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PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies (PROCEED): Rationale and Study Design From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

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Abstract

PROspective Evaluation of **C**hronic Pancreatitis for **E**pid**E**miologic and translational stu**D**ies (PROCEED) is the first prospective, observational cohort study of chronic pancreatitis in the US. The primary goals of PROCEED are to define disease progression, test the predictive capability of candidate biomarkers, and develop a platform to conduct translational and mechanistic studies in chronic pancreatitis. Using objective and consensus-driven criteria, PROCEED will enroll adults at different stages of chronic pancreatitis - controls, Suspected chronic pancreatitis and Definite chronic pancreatitis. In addition to collecting detailed information using structured case report forms and protocol-mandated evaluations at baseline and during follow-up, PROCEED will establish a linked biorepository of blood, urine, saliva, stool, pancreatic fluid and pancreatic tissue. Enrollment for PROCEED began in June 2017. As of July 1, 2018, nine clinical centers of the Consortium to study Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) are enrolling, and 350 subjects have completed baseline evaluation. In conclusion, PROCEED will provide the most accurate and reliable estimates to date on progression of chronic pancreatitis. The established cohort and biorepository will facilitate numerous analyses, leading to new strategies for diagnosis, methods to monitor disease progression, and treatment of chronic pancreatitis.

Keywords

Pancreas; Alcohol; tobacco; genetic; biorepository; cohort

INTRODUCTION

Chronic pancreatitis (CP) is characterized by persistent inflammation of the pancreas leading to fibrosis and organ dysfunction.[1] Clinical features of CP are highly variable and include minimal or no symptoms to debilitating pain, episode(s) of acute pancreatitis (AP), endocrine and/or exocrine insufficiency, local and/or systemic complications and pancreatic cancer. While there are known causes, in many cases the etiology remains elusive. Chronic pancreatitis profoundly affects quality of life commensurate with many severe chronic

medical conditions and cancers.[2] The estimated prevalence of CP ranges from 50 to 92 per 100,000 in the U.S. adult population.[3,4]

Most published studies on the progression of CP are old, originate mostly from non-U.S. centers, and consist predominantly of males with alcoholic CP.[5–11] The only large longitudinal study in the US was conducted in patients treated at the Mayo Clinic, Rochester, Minn from 1976–1982.[12] While these data provide insights into disease progression, predicting clinical course in individual patients remains difficult. Moreover, longitudinal data in patients with early-stage disease when definitive morphological changes of CP are not evident on cross-sectional imaging are needed.

In the past two decades, the etiologic profile of CP has broadened[13–15] and there is growing recognition that CP represents a disease continuum.[16,17] Improvements in radiologic and endoscopic imaging techniques have enabled better recognition of subtle morphological and functional changes in the pancreas,[18] but validated criteria for diagnosis of early-stage CP are lacking. Magnetic Resonance Cholangiopancreatography (MRCP) is transforming from qualitative to quantitative technique, focusing on detection of pancreatic fibrosis in addition to the traditional ductal imaging.[19,20] Endoscopic collection of pancreas fluid coupled with molecular analysis of this proximal biofluid has broadened the possibility of pancreas disease biomarker discovery and validation.[21] The clinical significance of pancreatogenic (type 3c) diabetes is beginning to be recognized.[22,23] While CP increases the risk of osteoporosis and fractures,[24–26] the underlying mechanisms are yet to be elucidated. Finally, a new mechanistic definition and conceptual framework to conduct research on the pathophysiology and evolution of CP and to potentially interrupt disease progression has been proposed, and awaits validation.[1,27]

Current management of CP is limited to symptomatic treatment of its clinical manifestations. Although animal models provide insights into pathogenesis,[28] these have not translated into curative treatments or prevention of progression. Major limitations include the inability to obtain histology at early stages of disease and lack of prospective well-characterized study populations with clinical and electronic health record (EHR) linkage. Of these, the latter is a feasible goal, and can provide a platform to not only understand disease progression, but also conduct studies of early diagnosis, prediction and prognosis, and ultimately new diagnostic and therapeutic approaches.

The Adult CP Working Group of the Consortium for the Study Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)[29] was tasked by its Steering Committee to design a longitudinal study of CP, which led to the conception and development of the PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies (PROCEED). In addition to addressing the primary objectives of the CPDPC, PROCEED will provide a platform for multiple translational and mechanistic studies.

Hypothesis and Objectives

The overarching goal of PROCEED is prospective ascertainment and follow-up of a well-phenotyped study population at different stages of CP to accurately define its progression and associated complications. Furthermore, collection of biological samples from study

subjects at predefined intervals will provide a platform to develop biomarkers of early diagnosis and prediction of disease progression, understand disease mechanisms, and discover genetic and other factors affecting susceptibility and progression.

PROCEED has four primary objectives – to:

1. establish a model longitudinal research cohort of adult subjects for the study of CP and its complications.
2. estimate the risk of progression from suspected to definite CP, and the risk of new-onset diabetes or exocrine pancreatic dysfunction in definite CP, and study how the risks are influenced by patient characteristics and conditions.
3. test the predictive capability of candidate biomarkers for the diagnosis and prognosis of CP.
4. develop a platform for conducting biomarker, genetic and mechanistic studies using clinical information and longitudinal biospecimens.

Through recruitment of subjects across clinical centers that span the U.S., and collection of data through standardized forms and common data elements, PROCEED will offer an opportunity to understand the similarities and variation during progression of CP across the nation. The cohort and linked biospecimens will provide the opportunity to address several secondary objectives through cross-sectional and longitudinal studies. PROCEED will, by nature, foster collaboration for generation of future hypotheses and new standards of care for pancreatitis. Transitioning some subjects from the pediatric (INternational Study Group of Pediatric Pancreatitis: In search for a cuRE [INSPPIRE-2])[30] to adult (PROCEED) cohort once they age is underway.

STUDY DESIGN

PROCEED is a prospective, observational, longitudinal cohort study of the natural history of CP. The study cohort consists of three well-phenotyped subcohorts representing different stages of CP. Since diagnosis, early detection and improved assessment of prognosis of CP are the main objectives, PROCEED is designed according to the prospective-specimen collection, retrospective-blinded-evaluation (PRoBE) principles,[31,32] serving as a platform for multiple Phase I, II, and III biomarker studies. Specifically, the control subcohort will be used in Phase I-II biomarker discovery and validation studies, serving as negative (no pancreatic disease controls) and positive control (chronic upper abdominal pain of suspected pancreatic origin) in comparison with patients in the other two sub-cohorts. Subjects with suspected and definite CP will be examined in Phase III biomarker studies. Biospecimens collected at baseline and during follow-up will enable studying early detection and progression to CP or development of new-onset diabetes using biomarkers. They also enable modeling of the risk factor-outcome relationship in a longitudinal context.

Study Organization

PROCEED is part of the CPDPC, a cooperative agreement grant funded by the National Cancer Institute (NCI) and the National Institute of Diabetes and Digestive and Kidney

Diseases (NIDDK). The participating sites, organizational structure of the CPDPC and its studies are provided elsewhere in this issue of the journal[29] and at http://cpdpc.mdanderson.org.

Study Subjects and Participating Sites

PROCEED will enroll participants 18 years and older divided into three main subcohorts: Controls, Suspected CP and Definite CP. Detailed inclusion and exclusion criteria are described in Tables 1–2. Study subjects will include males and females with no preference to gender, sex or minority status.

The choice of subjects is purposeful to recapitulate the natural history of CP cross-sectionally based on our current understanding and evaluate for disease progression during follow-up. Inclusion of subjects at each progressive stage of CP allows observation of transition from one stage to the next without having to observe all the transitions from healthy states in all subjects, which would require a much larger sample size. Definitions for each group were determined by consensus among the CPDPC investigators to constitute a minimum set of clear, objective, and reproducible selection criteria. Color coding for subcohorts (GREEN, YELLOW, RED zones) is used to facilitate presentation and represents a conceptual framework for the study objectives. Each subcohort is created with a specific rationale and corresponding sample sizes with adequate power to address the primary objectives of PROCEED.

The controls (GREEN zone) include subjects with no pancreas disease (i.e. no upper abdominal symptoms or diagnosis of pancreatic disease) and chronic upper abdominal pain of suspected pancreatic origin. Data from these subjects will be used to inform the distribution of candidate biomarkers in non-pancreatic disease groups for cross-sectional analyses compared with suspected and definite CP. The development of research procedures for the no pancreas disease controls are underway – enrollment for this group will commence once plans are finalized and approved by the CPDPC Data and Safety Monitoring Board. Therefore, description for study procedures in this paper refer to all other PROCEED groups.

Suspected CP (YELLOW zone) are subjects with indeterminate CP, one recent episode of AP, and recurrent AP (RAP). This represents a high-risk group for progression to definite CP and may be well-suited for intervention studies aiming at slowing disease progression. Definite CP (RED zone) includes subjects with obvious morphologic features of CP and provides an opportunity to understand the prevalence and progression of functional and morphological changes and complications of the disease. Of note, there is no universally accepted criteria to diagnose or classify the morphological appearance or severity of CP. The CPDPC investigators agreed upon using the Cambridge classification based on computed tomography (CT) scan and magnetic resonance imaging (MRI) and MRCP to assess morphological changes in the pancreas to group subjects into PROCEED and to evaluate the primary outcome, i.e. disease progression[33].

Enrollment for PROCEED began in June 2017. As of July 1, 2018, nine CPDPC clinical centers are enrolling into PROCEED, and 350 subjects have completed baseline procedures.

Baseline Assessment and Procedures

Table 3 summarizes information to be collected in case report forms (CRFs) completed for each study participant. The patient CRF will be self-administered, with a trained study coordinator available to answer questions and to verify subject responses. The coordinator will administer the coordinator CRF and complete the physician CRF with assistance of the physician investigator. PROCEED CRFs are modeled from the North American Pancreatitis Studies (NAPS2)[34–36] with modifications in wording of questions as needed to improve clarity and granularity of information collected. Questions were added to collect information not included in NAPS2 studies, e.g. socioeconomic status, frequency and duration of episodic pain, exposure to cigar, pipe, tobacco chewing and other substances, Patient-Reported Outcomes Measurement Information System (PROMIS) instruments,[37] details of endotherapy, surgery, and imaging findings.

Protocol-mandated evaluations include performance of CT scan and/or MRI/MRCP, assessment of diabetes, exocrine pancreatic function, and bone density testing (Table 4). An imaging working group standardized the definitions and features of CP and developed training materials for site radiologists. The rationale and details of imaging studies for use in CPDPC studies are described elsewhere.[38] Cross-sectional studies will be reviewed by at least one designated abdominal radiologist at each site to assign a Cambridge score, and record detailed information on pancreatic parenchymal, ductal and functional changes for *post hoc* analyses. Internal validation of Cambridge score assignment across sites will be performed through an interobserver variability study in a subset of subjects. Pancreatic findings on endoscopic ultrasound (EUS), if performed, will be systematically recorded.

All subjects will be asked to provide blood, clean-catch midstream urine, saliva and a stool sample.[39] A subset will undergo a clinical or research EUS or esophagogastroduodenoscopy (EGD) during which pancreas fluid will be collected from the duodenum after injection of secretin for biomarker analysis. Testing for pancreatic fluid electrolytes will be at the discretion of the study investigator.

Based on initial experience (~15% recruitment), modifications were made to inclusion criteria and CRFs (Tables 1–3, 5).

Follow-up Assessment and Procedures

The primary goal of longitudinal follow-up will be to assess for disease progression. In addition, information will be captured for changes from prior evaluation or new developments in demographics, socioeconomic status, relevant personal and family history, risk factor exposure, patient-reported outcomes, disease-related manifestations, treatments, and vital statistics.

All subjects will have a yearly follow-up study visit. Similar to baseline, CRFs will be completed for each in-person follow-up visit (Table 5). The currently accepted protocol-mandated study activities are shown in Table 4. Subjects in the suspected and definite CP subcohorts will be asked to provide a blood and urine sample at each follow-up visit. If not collected as part of baseline assessment, a subset may undergo pancreas fluid collection at the time of a clinically indicated or research EUS or EGD.

Missed or rescheduled visits, or incomplete assessments, deviations in protocol-mandated evaluations will be captured to understand the reasons for such occurrences. In case of a missed follow-up visit, available information will be captured from EHR.

Outcome Measures

Primary and secondary outcomes of the PROCEED study are outlined in Table 6.

Statistical Considerations

Several main study endpoints are failure-times, e.g. progression to definite CP (Yellow zone), AP episodes, new-onset diabetes (Red zone), pancreatic cancer, and death. Longitudinal data, failure-time data, and receiver operating characteristics (ROC) curve analysis will be the principal analytical approaches. Kaplan-Meier curves, Cox proportional hazards modeling, recurrent event analysis, and competing risks analysis will be the statistical tools.[40,41] Standard procedures for regression model development and diagnosis will be used.[42] Analysis of longitudinal data (e.g., morphological changes on MRI/MRCP, biomarkers, pancreas function, pain, quality of life, resource utilization) will be done using linear or generalized linear mixed models.[43,44] ROC curve analysis[45] will be used to study the diagnostic or prognostic properties of biomarkers in accordance to the PRoBE guideline for biomarker development.[31,32]

Advanced statistical methods will be used to deal with complications in the data. PROCEED will collect EHR data from clinical visits in addition to the scheduled study visits. As those visits may be triggered by a disease condition, they may cause bias to statistical results. In such a case, we will use statistical methods with adjustment for informative observational times.[46] Statistical methods for missing data and dropout will be used when the missingness is non-ignorable.[47] In early phase biomarker studies, it is desirable to conduct both covariate-matched and unmatched comparisons between cases and controls.[31,32] This will be achieved by frequency or propensity score weighting methods.[48] As a highly heterogeneous disease, CP progression may be characterized by multiple outcomes. Their correlation and co-evolution over time will be modeled by joint modeling techniques.[49,50]

The sample size is determined according to PRoBE guidelines.[32] In a rule-out diagnostic test comparing biomarkers between a control group (e.g., Green - chronic upper abdominal pain of suspected pancreatic origin) to the cases (e.g., Red - Definite CP), if the True Positive (TP, Sensitivity) = 95% and the False Positive (FP, 1-Specificity) = 75% under the null hypothesis, the proposed sample size enables the rejection of the null when the FP = 60% for non-invasive biomarkers (e.g. urine/blood/stool) and 50% for invasive biomarkers (e.g., pancreas fluid and tissue). In a rule-in test with FP = 5% and TP = 25% under the null hypothesis, the proposed sample size enables rejection of the null when the TP = 50% for non-invasive biomarkers and 60% for invasive biomarkers. The error margin of the fixed TP (rule-out) and FP (rule-in) is ± 4%. Type I error is 10% and power level is 95% for early phase studies. The proposed sample size also enables similar comparison among various other Green, Yellow and Red subgroups. No pancreas disease control group is created to establish the reference range of biomarkers and compare asymptomatic general population controls with subjects at various stages of CP.

The Yellow zone enables a Phase III biomarker study comparing subjects with and without progression to definite CP on their biomarker data 1–2 years before progression, with the goal of studying early detection of progression. With FP = 5% and TP = 25% under the null hypothesis, the proposed sample size enables the rejection of the null when the TP = 50% for non-invasive biomarkers and 60% for invasive biomarkers, after 10% data attrition during the longitudinal follow-up. The error margin of the fixed FP is ± 2%, the Type I error is 5%, and power level is 90%, and we assume that 7% subjects in the Yellow zone will progress to CP during a median follow-up of 4 years.

For the Red zone, the number of subjects contributing biospecimen is determined by similar ROC analysis as above. An important outcome for this sub-cohort is new-onset diabetes among those without diabetes at baseline (~60%). With a Type I error of 0.05, 10% data loss, a 20% incidence rate of diabetes over 4 years (5%/year), the proposed sample size can provide 90% power to detect a hazard ratio of 3 for a dichotomous exposure variable with prevalence between 20%–70%. This effect size is in line with some of the published risk factors for CP.[51,52]

Contingency Plans

Modifications to participating sites, data collection, protocol-mandated evaluations, follow-up schedule, and enrollment will be considered by the CPDPC Steering Committee, as deemed necessary.

DISCUSSION

PROCEED is the first prospective, longitudinal observational cohort study of CP in the United States. The study is innovative in several ways – in addition to enrolling subjects representing the complete clinical spectrum of CP, it will establish a biorepository consistent with the accepted principles of the PRoBE guideline to support translational studies including, but not limited to, diagnostic, predictive and prognostic biomarker testing. PROCEED will provide the research infrastructure to conduct numerous clinical and translational studies, which will lead to new strategies for diagnosis, methods to monitor disease progression and treatment of CP.

PROCEED builds upon the experience of conducting multicenter epidemiologic studies from the NIDDK-funded NAPS2 studies.[34–36] NAPS2 has made many novel observations with regard to the current clinical profile of CP, role of environmental and genetic risk factors in pancreatitis, quality of life and treatment of CP in the US.[2,53–57]. NAPS2 also inspired creation of the pediatric consortium (INSPPIRE)[58], and other pancreatitis cohorts in Europe.[59–62]

Accurate characterization of the progression of CP is the main focus of PROCEED. This is specifically relevant for patients at earlier stages, i.e. suspected CP or patients with definite CP who have not yet developed functional impairment or significant morphological destruction of the pancreas. Understanding the cumulative incidence and burden of clinical events in these groups is critical to model the risk factor-outcome relationship and inform the design of future randomized clinical trials. Chronic upper abdominal pain in the absence

of definite morphological changes of CP is far more common than CP. PROCEED will provide empiric data on how often and who among these individuals develop clinical manifestations of CP, which will be of immediate clinical relevance. Detailed morphological changes observed at baseline and during follow-up will help develop more accurate criteria to diagnose and monitor disease progression. Finally, detailed information on a variety of patient-centered and disease-related symptoms and outcomes, medication use, and treatments will allow numerous secondary analyses.

A major strength of PROCEED is that the development of biorepository and the conduct of biomarker studies follow the principles of the PRoBE guideline.[31,32] Originally developed for cancer biomarker studies by the Early Detection Research Network (EDRN), the basic principles of PRoBE apply to other medical research fields as well.[63,64] Specific recommendations on study design, study sample selection, sample size determination, and analytical methods help avoid common bias in biomarker research and enables better control of false positive findings in early phases of biomarker studies.

In preliminary studies, prostaglandin E2 levels in pancreatic fluid, and proteomic profiling of plasma and urine has shown promise in discriminating CP cases from controls.[65–68] An immediate use of the PROCEED biorepository will be to perform definitive studies for these and other promising biomarkers to develop clinical tests to rule-out or rule-in CP. Preclinical samples can be analyzed to predict future disease progression or development of clinically relevant events. Serial changes in biomarkers in samples can be correlated with clinical events or disease progression. PROCEED will provide a large cohort to characterize the microbiome profile specific to CP. Finally, the cohort offers opportunities to conduct genetic studies independently or in collaboration with other cohorts to define factors associated with susceptibility and progression of CP or its manifestations, such as pancreatogenic (type 3c) diabetes.[69]

PROCEED patients will have opportunities to co-enroll in ancillary studies of the CPDPC (Fig. 1). Participation will place little increased burden on study subjects, as they will undergo extensive evaluation in the PROCEED study. This brings substantial synergy to CPDPC studies by leveraging the infrastructure for recruitment and follow-up of study participants already in place. Rich data collection in PROCEED will allow these other studies to perform complimentary analyses that may not have been otherwise possible, e.g. clinical predictors of Type 3c diabetes[70]. Furthermore, it will significantly reduce costs for these projects when compared with a strategy of establishing new cohorts independent of the consortium.

In conclusion, successful completion of PROCEED will establish the first longitudinal research cohort for the study of CP in the United States. PROCEED will provide the most accurate and reliable estimates to date on progression of CP. In addition to the primary objectives, the established cohort will facilitate numerous integrative analyses for clinical and translational studies leading to new strategies for diagnosis, methods to monitor disease progression and treatment of CP.

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REFERENCES

1. Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. Pancreatology 2016;16:218–224. [PubMed: 26924663]
2. Amann ST, Yadav D, Barmada MM, et al. Physical and mental quality of life in chronic pancreatitis: a case-control study from the North American Pancreatitis Study 2 cohort. Pancreas 2013;42:293–300. [PubMed: 23357924]
3. Sellers ZM, MacIsaac D, Yu H, et al. Nationwide Trends in Acute and Chronic Pancreatitis Among Privately Insured Children and Non-Elderly Adults in the United States, 2007–2014. Gastroenterology 2018;155:469–478.e1. [PubMed: 29660323]
4. Yadav D, Timmons L, Benson JT, et al. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. Am J Gastroenterol 2011;106:2192–2199. [PubMed: 21946280]
5. Ammann RW, Akovbiantz A, Largiader F, et al. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. Gastroenterology 1984;86:820–828. [PubMed: 6706066]
6. Ammann RW, Buehler H, Muench R, et al. Differences in the natural history of idiopathic (nonalcoholic) and alcoholic chronic pancreatitis. A comparative long-term study of 287 patients. Pancreas 1987;2:368–377. [PubMed: 3628234]
7. Cavallini G, Frulloni L, Pederzoli P, et al. Long-term follow-up of patients with chronic pancreatitis in Italy. Scand J Gastroenterol 1998;33:880–889. [PubMed: 9754738]
8. Dani R, Mott CB, Guarita DR, et al. Epidemiology and etiology of chronic pancreatitis in Brazil: a tale of two cities. Pancreas 1990;5:474–478. [PubMed: 2381901]
9. Lankisch PG, Lohr-Happe A, Otto J, et al. Natural course in chronic pancreatitis. Pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. Digestion 1993;54:148–155. [PubMed: 8359556]
10. Maisonneuve P, Lowenfels AB, Mullhaupt B, et al. Cigarette smoking accelerates progression of alcoholic chronic pancreatitis. Gut 2005;54:510–514. [PubMed: 15753536]
11. Marks IN, Bank S, Louw JH. Chronic pancreatitis in the Western Cape. Digestion 1973;9:447–453. [PubMed: 4784706]
12. Layer P, Yamamoto H, Kalthoff L, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology 1994;107:1481–1487. [PubMed: 7926511]
13. Greer JB, Thrower E, Yadav D. Epidemiologic and Mechanistic Associations Between Smoking and Pancreatitis. Curr Treat Options Gastroenterol 2015;13:332–346. [PubMed: 26109145]
14. Majumder S, Takahashi N, Chari ST. Autoimmune Pancreatitis. Dig Dis Sci 2017;62:1762–1769. [PubMed: 28365915]
15. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology 2013;144:1292–302. [PubMed: 23622139]
16. Sankaran SJ, Xiao AY, Wu LM, et al. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015;149:1490–1500.e1. [PubMed: 26299411]
17. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252–1261. [PubMed: 23622135]
18. Coté GA, Smith J, Sherman S, et al. Technologies for imaging the normal and diseased pancreas. Gastroenterology 2013;144:1262–1271.e1. [PubMed: 23622136]

19. Tirkes T, Fogel EL, Sherman S, et al. Detection of exocrine dysfunction by MRI in patients with early chronic pancreatitis. Abdom Radiol (NY) 2017;42:544–551. [PubMed: 27660281]
20. Tirkes T, Lin C, Cui E, et al. Quantitative MR Evaluation of Chronic Pancreatitis: Extracellular Volume Fraction and MR Relaxometry. AJR Am J Roentgenol 2018;210:533–542. [PubMed: 29336598]
21. Hart PA, Topazian M, Raimondo M, et al. Endoscopic Pancreas Fluid Collection: Methods and Relevance for Clinical Care and Translational Science. Am J Gastroenterol 2016;111:1258–1266. [PubMed: 27481304]
22. Hart PA, Bellin MD, Andersen DK, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol 2016;1:226–237. [PubMed: 28404095]
23. Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study. Diabetes Care 2017;40:1486–1493. [PubMed: 28860126]
24. Duggan SN, Smyth ND, Murphy A, et al. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014;12:219–228. [PubMed: 23856359]
25. Munigala S, Agarwal B, Gelrud A, et al. Chronic Pancreatitis and Fracture: A Retrospective, Population-Based Veterans Administration Study. Pancreas 2016;45:355–361. [PubMed: 26199986]
26. Tignor AS, Wu BU, Whitlock TL, et al. High prevalence of low-trauma fracture in chronic pancreatitis. Am J Gastroenterol 2010;105:2680–2686. [PubMed: 20736937]
27. Whitcomb DC, Shimosegawa T, Chari ST, et al. International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. Pancreatology 2018.
28. Lerch MM, Gorelick FS. Models of acute and chronic pancreatitis. Gastroenterology 2013;144:1180–1193. [PubMed: 23622127]
29. Serrano J, Andersen DK, Forsmark CE, et al. Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer: From Concept to Reality. Pancreas 2018:47;208–1212. [PubMed: 29329157]
30. Uc A Perito ER, Phol JF, et al. INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE (INSPPIRE 2) Cohort Study: Design and Rationale From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Pancreas 2018;47:1222–1228 [PubMed: 30325861]
31. Pepe MS, Etzioni R, Feng Z, et al. Phases of biomarker development for early detection of cancer. J Natl Cancer Inst 2001;93:1054–1061. [PubMed: 11459866]
32. Pepe MS, Feng Z, Janes H, et al. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. J Natl Cancer Inst 2008;100:1432–8. [PubMed: 18840817]
33. Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. Pancreas 2014;43:1143–1162. [PubMed: 25333398]
34. Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). Pancreatology 2008;8:520–531. [PubMed: 18765957]
35. Wilcox CM, Sandhu BS, Singh V, et al. Racial Differences in the Clinical Profile, Causes, and Outcome of Chronic Pancreatitis. Am J Gastroenterol 2016;111:1488–1496. [PubMed: 27527745]
36. Wilcox CM, Yadav D, Ye T, et al. Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. Clin Gastroenterol Hepatol 2015;13:552–560; quiz e28–9. [PubMed: 25424572]
37. Health Measures. Transforming how health is measured Available at http://www.healthmeasures.net/explore-measurement-systems/promis. Accessed July 7, 2018.

38. Tirkes T, Shah Z, Takahashi N, et al. Evaluation of Chronic Pancreatitis by CT, MRI, and MRCP: Reporting Standards from the Adult Chronic Pancreatitis Working Group for the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) Under review.
39. Fisher WE, Cruz-Monserrate Z, McElhany AL, et al. Standard Operating Procedures for Biospecimen Collection, Processing, and Storage: From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Pancreas 2018;47:1213–1221 [PubMed: 30325860]
40. Cook RJ, Lawless J. The statistical analysis of recurrent events New York, NY: Springer-Verlag; 2007.
41. Klein JP, Moeschberger M. Survival Analysis: Techniques for Censored and Truncated Data New York, NY: Springer-Verlag; 1997.
42. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis (2nd ed). New York, NY: Springer-Verlag; 2015.
43. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data New York, NY: Springer-Verlag; 2000.
44. Verbeke G, Molenberghs G. Models for Discrete Longitudinal Data New York, NY: Springer-Verlag; 2005.
45. Pepe MS. The Statistical Evaluation of Medical Tests for Classification and Prediction Oxford, United Kingdom: Oxford Press; 2004.
46. McCulloch CE, Neuhaus JM, Olin RL. Biased and unbiased estimation in longitudinal studies with informative visit processes. Biometrics 2016;72:1315–1324. [PubMed: 26990830]
47. Fitzmaurice G, Davidian M, Verbeke G, eds, et al. Longitudinal Data Analysis Boca Raton, FL: Chapman and Hall/CRC; 2008.
48. Huang Y Evaluating and comparing biomarkers with respect to the area under the receiver operating characteristics curve in two-phase case-control studies. Biostatistics 2016;17:499–522. [PubMed: 26883772]
49. Elashoff R, Li G, Li N. Joint Modeling of Longitudinal and Time-to-Event Data Boca Raton, FL: Chapman and Hall/CRC; 2016.
50. Hatfield LA, Boye ME, Carlin BP. Joint modeling of multiple longitudinal patient-reported outcomes and survival. J Biopharm Stat 2011;21:971–991. [PubMed: 21830926]
51. Maisonneuve P, Frulloni L, Mullhaupt B, et al. Impact of smoking on patients with idiopathic chronic pancreatitis. Pancreas 2006;33:163–168. [PubMed: 16868482]
52. Malka D, Hammel P, Sauvanet A, et al. Risk factors for diabetes mellitus in chronic pancreatitis. Gastroenterology 2000;119:1324–1332. [PubMed: 11054391]
53. Coté GA, Yadav D, Slivka A, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. Clin Gastroenterol Hepatol 2011;9:266–273; quiz e27. [PubMed: 21029787]
54. Glass LM, Whitcomb DC, Yadav D, et al. Spectrum of use and effectiveness of endoscopic and surgical therapies for chronic pancreatitis in the United States. Pancreas 2014;43:539–43. [PubMed: 24717802]
55. 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:e1004376. [PubMed: 25033378]
56. Whitcomb DC, LaRusch J, Krasinskas AM, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet 2012;44:1349–1354. [PubMed: 23143602]
57. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med 2009;169:1035–1045. [PubMed: 19506173]
58. Morinville VD, Lowe ME, Ahuja M, et al. Design and implementation of INSPPIRE. J Pediatr Gastroenterol Nutr 2014;59:360–364. [PubMed: 24824361]
59. Ahmed Ali U, Issa Y, van Goor H, et al. Dutch Chronic Pancreatitis Registry (CARE): design and rationale of a nationwide prospective evaluation and follow-up. Pancreatology 2015;15:46–52. [PubMed: 25511908]

60. Fernandez M, Arvanitakis M, Musala C, et al. The Belgian national registry on chronic pancreatitis: A prospective multi-centre study covering more than 800 patients in one year. Pancreatology 2017;17:572–579. [PubMed: 28600220]

61. Olesen SS, Poulsen JL, Drewes AM, et al. The Scandinavian baltic pancreatic club (SBPC) database: design, rationale and characterisation of the study cohort. Scand J Gastroenterol 2017;52:909–915. [PubMed: 28471312]

62. Szucs A, Marjai T, Szentesi A, et al. Chronic pancreatitis: Multicentre prospective data collection and analysis by the Hungarian Pancreatic Study Group. PLoS One 2017;12:e0171420. [PubMed: 28207747]

63. Bhangoo RS, Hall IE, Reese PP, et al. Deceased-donor kidney perfusate and urine biomarkers for kidney allograft outcomes: a systematic review. Nephrol Dial Transplant 2012;27:3305–3314. [PubMed: 22498916]

64. Mansour SG, Puthumana J, Coca SG, et al. Biomarkers for the detection of renal fibrosis and prediction of renal outcomes: a systematic review. BMC Nephrol 2017;18:72. [PubMed: 28219345]

65. Conwell DL, Muntel J, Ahmed S, et al. The Ohio State University Pancreas Disorders Network U-BioCHIP Platform: An Update. In Abstracts of Papers Submitted to the 48th Meeting of the American Pancreatic Association, November 8–11, 2017, San Diego, California Pancreas 2017;46:1395abstr.

66. Abu Dayyeh BK, Conwell D, Buttar NS, et al. Pancreatic juice prostaglandin e2 concentrations are elevated in chronic pancreatitis and improve detection of early disease. Clin Transl Gastroenterol 2015;6:e72. [PubMed: 25630864]

67. Bennike TB, Bellin MD, Xuan Y, et al. A Cost-Effective High-Throughput Plasma and Serum Proteomics Workflow Enables Mapping of the Molecular Impact of Total Pancreatectomy with Islet Autotransplantation. J Proteome Res 2018;17:1983–1992. [PubMed: 29641209]

68. Paulo JA, Kadiyala V, Banks PA, et al. Mass Spectrometry-Based (GeLC-MS/MS) Comparative Proteomic Analysis of Endoscopically (ePFT) Collected Pancreatic and Gastroduodenal Fluids. Clin Transl Gastroenterol 2012;3:e14. [PubMed: 23238231]

69. Goodarzi MO, Nagpal T, Greer P, et al. Genetic Risk Score to Differentiate Pancreatogenic Diabetes due to Chronic Pancreatitis from Type 2 Diabetes Mellitus Under review.

70. Hart PA, Andersen DK, Mather KJ, et al. Evaluation of a Mixed Meal Test for Diagnosis and Characterization of PancrEaTogEniC DiabeTes Secondary to Pancreatic Cancer and Chronic Pancreatitis: Rationale and Methodology for the DETECT Study From the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer. Pancreas 2018;47:1239–1243 [PubMed: 30325863]

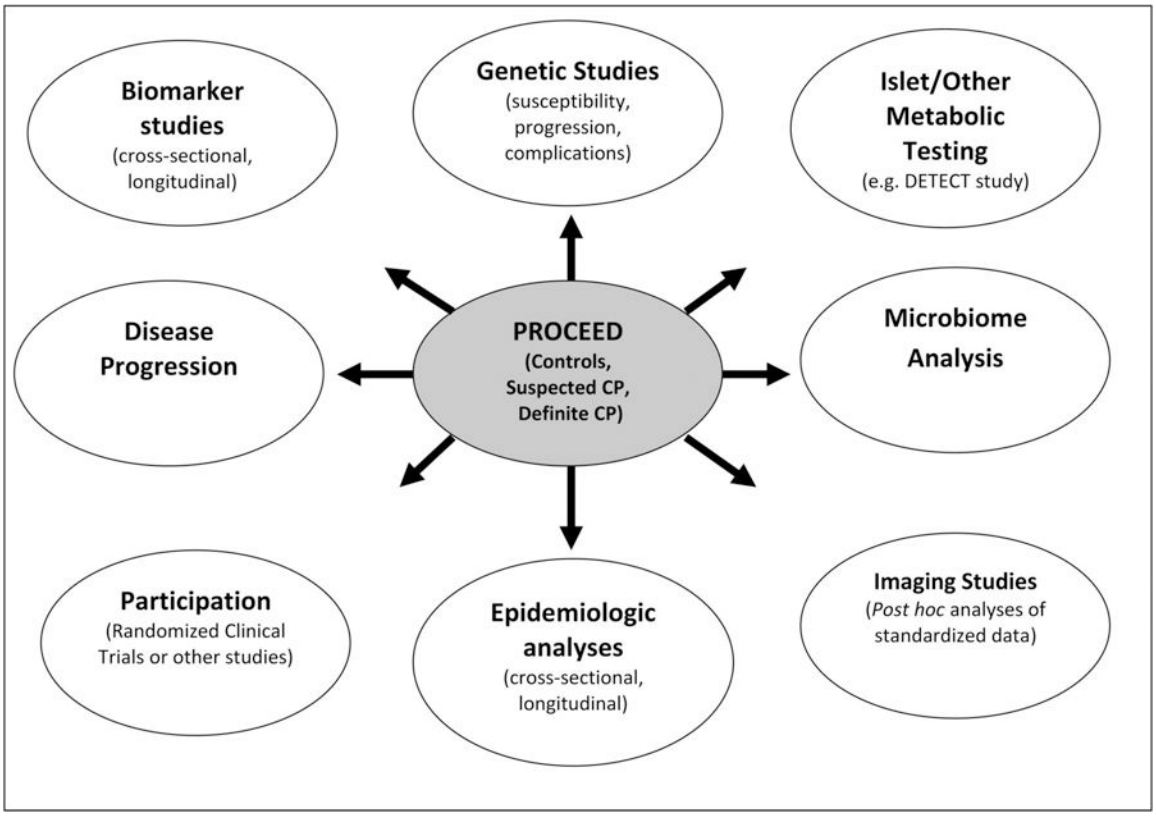

FIGURE 1.

Representative studies and analyses that will be conducted from the PROCEED cohort and biorepository.

TABLE 1.

Inclusion Criteria and Sample Size for PROCEED[*†]

	Controls (GREEN Zone)	Suspected Chronic Pancreatitis (YELLOW Zone)			
	Chronic Abdominal Pain of Suspected Pancreatic Origin[‡]	Indeterminate CP	AP (one attack)[§]	RAP[§]	Definite Chronic Pancreatitis (RED Zone) [§‖]
Sample size	250	165	165	330	660
Pancreatic fluid collection[¶]	100	83	83	165	45
Inclusion criteria (all subjects)	● Sign an informed consent indicating that they are aware of the investigational nature of this study and willing to undergo study interventions, and authorizing the use of their protected health information for research purposes ● Meet one set of group-specific inclusion criteria ● Must be ≥18 years old and ≤75 years at the time of enrollment				
Inclusion criteria (Group specific - subject should meet all criteria, unless otherwise specified)	● Pancreatic-type abdominal pain of ≥3 months duration[#] ● No history of AP or CP ● Normal CT scan and MRI/MRCP[**] ● No prior endoscopic sphincterotomy or pancreatic surgery	● Pancreatic-type abdominal pain of ≥3 months duration[#] ● No history of AP or CP ● Cambridge grade 1–2 on CT scan or MRI/MRCP[**] ● No prior endoscopic sphincterotomy or pancreatic surgery	● One documented attack of AP in the preceding 18 months[††‡‡] ● Imaging evidence of AP on CT scan or MRI/MRCP ● Cambridge grade <III on CT scan and/or MRI/MRCP[**] ● Pancreatic necrosis, if present, is <50%[§§] ● No prior pancreatic surgery[¶¶]	● Two or more attacks of AP[††‡‡‖‖] ● Cambridge grade < III on CT scan and/or MRI/MRCP[**] ● No prior pancreatic surgery[¶¶]	● Presence of unequivocal CP, i.e. Cambridge grade 3 or 4, and/or parenchymal and/or ductal calcifications by CT scan or MRI/MRCP,[##] OR ● Pancreatic histology diagnostic of CP (including findings of fibrosis [Ammann's ≥6], chronic inflammation, and acinar loss)

[*] This table does not describe the No Pancreas Disease Controls (GREEN I) group. Enrollment for this group will begin after plans are finalized and approved by the Data Safety and Monitoring Board.

[†] Modifications made to inclusion criteria (after ~15% recruitment): Age criteria adjusted from 65 to 75 years; duration of abdominal pain requirement for chronic abdominal pain of suspected pancreatic origin and indeterminate CP groups reduced from 6 to 3 months; for AP group, requirement of abdominal pain of ≥3 months removed, and enrollment requirement for imaging changes included; for AP and RAP groups, endotherapy performed prior to enrollment is acceptable as mentioned below; time frame for imaging adjusted from 12 to 24 months before enrollment.

[‡] GREEN II subgroup

[§] Subjects in yellow and red zone will be recruited at least 1 month (discharge from hospital, *if applicable*) after an episode of AP to avoid confounding of biomarkers in biological samples.

[‖] No more than 40% of definite CP patients will be diabetic at enrollment.

[¶] Pancreatic fluid will be collected from the duodenum during EGD or EUS for 20 minutes for biomarker analyses, and up to 60 minutes for clinical purposes after intravenous secretin injection.

[#] Patient referred to a pancreas or gastroenterology clinic or hospitalized for evaluation of unexplained upper abdominal pain for which a pancreatic origin is considered in the differential diagnosis. Pancreatic-type pain is defined as epigastric pain that is often constant, often worsens post-prandially, and may radiate to the back. This can be associated with serum lipase and/or amylase elevations that do not meet the threshold for diagnosis of AP, i.e. <3-fold above the upper limit of normal.

[**] CT scan and MRI/MRCP at baseline will be performed ≤24 months prior to enrollment or within 6 months after study enrollment. CT and MRI scans will be intravenous contrast-enhanced and MRCP with secretin (a non-contrast MRI and MRCP without secretin prior to enrollment is acceptable).

[††] AP is defined as upper abdominal pain together with elevation of serum amylase and/or lipase ≥3-fold above the upper limit of normal, and/or features of AP on cross-sectional imaging.

[‡‡] Etiology of AP should not be attributable to gallstones (suspected or definite), medications, trauma or autoimmune pancreatitis.

[§§] A minimum of 30% patients in the AP group will have pancreatic necrosis.

[¶¶] Prior endoscopic retrograde cholangiopancreatography (ERCP) or endotherapy in patients in AP or RAP is acceptable if performed after the onset of pancreatitis for treatment of symptoms or complications, or to prevent further attacks of pancreatitis.

[‖‖] Separated by at least 1 month, with complete symptom resolution between the episodes.

[##] A non-contrast CT or MRI/MRCP documenting Cambridge 3 or 4 stage is acceptable for enrollment as Definite CP.

AP indicates acute pancreatitis; CP, chronic pancreatitis; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; RAP, recurrent acute pancreatitis.

TABLE 2.

Exclusion Criteria for PROCEED*

1. History of autoimmune or traumatic pancreatitis, or sentinel attack of acute necrotizing pancreatitis which results in suspected disconnected duct syndrome.
2. Primary pancreatic tumors - pancreatic ductal adenocarcinoma, suspected cystic neoplasm (>1 centimeters in size or main duct involvement), neuroendocrine tumors, and other uncommon tumors.
3. Pancreatic metastasis from other malignancies.
4. History of solid organ transplant, HIV/AIDS.
5. Known isolated exocrine pancreatic insufficiency (e.g. in the absence of any eligible inclusion criteria).
6. Medical or psychiatric illnesses or ongoing substance abuse that in the investigator's opinion would compromise the subjects' ability to tolerate study interventions or participate in longitudinal follow up.
7. Patients with known abnormal creatinine (glomerular filtration rate <30) or renal failure (applies to patients in Chronic Abdominal Pain of Suspected Pancreatitis Origin [Green II group] and Yellow subcohort).
8. Failure to agree for longitudinal follow-up.
9. Known Pregnancy. All participants of childbearing potential, except if post-menopausal [i.e. no menses for ≥2 years] or had a hysterectomy, bilateral tubal ligation/clip (surgical sterilization) or surgical removal of both the ovaries), must have a negative urine or serum B-HCG pregnancy test documented within 2 days prior to any endoscopic or radiologic procedures done for research purposes. Any standard of care tests will follow institutional policies regarding pregnancy test.
10. Currently incarcerated.
11. Inability to get MRI/MRCP (in patients in Chronic Abdominal Pain of Suspected Pancreatitis Origin [Green II group] and Yellow subcohort).

* Except No Pancreas Disease Controls (GREEN I) group

TABLE 3.

Summary of Baseline Data Collection for PROCEED[*†]

Patient CRF

- Demographics, socioeconomic status
- PROMIS Global health instrument
- PROMIS-29 instrument (assesses anxiety, depression, fatigue, emotional health)
- PROMIS nociceptive and neuropathic pain instruments
- Diet and lifestyle[‡]

Coordinator CRF

- Abdominal pain (presence, severity and pattern, frequency and duration of episodic pain)
- Disability, days of work/school missed in past 30 days
- Hospitalizations and emergency rooms visits related to abdominal pain or pancreatitis (past 12 months and lifetime)
- Exposure to tobacco products (cigarette smoking, cigar/pipe, chewing), passive smoking
- Alcohol consumption: Ever, current, during maximum drinking period in life, TWEAK questions (*At-Risk* drinking)
- Other substance use
- Enteral and parenteral nutrition in the preceding year
- Biospecimen collection

Physician CRF

- Serum pancreatic enzyme elevation(s) (Green II group and Indeterminate CP)
- AP and RAP: Age at first attack, number, severity
- CP: Symptoms, age at presentation and diagnosis, detection of calcifications
- Physician-defined etiology
- Risk factors (TIGAR-O classification)
- Details of endoscopic therapy and surgery (including cholecystectomy)
- Medication use (PERT, NSAIDS, aspirin, narcotics, neuromodulating agents, diabetic medications, vitamin and antioxidants, medications for osteoporosis, calcium, proton pump inhibitors, statin)
- Complications and other treatments (e.g. celiac plexus block, percutaneous drainage of fluid collections, pseudoaneurysm, etc.) not captured in previous sections
- Personal history, Charlson co-morbidity index
- Relevant Family history
- Findings on laboratory tests, EUS, CT scan and MRI/MRCP
- Diabetes, exocrine pancreatic function, bone health assessment (DEXA scan)

[*] Except No Pancreas Disease Control (GREEN I) group.

[†] Modifications made to CRFs after ~15% recruitment: TWEAK questions replaced AUDIT (TWEAK will be administered to previously enrolled subjects during follow-up visit); abdominal pain and disability section moved to coordinator CRF; questions on enteral and parenteral nutrition added

[‡] For microbiome studies

AP indicates acute pancreatitis; CP, chronic pancreatitis; CRF, case report form; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; NSAIDS, non-steroidal anti-inflammatory agents; PERT, pancreatic enzyme replacement therapy; PROMIS, *Patient-Reported Outcomes Measurement Information System;* RAP, recurrent acute pancreatitis

TABLE 4.

Study Activities at Baseline Assessment and During Follow-up for the PROCEED Groups [*]

		Follow up (±3 months)			
	Baseline	**Year 1**	**Year 2**	**Year 3**	**Year 4**
All Subjects					
Participant CRF	X	X	X	X	X
Coordinator CRF	X	X	X	X	X
Physician CRF	X	X	X	X	X
Chronic Upper Abdominal Pain of Suspected Pancreatic Origin (GREEN II Group)					
MRI and MRCP [†]	X				
CT scan abdomen [†]	X				
EUS or EGD with pancreatic fluid collection [‡]	X				
Biospecimen collection: blood, urine, saliva, stool	X				
Suspected Chronic Pancreatitis (YELLOW Subcohort)					
MRI and MRCP [†]	X	X		X	
CT Scan abdomen [†]	X		X		X
EUS or EGD with pancreatic fluid collection [‡]	X				
Biospecimens: blood & urine	X	X	X	X	X
Biospecimens: saliva & stool	X				
Fecal elastase, HbA1c, blood glucose, *if indicated* [§]	X	X	X	X	X
Definite Chronic Pancreatitis (RED Subcohort)					
CT scan abdomen and/or MRI/MRCP	X				
CT scan abdomen [†]		X		X	
EUS or EGD w/ pancreatic fluid collection [‡]	X				
Biospecimens: blood & urine	X	X	X	X	X
Biospecimens: saliva & stool	X				
Fecal elastase, HbA1c, blood glucose, *if indicated* [§]	X	X	X	X	X
DEXA scan [‖]	X			X	

Follow-up plans will be similar beyond year 4.

[*] Except No Pancreas Disease Control (GREEN I Group).

[†] Baseline CT and MRI/MRCP will be performed ≤24 months prior to enrollment OR within 6 months after study enrollment. Follow-up imaging will be performed within 3 months of follow-up visit. A high-quality imaging study performed within 6 months prior to follow-up will be acceptable. Alternate imaging of suitable quality performed for clinical purposes during follow-up is acceptable (e.g. CT at year one follow-up instead of MRI/MRCP in Yellow subcohort). During follow-up, a non-contrast imaging is acceptable if subject cannot receive contrast, and a CT scan will replace MRI/MRCP if such imaging is precluded, e.g. due to joint replacement, etc.

[‡] After enrollment or during follow-up.

[§] Diabetes will be defined by American Diabetes Association (ADA) criteria: Abnormal values on two of the following tests or two abnormal values of the same test: a) Fasting blood sugar ≥126 mg/dl; b) HbA1c ≥6.5%; c) Random blood glucose ≥200 mg/dl OR use of anti-diabetic medications; exocrine insufficiency at baseline will be defined by a clinical history of steatorrhea or fecal elastase of <100 mcg/gram stool or quantitative fecal

fat of >7 grams per day on a 100 grams fat diet; and during follow-up by a fecal elastase of <100 mcg/gram stool. Laboratory testing consistent with diabetes at anytime before or normal or one abnormal testing for diabetes performed within 6 months before or within 3 months after enrollment is acceptable. Laboratory test results consistent with exocrine insufficiency at any time before, or normal tests within 12 months prior to enrollment, and fecal elastase test results within 3 months after enrollment is acceptable. Testing for diabetes or fecal elastase performed for clinical purposes within 6 months of follow-up visits is acceptable.

// DEXA will be performed at baseline if not completed in the preceding 3 years and will be completed at 3 yearly intervals during follow-up.

CRF indicates case report form; CT scan, computed tomography; DEXA, dual-energy x-ray absorptiometry; EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; PERT, pancreatic enzyme replacement therapy

TABLE 5.

Summary of Follow-up Data Collection for PROCEED

Patient CRF
● Demographics, socioeconomic, employment and marital status
● PROMIS instruments: Global health; PROMIS-29; nociceptive and neuropathic pain
Coordinator CRF
● Pain experience (presence, severity and pattern, frequency and duration of episodic pain)
● Disability – continuing or new
● Days of work/school missed in past 30 days
● Hospitalizations and emergency rooms visits related to abdominal pain or pancreatitis since last visit
● Current exposure to tobacco products (cigarette smoking, cigar/pipe, chewing, e-cigarettes)
● Current alcohol consumption
● Current exposure to other substances
● Use of enteral and parenteral nutrition in the preceding year
● Biospecimen collection
Physician CRF
● Transition to another study group (e.g. progression from YELLOW to RED zone)
● Details of AP and RAP (number, severity) since last visit
● Details of CP diagnosis, detection of calcifications
● Physician-defined etiology, *if applicable in relevant groups (GREEN II or indeterminate CP)*
● Genetic testing results, *if performed*
● Details of endoscopic therapy and surgery (including cholecystectomy) since last visit
● Medication use (similar to baseline; continuing or new)
● Complications and treatment of CP (e.g. celiac plexus block, percutaneous drainage of fluid collections, pseudoaneurysm, etc.) not captured in previous sections since last visit
● Development of pancreatic cancer, other pancreatic tumors, other cancers
● Other relevant personal and family history
● Findings on laboratory tests, EUS, CT scan and MRI/MRCP
● Diabetes, Exocrine pancreatic dysfunction, bone health assessment (DEXA scan), *if indicated*
Death Notification CRF
● Vital statistics
● Cause of death

AP indicates acute pancreatitis; CP, chronic pancreatitis; CRF, case report form; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; RAP, recurrent acute pancreatitis

TABLE 6.

Key Outcome Measures for PROCEED

PROCEED Subcohort(s) for Comparison	Outcomes (Category)	Primary Outcomes
Primary Objectives		
Suspected CP	Disease progression	● Transition to Definite CP: Cambridge 3–4 changes on CT scan and/or MRI/MRCP during follow up
Definite CP	Disease progression	● Diagnosis of new-onset diabetes (ADA criteria) ● Diagnosis of exocrine pancreatic dysfunction (fecal elastase)
Controls Suspected CP Definite CP	Predictive ability of biomarkers for diagnosis or prognosis	● Distribution of candidate biomarkers ● Disease progression during follow-up (as above)
Secondary Objectives (selected) *		
Suspected CP Definite CP	Pain	● Presence, severity, temporal nature of pain, medication use ● Pain type - Neuropathic, Nociceptive
Suspected CP Definite CP	Disability and health-care utilization	● Days of work/school missed ● Disability ● Hospitalizations, emergency room visits
Suspected CP Definite CP	Health-related quality of life	● PROMIS Global health instrument ● PROMIS 29 instrument
Controls Suspected CP Definite CP	Morphological progression of disease	● Qualitative and quantitative changes on CT scan and MRI/MRCP during follow-up
Definite CP	Bone health	● DEXA scan results ● Calcium, vitamin D ● Medication use
Definite CP	Pancreatic cancer	● Diagnosis of pancreatic cancer during follow-up
Controls Suspected CP Definite CP	Susceptibility and progression of CP	● Genetic test results

* Only selected measures shown; many additional analyses will also be feasible

CP indicates chronic pancreatitis; CT, computed tomography; DEXA, dual-energy x-ray absorptiometry; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography