
Systematic Review and Meta-Analysis

2 databases queried

3,528 studies identified

138 studies included

- 17 on AP
- 21 on RAP
- 86 on CP
- 36 on pancreatitis not otherwise specified (NOS)



Results

Pooled Prevalence of at least one *CFTR* pathogenic variant:

AP: 8.0% (95% CI: 4.3 – 14.4%)
RAP: 16.4% (95% CI: 10.2 – 25.4%)
CP: 15.3% (95% CI: 12.2 – 19.0%)
NOS: 25.0% (95% CI: 17.5 – 34.3%)

- Higher for **idiopathic** vs known etiologies
- Higher for **pediatric** vs adult populations
- No significant difference between abstracts vs manuscripts

Jiang et al. *Clin Trans Gastroenterol* 2025. doi:10.14309/ctg.0000000000000846

Clinical and Translational GASTROENTEROLOGY

[1]Division of Gastroenterology, Hepatology, and Nutrition, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [2]Division of Medical Genetics, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [3]Center for Biostatistics, Secondary Data Core, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [4]Division of Gastroenterology, Hepatology, and Nutrition, Nationwide Children's Hospital, Columbus, Ohio, USA. **Correspondence:** Mitchell L. Ramsey, MD. E-mail: Mitchell.Ramsey@osumc.edu.
*Authors contributed equally and acknowledge shared co-first authorship.
Received February 5, 2025; accepted April 11, 2025; published online April 18, 2025

METHODS: **A systematic search using synonyms for *CFTR* and pancreatitis was performed in Embase and Pubmed databases. The primary outcome was the frequency of subjects with at least one *CFTR* PV among those who underwent germline *CFTR* testing. Subgroup analyses included age, pancreatitis etiology, and genetic testing strategy. Confidence intervals (CIs) were obtained using the exact binomial method (Clopper-Pearson), and a Sidik-Jonkman random-effects model was used to calculate pooled prevalence.**

RESULTS: **In total, 138 studies were included in the final analysis; 17 (n = 1,873) reported populations with AP, 21 (n = 1,172) with RAP, 86 (n = 13,428) with CP, and 36 (n = 4,521) with unspecified pancreatitis type. The pooled prevalence of at least one *CFTR* PV was 8.0% (95% CI: 4.3%–14.4%) of AP, 16.4% (95% CI: 10.2%–25.4%) of RAP, 15.3% (95% CI: 12.2%–19.0%) of CP, and 25.0% (95% CI: 17.5%–34.3%) of unspecified pancreatitis. Heterogeneity was high in each phenotype (I^2 value range 88.3%–96.7%).**

DISCUSSION: **These findings underscore the complex landscape of *CFTR* PVs in pancreatitis, emphasizing the importance of tailored approaches in addressing this genetic component across diverse patient groups and phenotypic presentations. In addition, these data are useful for pretest genetic counseling and provide a justification for developing *CFTR*-directed interventions.**

KEYWORDS: genetic testing; idiopathic pancreatitis; CFTR-related disorder; meta-analysis

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B302

Clinical and Translational Gastroenterology 2025;16:e00846. https://doi.org/10.14309/ctg.0000000000000846

INTRODUCTION

Benign disorders of the exocrine pancreas, such as acute pancreatitis (AP) and chronic pancreatitis (CP), are common and significantly affect quality of life (1–3). According to the sentinel AP event model, recurrent attacks of AP cause progressive damage to the pancreas and ultimately lead to CP, which may be accompanied by pancreatogenic diabetes, exocrine pancreatic insufficiency, and chronic pain (4). It is therefore critically important to identify the etiology of AP to better understand and improve its natural history.

Historically, most cases of AP were attributed to gallstones or alcohol, with a smaller proportion attributed to metabolic conditions such as hypertriglyceridemia. Since the 1993 discovery of the gene causing hereditary pancreatitis, *PRSS1*, genetic testing has been increasingly used to investigate previously unexplained AP or CP (5,6). Currently, germline genetic testing for a minimum of *CFTR*, *CTRC*, *PRSS1*, and *SPINK1* is recommended for individuals with a pancreatitis-associated disorder for which the etiology is unclear (7). Among these genes, pathogenic variants (PVs) in *CFTR* are the most common genetic risk factor of AP or CP and have been reported at high rates among individuals with both idiopathic CP and alcohol-related CP (8,9).

The cystic fibrosis transmembrane conductance regulator (CFTR) ion channel is integral to maintenance of high pH and low fluid viscosity in the pancreatic ductal system (9,10). Recent treatment advances for persons living with cystic fibrosis (CF) have shown that CFTR-activating drugs can improve CFTR function assessed by sweat chloride levels, recurrences of AP, and measures of pancreatic exocrine function (11). These data provide additional evidence of the close relationship between CFTR function and exocrine pancreatic function, which affects risk of pancreatitis.

Despite the importance of CFTR function in determining pancreatitis risk, the prevalence of *CFTR* PVs among individuals with exocrine pancreatic disorders has not been clearly established. Prior case series have assessed the association between *CFTR* PVs among populations with various pancreatic disorders, but these studies are limited by small populations, selection bias, and/or limitations in genetic testing strategy. To determine the prevalence of *CFTR* PVs, we performed a systematic review and meta-analysis aiming to capture all cross-sectional studies where germline *CFTR* testing was performed among individuals with pancreatic disorders, including AP, recurrent AP (RAP), and CP. We hypothesized that *CFTR* PVs would be highly prevalent and that prevalence would be highest among individuals with CP.

METHODS

Search strategy

This systematic review was registered (PROSPERO registration no. CRD42022313485) and performed according to the Meta-Analysis Of Observational Studies in Epidemiology guidelines (12). Literature search was conducted on May 31, 2024, in Excerpta Medica (Embase) and the National Library of Medicine (PubMed), using search terms relating to "*CFTR*" and "pancreatitis" (see Supplementary Table 1, http://links.lww.com/CTG/B302). All encountered studies were imported to a project-specific library using the Covidence web-based platform (Melbourne, Australia). This software removed duplicate entries that were encountered in more than one database.

Eligibility criteria and study selection

Three investigators independently screened the titles and abstracts for relevance and appropriate study type, with each reference screened by 2 investigators. Disputes were resolved by discussion with the senior author. Studies were considered for inclusion if they met the following criteria: (i) human subjects; (ii) cohort, case-control, case series, or retrospective observational study design; (iii) included *CFTR* genetic testing results; (iv) patients were not members of the same family; (v) full text of abstract or manuscript available in English language; and (vi) study population was not limited to participants with known CF. Conference abstracts were eligible for inclusion. After irrelevant studies were excluded, the remaining studies underwent full-text

review by 2 investigators, which included review of reference lists to identify additional studies which might be relevant. Articles were excluded at this stage if they were review articles, case reports, or presented duplicate or overlapping data. Studies with insufficient data to calculate pooled prevalence were excluded.

Data collection and organization

Two investigators independently performed data extraction from each study, with conflicts resolved by the senior author. Extracted data included first author, year of publication, country in which the study was completed, mean (SD) or median (interquartile range) age of subjects, number of subjects included, and number of subjects with a *CFTR* PV. Specific variants in *CFTR* were not recorded due to the high frequency of missingness; therefore, pathogenicity of variants was determined by each study author and could not be re-evaluated according to current definitions. We recorded pancreatitis type, age category (pediatric, adult, or mix of pediatric and adult subjects), and any special population features such as comorbid pancreas divisum when they were provided. Studies which did not denote the chronicity of pancreatitis or grouped patients with AP and CP together were classified as pancreatitis not otherwise specified (NOS). Genetic testing modality data were reviewed by 2 investigators and recorded as one of the following categories: (i) targeted panel, (ii) full gene sequencing, (iii) a mix of both targeted and full sequencing, or (iv) not reported.

Quality assessment

The Joanna Briggs critical appraisal instrument for studies reporting prevalence data was used to evaluate the quality and risk of bias for each study (13). Two reviewers independently conducted this assessment for each study. This instrument objectively assesses quality in 9 areas ranging from sampling time frame, selection method, and data analysis, among others. After objectively assessing each area, each article is assigned an overall appraisal as include, exclude, or seek further information.

Statistical analysis

Descriptive statistics elucidated the frequency and percentages of *CFTR* PVs. Individual study confidence intervals (CIs) for PV prevalence were obtained using the Clopper-Pearson Exact Method. A logit transformation was used to stabilize the variances; however, these results were back-transformed to the original proportion scale for interpretation. Owing to anticipated heterogeneity among meta-analyses, a random-effects model was used. This was quantitatively assessed considering various heterogeneity measures (τ^2, I^2, and H^2) across different methods (Sidik-Jonkman, restricted maximal likelihood, DerSimonian-Laird, and Hedges). Largely, these methods agreed on the overall effect size, and each confirmed high heterogeneity. Conforming with standard practices for meta-analyses, we report the most commonly used heterogeneity measure, I^2, to quantify the total amount of variation. For these analyses, I^2 values were 80% or higher, indicating very high levels of heterogeneity. This was consistently observed across all methods, affirming the need for a random-effects model for pooled prevalence calculations. The Sidik-Jonkman approach was chosen to better handle between-study variation (τ^2), offering a more conservative model with wider CIs, increasing the likelihood of capturing the true prevalence. Forest plots depicted individual pooled prevalence with corresponding 95% CIs, whereas funnel plots were generated to visually inspect potential publication bias or systematic heterogeneity. These statistical analyses were executed using STATA version 18 (StataCorp, College Station, TX).

Pooled prevalence estimates derived from subgroup analyses were used to calculate odds ratios. These estimates were used in combination with the observed event totals to calculate CIs and asses statistical significance through 2-sided α levels of 0.05. The analyses compared prevalence differences between adult and pediatric population, idiopathic and nonidiopathic etiology, and genetic testing strategy. To minimize heterogeneity, studies that overlapped categories (i.e., included both pediatric and adult subjects) or had indeterminate classifications were excluded from these analyses. Calculations for odds ratios (ORs) and 95% confidence intervals (CIs) were performed using Microsoft Excel Version 2407 (Microsoft, Redmond, WA).

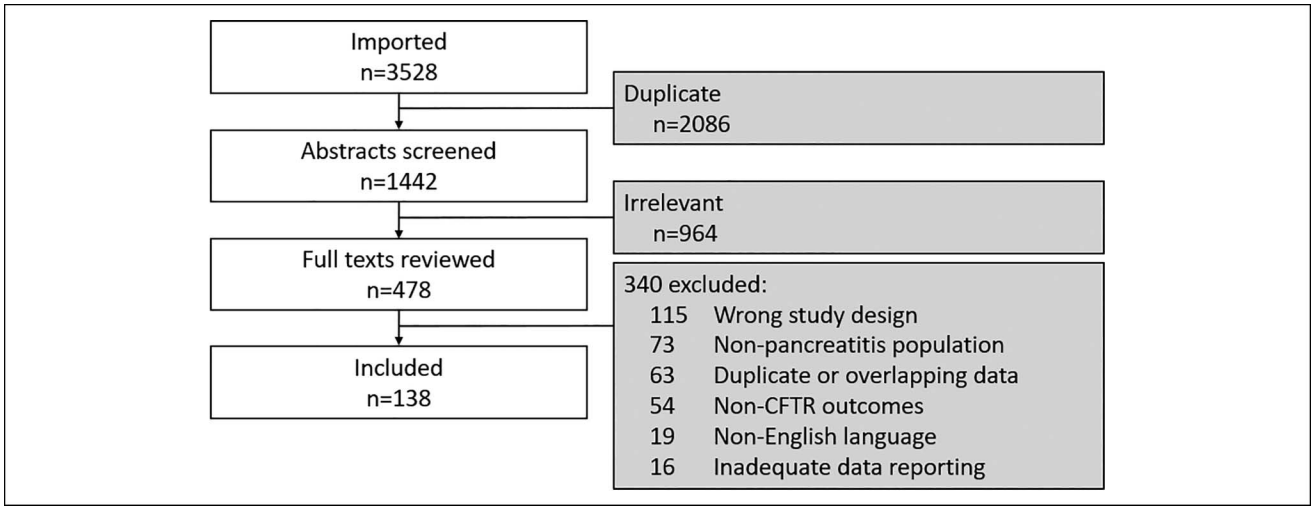


Figure 1. Study flow diagram, according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) reporting standards.

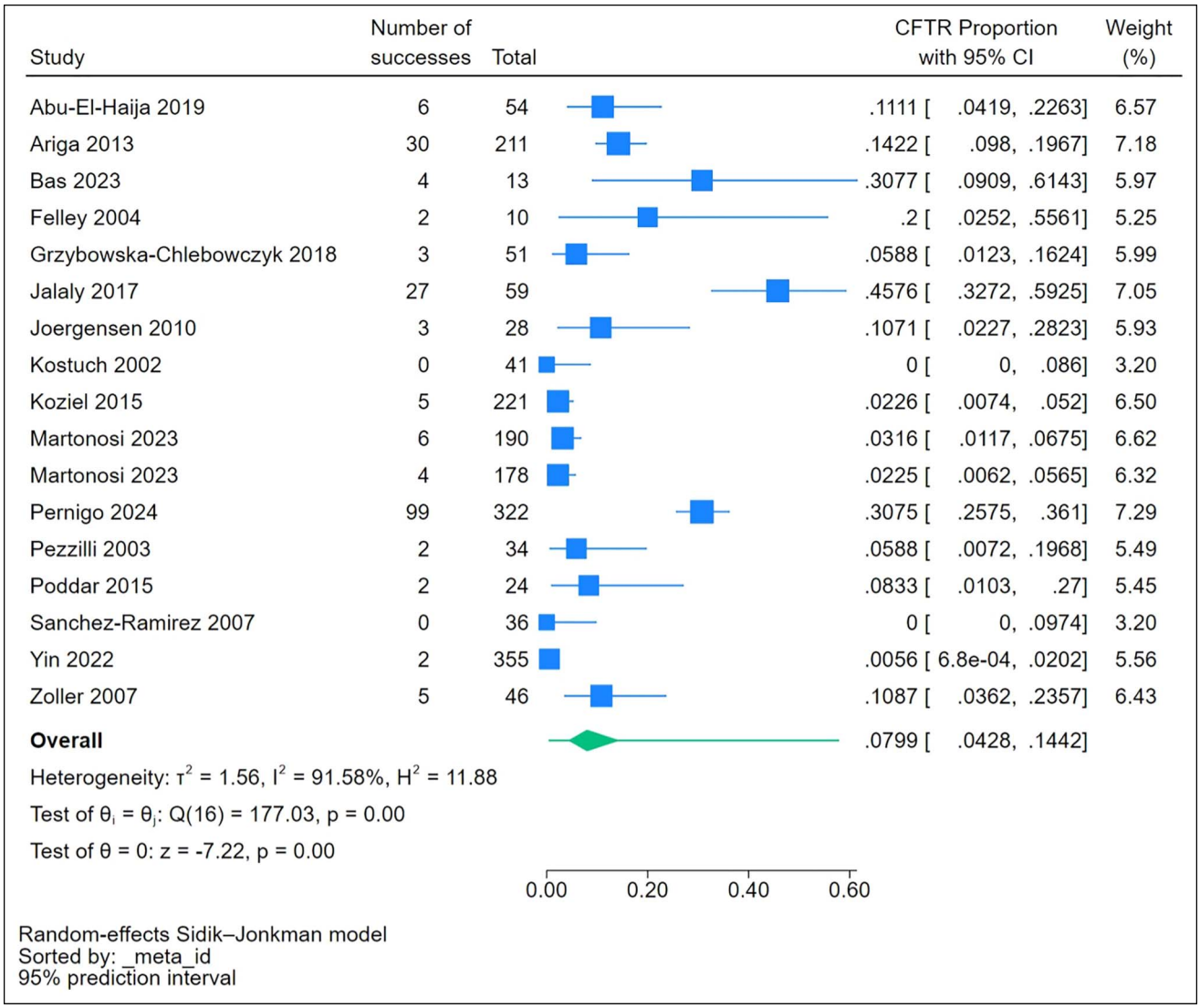


Figure 2. Forest plot illustrating the prevalence of pathogenic variants in *CFTR* among 17 studies which included 1,873 subjects with acute pancreatitis (AP). *CFTR*, cystic fibrosis transmembrane conductance regulator.

RESULTS

Study selection

From the original 3,528 references identified through our database search, 2,086 duplicates were excluded. Title and abstract screening excluded 964 irrelevant studies. The remaining studies underwent full-text review, and 340 additional publications were excluded because of incorrect study design (n = 115), nonpancreatitis population (n = 73), duplicate or overlapping cohorts (n = 63), non-*CFTR* outcomes (n = 54), non-English language (n = 19), or inadequate data reporting (n = 16) (Figure 1).

In total, 138 studies that discussed *CFTR* PV prevalence in cohorts with pancreatitis were included in our final analysis. Studies recruited from various countries and were published between 1998 and 2024 (see Supplementary Table 2, http://links.lww.com/CTG/B302). Within these studies, 17 reported populations with AP, 21 with RAP, 86 with CP, and 36 with pancreatitis that was incompletely defined or mixed AP and CP participants together, which were categorized as pancreatitis NOS. All studies had an acceptable risk of bias according to the Joanna Briggs tool. There was a high level of missing data in published studies: most studies did not report participants' ages or report specific *CFTR* variants. Heterogeneity was high across all studies and could not be resolved statistically even with random-effects models given the limited data in most reports. Abstracts were excluded in a sensitivity analysis, and no significant differences in pooled prevalence were identified (see Supplementary Table 7, http://links.lww.com/CTG/B302).

Acute pancreatitis

Among studies including participants with AP, germline genetic testing for *CFTR* was conducted in a total of 1,873 participants. The overall pooled prevalence of pathogenic *CFTR* variants was 8.0% (95% CI: 4.3%–14.4%; I^2 = 89.2%) (Figure 2). No participants with AP were diagnosed with CF.

Table 1. Odds ratio of identifying a pathogenic variant in *CFTR* in etiology, age, and genetic testing strategy subgroups according to disease phenotype

	AP	RAP	CP	Pancreatitis, NOS
Etiology				
Idiopathic	5.77 (3.54–9.42), $P < 0.0001$	0.99 (0.71–1.36), n.s	1.47 (1.33–1.63), $P < 0.0001$	1.63 (1.41–1.88), $P < 0.0001$
Other	Reference	Reference	Reference	Reference
Age				
Pediatric	0.85 (0.43–1.70), n.s	0.97 (0.68–1.37), n.s	1.21 (1.06–1.37), $P = 0.0044$	2.62 (2.20–3.12), $P < 0.0001$
Adult	Reference	Reference	Reference	Reference
Genetic testing strategy				
Full sequencing	2.16 (1.47–3.15), $P < 0.0001$	1.82 (1.09–3.04), $P = 0.023$	1.46 (1.31–1.64), $P < 0.0001$	2.82 (2.29–3.48), $P < 0.0001$
Targeted panel	Reference	Reference	Reference	Reference

Data are reported as odds ratio (95% confidence interval), *P* value.
AP, acute pancreatitis; *CFTR*, cystic fibrosis transmembrane conductance regulator; CP, chronic pancreatitis; NOS, not otherwise specified; RAP, recurrent acute pancreatitis.

In subgroup analyses, *CFTR* PVs were significantly more prevalent among participants with idiopathic pancreatitis compared with other etiologies (OR: 5.77, 95% CI: 3.54–9.42, $P < 0.0001$). The pooled prevalence in idiopathic pancreatitis was 27.1% (95% CI: 9.61%–56.6%) compared with 6.06% for other etiologies (95% CI: 3.21%–11.4%). More PVs were detected by full sequencing than targeted panels (OR: 2.16, 95% CI: 1.47–3.15, $P < 0.0001$). There were no significant differences in the prevalence of *CFTR* PVs according to age category (Table 1, see Supplementary Table 3, http://links.lww.com/CTG/B302).

Recurrent acute pancreatitis

Among studies including participants with RAP, germline genetic testing for *CFTR* was conducted in a total of 1,172 participants. The pooled prevalence of pathogenic *CFTR* variants was 16.4% (95% CI: 10.2%–25.4%; $I^2 = 88.3\%$) (Figure 3). A total of 7 participants were diagnosed with CF (0.6%).

In subgroup analyses, *CFTR* PVs were significantly more prevalent when full sequencing was used compared with targeted panel testing (OR: 1.82, 95% CI: 1.09–3.04, $P = 0.023$), but there were no significant differences in the prevalence of *CFTR* PVs according to etiology or participant age (Table 1, see Supplementary Table 4, http://links.lww.com/CTG/B302).

Chronic pancreatitis

Among studies including participants with CP, germline genetic testing for *CFTR* was conducted in a total of 13,428 participants. The pooled prevalence of *CFTR* PVs was 15.3% (95% CI: 12.2–19.0%; $I^2 = 95.7\%$) (Figure 4, see Supplementary Figure 1, http://links.lww.com/CTG/B302). A total of 17 participants were diagnosed with CF (0.13%).

In subgroup analyses, *CFTR* PVs were significantly more prevalent among participants with idiopathic etiology compared with other etiologies (OR: 1.47, 95% CI: 1.33–1.63, $P < 0.0001$) and among pediatric participants compared with adult participants (OR: 1.21, 95% CI: 1.06–1.37, $P = 0.004$). Studies using full sequencing showed a higher prevalence of CFTR PVs than those which used targeted panel testing (OR: 1.46, 95% CI: 1.31–1.64, $P < 0.0001$) (Table 1, see Supplementary Table 5, http://links.lww.com/CTG/B302).

Pancreatitis, not otherwise specified

Among studies including participants with pancreatitis which was not clearly defined as AP, RAP, or CP, germline genetic testing for *CFTR* was conducted in a total of 4,521 participants. The pooled prevalence of CFTR PVs was 25.0% (95% CI: 17.5%–34.3%; $I^2 = 96.7\%$) (Figure 5, see Supplementary Figure 2, http://links.lww.com/CTG/B302). A total of 61 participants were diagnosed with CF (1.4%).

In subgroup analyses, *CFTR* PVs were more prevalent among idiopathic etiology than other etiologies (OR: 1.63, 95% CI: 1.41–1.88, $P < 0.0001$) and among pediatric participants compared with adult participants (OR: 2.62, 95% CI: 2.20–3.12, $P < 0.0001$). Finally, studies using full sequencing showed a higher prevalence of CFTR PVs than those which used targeted panel testing (OR: 2.82, 95% CI: 2.29–3.48, $P < 0.0001$) (Table 1, see Supplementary Table 6, http://links.lww.com/CTG/B302).

DISCUSSION

In this systematic review and meta-analysis including >10,000 participants across 138 separate studies, we demonstrate that *CFTR* PVs are prevalent among individuals with pancreatitis, ranging from 8.0% to 25.0%. Among individuals with a single AP episode, 8.0% had at least one CFTR PV, whereas individuals with recurrent AP or CP had nearly 2-fold higher prevalence at 16.4%–15.3%, respectively. Subgroups of patients may have higher prevalence, such as those with idiopathic AP for whom prevalence is as high as 30.6%. These estimates reflect a clinically significant subpopulation of individuals with pancreatitis for whom a genetically predisposing risk factor can be identified.

Our systematic review identified several important insights into germline *CFTR* variants among individuals with pancreatitis. First, the included studies are extremely heterogeneous. Various factors, including differences in study design, population demographics, and genetic testing methodologies likely contribute to this variability. This means a careful interpretation of the pooled prevalence data is required, considering specific study

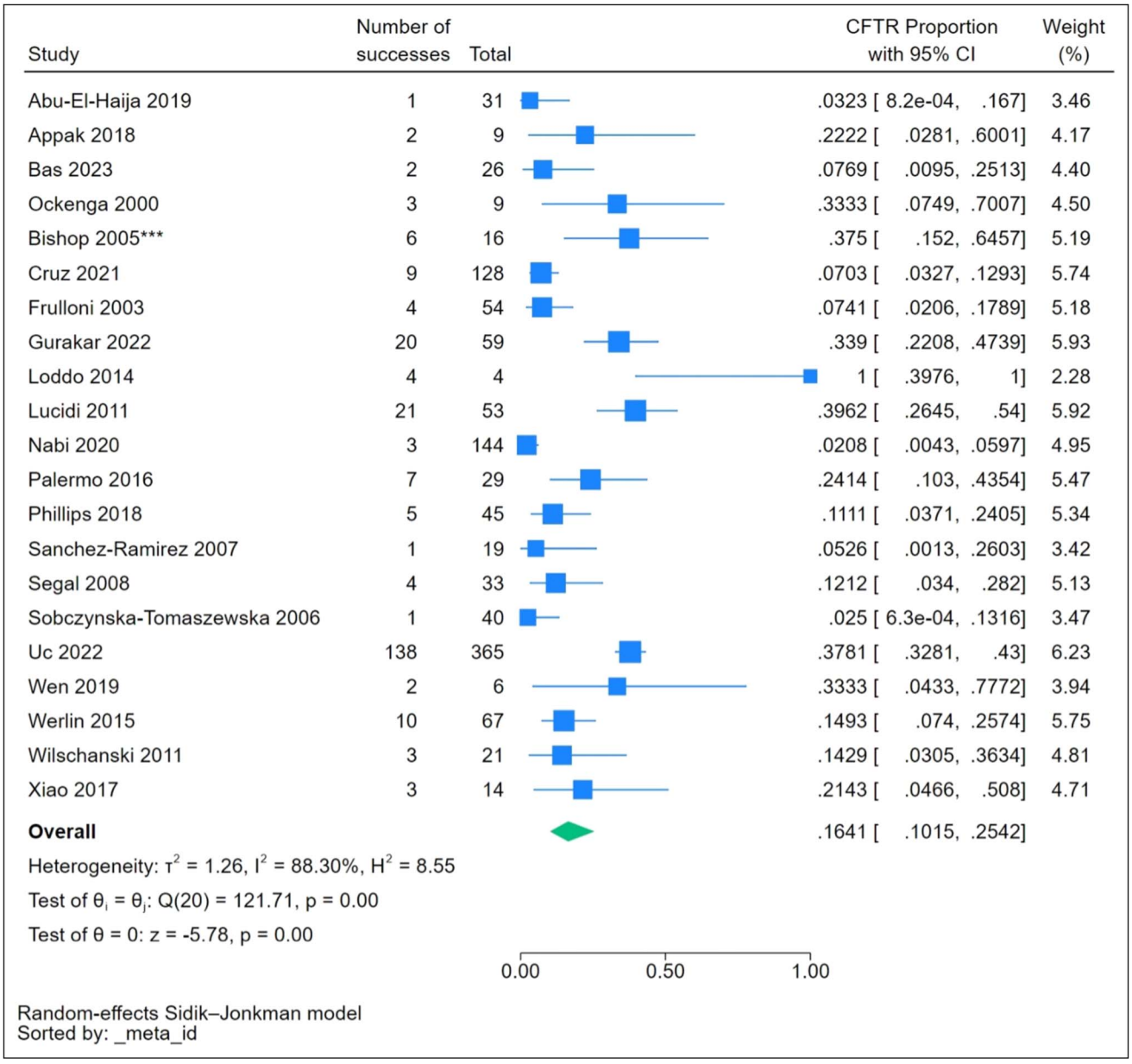


Figure 3. Forest plot illustrating the prevalence of pathogenic variants in *CFTR* among 21 studies which included 1,172 subjects with recurrent acute pancreatitis (RAP). *CFTR*, cystic fibrosis transmembrane conductance regulator.

contexts when integrating these findings. Second, the methods of germline genetic testing are variable which, in part, reflects the development of more sophisticated genetic testing methods and the increasing availability of these tests worldwide. We broadly categorized these testing strategies to full sequencing or targeted panel testing for our subgroup analysis, which generally demonstrated increased detection of PVs with full sequencing rather than targeted panels. Notably, some studies used targeted panels which included the American College of Medical Genetics and Genomics recommended 23 variant panel (14), others used targeted panels to only assess a few specific variants (15,16), while others used more extensive panels (17). Future work will be required to develop the impact of each genetic testing strategy with greater resolution. Third, participant ages were not consistently reported in the selected studies, which dictated the need to dichotomize this variable into pediatric and adult age categories. Studies that did report mean or median participant age generally reported age at the time of genetic testing rather than age at disease onset. Fourth, specific variants were reported in some, but not all, studies. Those studies that did report specific variants very rarely included a local control population to permit calculation of pancreatitis risk according to specific variant. Overall, these observations suggest future directions for genetics studies among individuals with pancreatitis to improve homogeneity and subsequent conclusions than can be made from the pooled data.

With these limitations in mind, we report that approximately 16% of individuals with RAP or CP who complete genetic testing

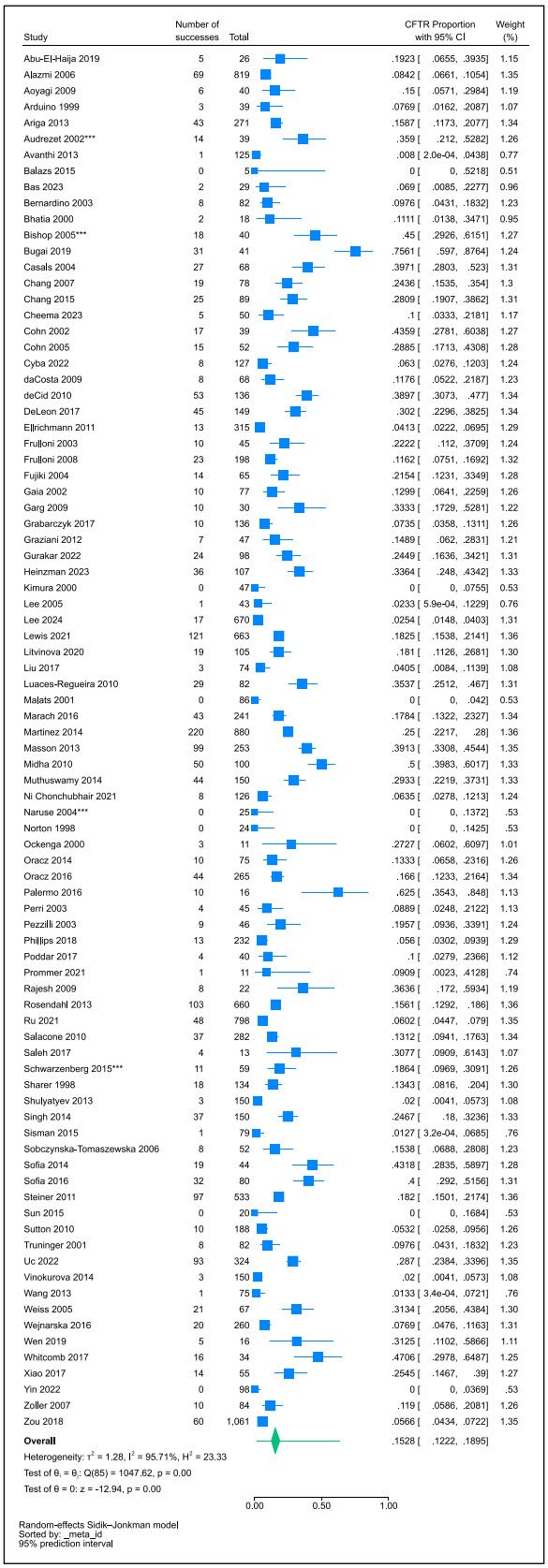


Figure 4. Forest plot illustrating the prevalence of pathogenic variants in *CFTR* among 86 studies which included 13,428 subjects with chronic pancreatitis (CP). *CFTR*, cystic fibrosis transmembrane conductance regulator.

will have at least one PV in *CFTR*, which is 3–5 folds higher than the carrier frequency in the general population (18–20). Thus, one concrete benefit to germline genetic testing among individuals with pancreatitis is to identify *CFTR* carrier status, which has implications for preconception counseling. In addition, we report that between 0.6 and 1.4% of individuals with RAP, CP, or pancreatitis NOS were diagnosed with CF, which is significantly higher than the general population rate of 0.02%–0.04% (21,22). Identifying a diagnosis of CF has numerous implications for management, including potential eligibility for treatment with CFTR modulating drugs.

Our subgroup analyses identified significant differences between adult and pediatric populations, as well as idiopathic and known etiologies of pancreatitis. Prevalence was higher in pediatric versus adult populations in the CP and NOS analyses. This is consistent with relatively early manifestation of CFTR-related disorders, which may also have more severe presentations during childhood. In addition, children typically have less exposure to nongenetic, environmental triggers such as cigarette smoking and alcohol. Prevalence was also significantly higher in idiopathic cohorts compared with those with known "Other" etiologies in the AP, CP, and NOS studies. Other causes primarily comprised alcoholic or gallstone pancreatitis. Less common causes included pancreatitis because of hyperlipidemia (23), drug-induced (24), familial pancreatitis (25), and inflammation in the setting of pancreas divisum (26). In the included studies, all participants underwent testing to help clarify possible impacts of germline genetics when there already is an existing trigger. At present, genetic testing is recommended only when the etiology is unclear (7). Additional study would be required to clarify potential benefits of testing for patients with other recognized causes of pancreatitis.

Over the past 10 years, CFTR modulating drugs have revolutionized CF care (27–29). At present, CFTR modulators are labeled for persons living with CF with specific *CFTR* variants proven to respond to the medication *in vivo* or *in vitro* (30). In these individuals, CFTR modulators improve CFTR function in sweat glands (reduced sweat chloride), the sinopulmonary system (improved forced expiratory volume on one second (FEV1)), and the reproductive system (improved fertility in males and females). CFTR modulators have a variety of effects on the digestive system, including reduced pancreatic inflammation and improved exocrine function in a subset of individuals (11,31–33). For individuals with pancreas-sufficient CF, CFTR modulators dramatically reduce the frequency of AP (11,34). Thus, among individuals with RAP or early CP who are diagnosed with CF, CFTR modulator therapy represents an opportunity for a precision medicine approach. We report that the frequency of diagnosing CF among patients with RAP or CP is low (0.6%–1.35%), but, when identified, treatment with CFTR modulators may dramatically improve the disease course. Notably, use of CFTR modulators to improve pancreatic function among *CFTR* PV carriers (i.e., CFTR-related disorder) who do not meet diagnostic criteria for CF has not been reported. We speculate that CFTR modulators will improve exocrine function and reduce pancreatitis frequency in this population, but prospective studies are needed.

Several limitations must be considered when interpreting the findings of this systematic review. In an attempt to maximize coverage of the available literature, we included conference abstracts which are not rigorously peer-reviewed and susceptible

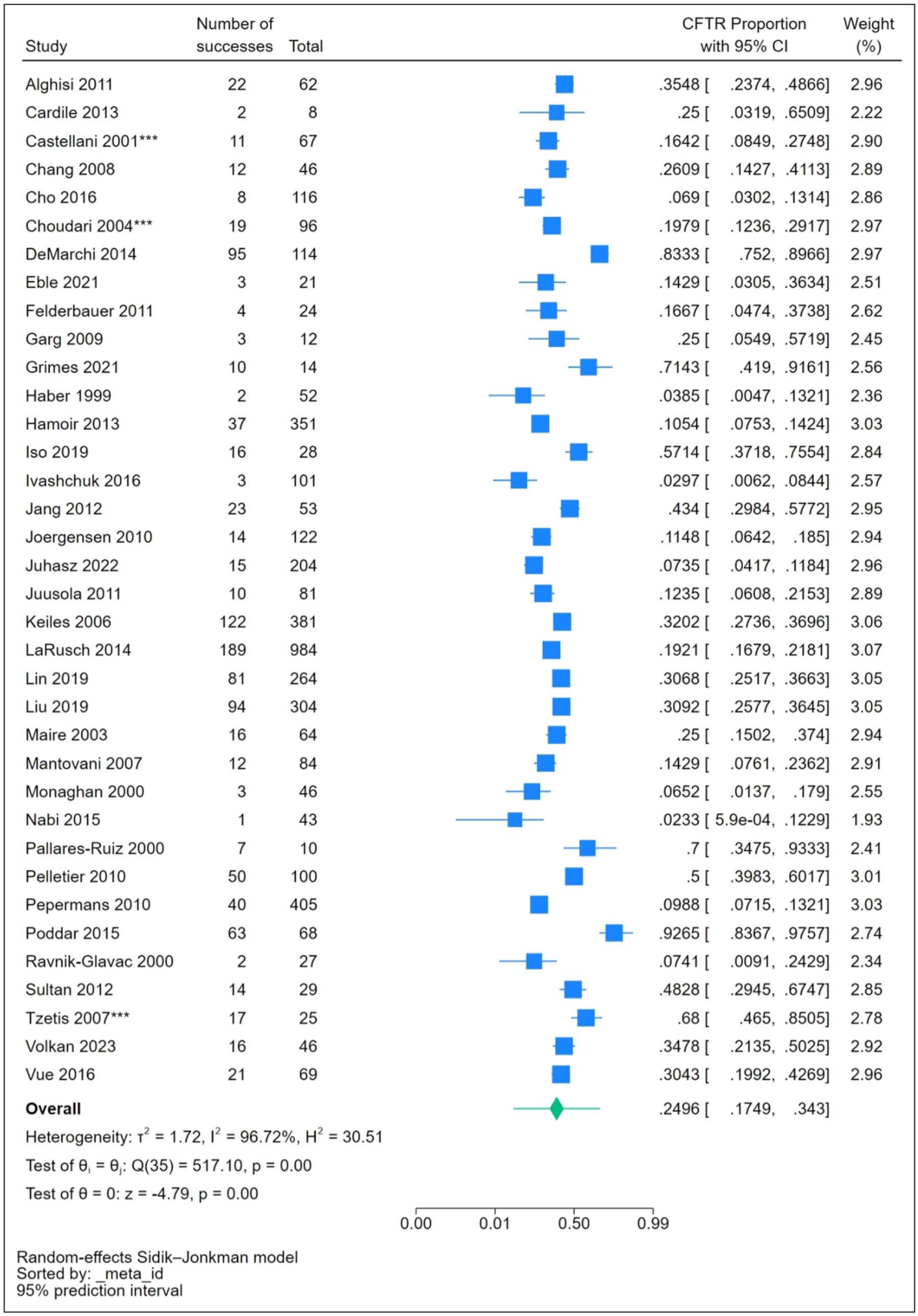


Figure 5. Forest plot illustrating the prevalence of pathogenic variants in *CFTR* among 36 studies which included 4,521 subjects with pancreatitis, not otherwise specified (NOS)*. *Pancreatitis NOS includes cohorts where the pancreatitis phenotype was not clearly described, or where results from AP and CP were pooled together. AP, acute pancreatitis; *CFTR*, cystic fibrosis transmembrane conductance regulator; CP, chronic pancreatitis.

to greater potential bias. Ultimately, abstracts constituted less than 25% of the included studies. An additional limitation is that selection or referral bias is an unmeasured confounder in many studies. The case finding strategy was not always clearly defined in the included studies, and many were conducted at tertiary referral centers. Finally, we identified significant heterogeneity between included studies, and this heterogeneity could not be resolved statistically. This is due to the large number of studies included, each with varying methodologies, sample characteristics, and patient selection. As a result, we limited the number and type of subgroup analyses to simple categories that could be assessed in all studies. We compared 2 categories and excluded studies which overlapped categories, such as the subgroup analysis of genetic testing strategy, which compared full *CFTR* sequencing with targeted panel testing, and excluded studies which used a combination of both or did not report their testing strategy. Similarly, we compared pediatric series with adult series and excluded any studies which included overlapping ages. Ultimately, this limited the sample size of subgroup analyses but was intended to increase the rigor of our findings.

Despite the limitations of available reported data, our study has many strengths. We compiled all studies reporting germline *CFTR* testing among individuals with pancreatitis and analyzed these according to pancreatitis phenotype. Our classification of AP, RAP, and CP are based on firm objective criteria, and we have pooled other cases into a pancreatitis not otherwise specified (NOS) category to retain these additional cases in our study, although this group is expectedly heterogeneous, and only limited conclusions can be drawn from the data. In addition to pancreatitis phenotype, we clarified etiology for all studies and performed subgroup analyses among these to determine the prevalence of *CFTR* PVs among idiopathic cases compared with cases with other identified etiologies. Finally, we determined the pooled prevalence by including all studies in each disease phenotype using meta-analyses statistical methodologies, which makes our results more generalizable than individual center data. These results are useful for counseling before germline genetic testing and inform researchers about the potential patient population with *CFTR*-related pancreatitis who may benefit from future clinical studies.

CONFLICTS OF INTEREST

Guarantor of the article: Mitchell L. Ramsey, MD.

Specific author contributions: M.L.R.: conceptualization. M.R., J.J., G.W., S.H., M.E.R.: methodology. J.J., G.W., S.M., M.L.R.: data curation. S.H., M.E.R., Y.G.: formal analysis. J.J.: writing–original draft. M.L.R.: writing–review and editing. M.L.R.: supervision.

Financial support: Research reported in this publication was supported by the National Cancer Institute and National Institute of Diabetes And Digestive and Kidney Diseases (NIDDK) under award number U01DK108327 (The Ohio State University). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. A.J.F. and M.L.R. receive grant support from the Cystic Fibrosis Foundation (CFF).

Potential competing interests: No conflicts of interest exist. A.J.F. discloses grant support from Anagram Therapeutics and has served as a consultant for Takeda, Alcresta and BridgeBio.

Study Highlights

WHAT IS KNOWN

- ✓ Pathogenic variants (PVs) in cystic fibrosis transmembrane conductance regulator (*CFTR*) are the most common genetic risk factor of pancreatitis, but the prevalence has not been well defined.

WHAT IS NEW HERE

- ✓ PVs in *CFTR* are encountered in 16.4% and 15.3% of individuals with recurrent acute pancreatitis or chronic pancreatitis.
- ✓ Cystic fibrosis was identified in up to 1.4% of individuals presenting with pancreatitis.
- ✓ *CFTR* PV prevalence varies by pancreatitis phenotype, pancreatitis etiology, and age at time of genetic testing.

REFERENCES

1. 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):122–34.
2. Machicado JD, Gougol A, Stello K, et al. Acute pancreatitis has a long-term deleterious effect on physical Health related quality of life. Clin Gastroenterol Hepatol 2017;15(9):1435–43.e2.
3. Machicado JD, Amann ST, Anderson MA, et al. Quality of life in chronic pancreatitis is determined by constant pain, disability/unemployment, current smoking, and associated co-morbidities. Am J Gastroenterol 2017;112(4):633–42.
4. Whitcomb DC. Central role of the sentinel acute pancreatitis event (SAPE) model in understanding recurrent acute pancreatitis (RAP): Implications for precision medicine. Front Pediatr 2022;10:941852.
5. Shelton C, Solomon S, LaRusch J, et al. PRSS1-related hereditary pancreatitis. In: Adam MP, Feldman J, Mirzaa GM, et al (eds.). GeneReviews. Seattle, WA, 1993.
6. Whitcomb DC, Preston RA, Aston CE, et al. A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996;110(6): 1975–80.
7. Gardner TB, Adler DG, Forsmark CE, et al. ACG clinical guideline: Chronic pancreatitis. Am J Gastroenterol 2020;115(3):322–39.
8. Berke G, Gede N, Szadai L, et al. Bicarbonate defective CFTR variants increase risk for chronic pancreatitis: A meta-analysis. PLoS One 2022; 17(10):e0276397.
9. LaRusch J, Jung J, General IJ, et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. Plos Genet 2014;10(7):e1004376.
10. Hwang TC, Braakman I, van der Sluijs P, et al. Structure basis of CFTR folding, function and pharmacology. J Cyst Fibros 2023;22(Suppl 1): S5–S11.
11. Ramsey ML, Li SS, Lara LF, et al. Cystic fibrosis transmembrane conductance regulator modulators and the exocrine pancreas: A scoping review. J Cyst Fibros 2023;22(2):193–200.
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283(15):2008–12.
13. Munn Z, Moola S, Lisy K, et al. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015; 13(3): 147–53.
14. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med 2004;6(5):387–91.
15. Sánchez-Ramírez CA, Larrosa-Haro A, Flores-Martínez S, et al. Acute and recurrent pancreatitis in children: Etiological factors. Acta Paediatr 2007;96(4):534–7.
16. Lee KH, Ryu JK, Yoon WJ, et al. Mutation analysis of SPINK1 and CFTR gene in Korean patients with alcoholic chronic pancreatitis. Dig Dis Sci 2005;50(10):1852–6.

17. Juusola J, Ferreira-Gonzalez A. Effectiveness of an expanded mutation panel versus the acmg recommended panel in detecting CFTR mutations in pancreatitis patients. J Mol Diagn 2011;13:719.
18. Monaghan KG, Bluhm D, Phillips M, et al. Preconception and prenatal cystic fibrosis carrier screening of African Americans reveals unanticipated frequencies for specific mutations. Genet Med 2004;6(3):141–4.
19. Rohlfs EM, Zhou Z, Heim RA, et al. Cystic fibrosis carrier testing in an ethnically diverse US population. Clin Chem 2011;57(6):841–8.
20. Zvereff VV, Faruki H, Edwards M, et al. Cystic fibrosis carrier screening in a North American population. Genet Med 2014;16(7):539–46.
21. Hamosh A, FitzSimmons SC, Macek M Jr., et al. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J Pediatr 1998;132(2):255–9.
22. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet 2009;373(9678): 1891–904.
23. Chang YT, Chang MC, Su TC, et al. Association of cystic fibrosis transmembrane conductance regulator (CFTR) mutation/variant/ haplotype and tumor necrosis factor (TNF) promoter polymorphism in hyperlipidemic pancreatitis. Clin Chem 2008;54(1):131–8.
24. Grimes AC, Chen Y, Bansal H, et al. Genetic markers for treatment-related pancreatitis in a cohort of Hispanic children with acute lymphoblastic leukemia. Support Care Cancer 2021;29(2):725–31.
25. Ravnik-Glavac M, Dean M, di Sant'Agnese P, et al. Evidence that hereditary pancreatitis is genetically heterogeneous disorder. Pflugers Arch 2000;439(3 Suppl l):R50–2.
26. Wen J, Li T, Liu L, et al. Long-term outcomes of therapeutic ERCP in pediatric patients with pancreas divisum presenting with acute recurrent or chronic pancreatitis. Pancreatology 2019;19(6):834–41.
27. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011; 365(18):1663–72.
28. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-Ivacaftor in Patients with cystic fibrosis homozygous for Phe508del. N Engl J Med 2017;377(21):2013–23.
29. Volkova N, Moy K, Evans J, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. J Cyst Fibros 2020;19(1):68–79.
30. Trikafta (Elexacaftor, Tezacaftor, and Ivacaftor Tablets; Ivacaftor Tablets) [package Insert]. Boston, MA: Vertex Pharmaceuticals; 2023.
31. Megalaa R, Gopalareddy V, Champion E, et al. Time for a gut check: Pancreatic sufficiency resulting from CFTR modulator use. Pediatr Pulmonol 2019;54(8):E16–e18.
32. Ramsey ML, Gokun Y, Sobotka LA, et al. Cystic fibrosis transmembrane conductance regulator modulator use is associated with reduced pancreatitis hospitalizations in patients with cystic fibrosis. Am J Gastroenterol 2021;116(12):2446–54.
33. Sadras I, Cohen-Cymberknoh M, Kerem E, et al. Acute pancreatitis in pancreatic-insufficient cystic fibrosis patients treated with CFTR modulators. J Cyst Fibros 2023;22(4):777–9.
34. Akshintala VS, Kamal A, Faghih M, et al. Cystic fibrosis transmembrane conductance regulator modulators reduce the risk of recurrent acute pancreatitis among adult patients with pancreas sufficient cystic fibrosis. Pancreatology 2019;19(8):1023–6.