Individualized Pain Treatment in Chronic Pancreatitis (INPAIN)

An International, Multicenter, Investigator-Initiated, Prospective, Cohort Study

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Objectives: Pain is the foremost complication of chronic pancreatitis (CP), affecting about 70% of patients. However, the pathophysiological understanding and management of CP-related pain are complex, likely as patients have diverse "pain phenotypes" responding differently to treatment. This study aims to develop a bedside test panel to identify distinct pain phenotypes, investigate the temporal evolution, and determine whether they can be used to predict treatment response.

Methods: The INPAIN study is an international, multicenter, observational, longitudinal cohort study consisted of 4 substudies. The studies will prospectively enroll 400 CP patients (50 without pain and 350 with pain) and 50 control subjects, conducting biannual observations for 4 years. The test panel is consisted of comprehensive subjective and objective assessment parameters. Statistical analysis strategies differ across the substudies. A model to predict treatment efficacy will be developed using various machine learning techniques, including an artificial intelligence approach, with internal cross-validation. Trajectories in pain parameters will be characterized by graphical analysis and mixed effect models.

Discussion: The INPAIN study aims to comprehensively understand pain in CP through a test panel developed for routine clinical use. This tool has the potential to personalize treatments, improve clinical practice, enhance patient care, improve quality of life, and minimize treatment side effects.

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CP is a relatively common disease, with a prevalence of 150 per 100,000 individuals worldwide.[1,2] It is associated with high morbidity and mortality, and the foremost complication is pain, which affects about 70% of patients.[3,4] Pain associated with CP is the leading contributor to reduced quality of life and an increased risk of hospitalization.[2]

The origin of pain in CP is a complex interplay between several factors where the most important are likely chronic inflammation and nerve damage. This interaction affects central pain processing by increasing neuronal sensitization and impairing modulatory pathways.[5–7] The assessment, characterization, and treatment of CP-related pain have significant challenges. Patient-reported outcomes, morphological changes in the pancreas, and assessment of pancreatic function have all poor correlation with the patient's experience of pain.[5] The key challenge in pain assessment lies in distinguishing peripheral visceral/pancreatic pain from pain associated with central nervous system alterations.

The response to pain-relieving therapy is complicated and depends on various individual factors.[8] The most important predictor for treatment response is whether the pain is predominantly of peripheral (increased firing in pancreatic nerves) or central (sensitized brain pathways) origin.[9] It is difficult to determine whether peripheral or central sensitization is present.[10] Recent advancements from our study group have shown that the pain system in individual CP patients can be explored (degree and spread of central sensitization and control mechanisms) with bedside quantitative sensory testing (P-QST).[10] Additionally, we observed that P-QST can predict responses to pain-relieving therapy for CP to some extent.[11] However, P-QST assesses only a part of the pain response.[10] Achieving a comprehensive patient phenotype requires additional data, including affective, cognitive, and social factors in the pain experience.[10] Furthermore, autonomic responses, brain networks, structural changes in the pancreas, and different metabolomic and genetic factors are needed to fully characterize the pain system for individualized patients[12] – Figure 1. The "Individualized Pain Treatment in Chronic Pancreatitis" (INPAIN) study aims to develop a bedside test panel to identify distinct pain

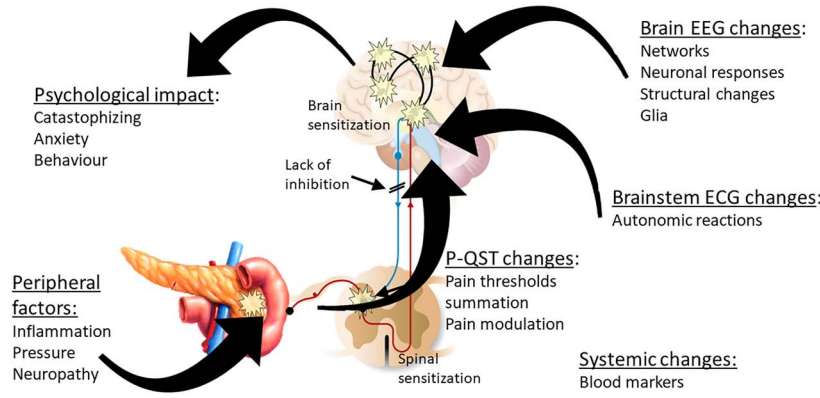

FIGURE 1. Schematic illustration of the different pain components and their consequences in chronic pancreatitis.

phenotypes using subjective and objective features and to use these in personalized treatment.

HYPOTHESIS AND OBJECTIVES

The INPAIN study aims to develop a bedside test panel using a combination of features as depicted in Table 1. The INPAIN study is consisted of four substudies with the following objectives:

–Substudy 1: Development and optimization of the technical quality, reliability, and validity of a bedside test panel and associated questionnaires for pain assessment in CP;
–Substudy 2: Characterization of the pain pathophysiology in CP;
–Substudy 3: Development of machine learning–based prediction models for the prediction of treatment outcomes of pain-relieving therapies in CP;
–Substudy 4: To characterize the temporal evolution of pain and its psychosocial consequences in CP.

Table 1 provides an overview of the studies. The perspective is to reduce pain with minimal adverse effects to treatment, leading to improved quality of life. Socio-economically, the trial can potentially reduce the cost of treatment, sick leave, and

TABLE 1. Overview of Studies Part of the Individualized Pain Treatment in Chronic Pancreatitis (INPAIN) Study

	INPAIN Substudy 1	INPAIN Substudy 2	INPAIN Substudy 3	INPAIN Substudy 4
Purpose	Technical development	Characterization of pain pathophysiology	Prediction of treatment response to pain-relieving therapies	Characterization of the temporal evolution of pain
Design	Cross-sectional	Cross-sectional	Longitudinally for 3 months	Longitudinally, biyearly for 4 years
Sample size	NA (study dependent)	Total, n = 150 Controls, n = 50 Painful CP, n = 50 Painless CP, n = 50	n = 200 painful CP	n = 400 CP
Test panel	NA	Advanced test panel†	Advanced test panel†	Basic test panel*
Outcomes	Explorative	Explorative	Primary: – SF-COMPAT Secondary: – BPI – HADS – PCS – PSQI – EORTC-QLQ-C30 – PGIC – P-QST	– SF-COMPAT – BPI – HADS – PCS – PSQI – EORTC-QLQ-C30 – P-QST
Statistical analysis	Descriptive statistics and groupwise comparisons	Descriptive statistics, groupwise comparisons, and machine learning	Prediction models based on machine learning	Mixed-effect models and graphical analyses

*The basic test panel is consisted of six questionnaires (the SF-COMPAT, BPI, HADS, PCS, PSQI, EORTC-QLQ-C30), P-QST, blood samples, and imaging (computed tomography).

†The advanced test panel includes all elements of the basic test panel, along with neurophysiological measurements (combined electrocardiography and electroencephalography).

BPI indicates Brie Pain Inventory; CP, chronic pancreatitis; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life; HADS, Hospital Anxiety and Depression Scale; NA, not applicable; P-QST, quantitative sensory testing for pain in chronic pancreatitis; PCS, Pain Catastrophizing Scale; PGIC, Patient's Global Impression of Change; PSQI, Pittsburgh Sleep Quality Index; SF-COMPAT, Short-Form Comprehensive Pain Assessment Tool.

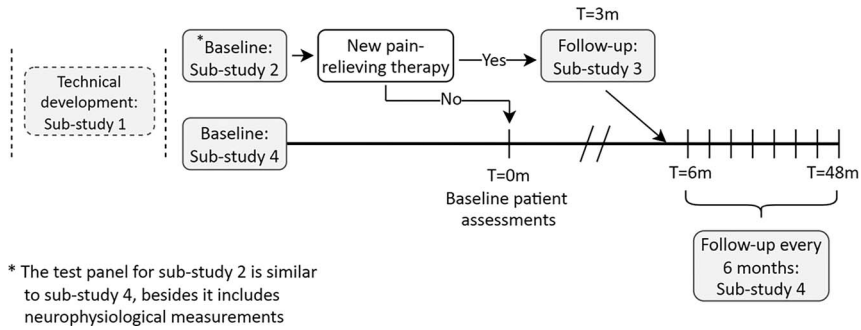

FIGURE 2. Study flow diagram of the four INPAIN substudies over time (T).

retirement. The INPAIN study will foster a generation of innovative hypotheses and establish new standards of care for CP. Finally, the techniques may lead to spin-offs into other diseases associated with pain and increase our general understanding of chronic pain.

Study Design

The INPAIN study is an international, multicenter, investigator-initiated, observational, longitudinal cohort study that seeks to better understand and characterize pain in patients with CP and predict the most sufficient pain-relieving therapies. The study flow of the INPAIN study is illustrated in Figure 2. Subjects will undergo baseline assessments using either a basic or advanced test panel, where the selection is based on the capabilities of the enrollment institutions. The advanced test panel developed in substudy 1 is utilized in the pain phenotyping cross-sectional study (substudy 2) and the longitudinal prediction study (substudy 3). The basic test panel is used for the longitudinal study (substudy 4).

Study Organization

The INPAIN study is part of the International Pancreatic Pain Consortium. The participating institutions are reported

TABLE 2. Collaborating Institutions of the International Pancreatic Pain Consortium and Their Participation in the Individualized Pain Treatment in Chronic Pancreatitis (INPAIN) Substudies

Institution	INPAIN Substudy 1	INPAIN Substudy 2	INPAIN Substudy 3	INPAIN Substudy 4
Aalborg University Hospital, Aalborg, Denmark	X	X	X	X
John's Hopkins Medicine, Baltimore, MD	X	X	X	X
Asian Institute of Gastroenterology, Hyderabad, India	X	X	X	X
All-India Institute of Medical Science, New Delhi, India	X	X	X	X
University of Pittsburgh Medical Center, Pittsburgh, PA	X	X	X	X
Semmelweis University, Budapest, Hungary	X	X	X	X
New Zealand College of Chiropractic, Auckland, New Zealand	X	X	X	X
Hospital General Universitario Dr. Balmis, Alicante, Spain		X	X	X
Oslo University Hospital, Oslo, Norway		X	X	X
Universitäts Klinikum Heidelberg, Heidelberg, Germany		X	X	X
Methodist Health System, Dallas, TX				X
Indiana University Health, Indianapolis, IN				X
Brigham and Women's Hospital, Boston, MA				X
University of Auckland, Auckland, New Zealand	X			
Cincinnati Children's, Cincinnati, OH*		X		X

*The INPAIN study is used as a reference for children with chronic pancreatitis.

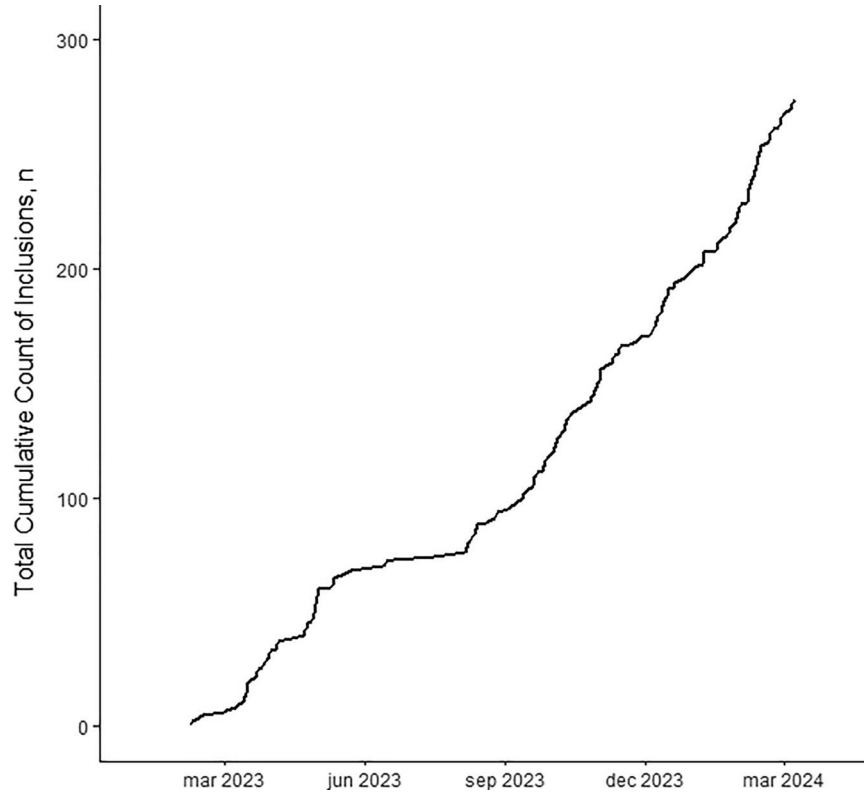

FIGURE 3. The Total Cumulative count of included participants in the INPAIN study.

in Table 2.[9] All the institutions have extensive experience in CP management. Patients with CP will be identified and enrolled at the outpatient clinic at these institutions. Patient enrollment started in March 2023, and as of March 2024, 276 subjects had completed the baseline assessment; see Figure 3.

Study Subjects

The INPAIN study will enroll definitive CP patients,[13] categorized into three main subgroups: (1) painful CP patients, (2) painless CP patients, and (3) control subjects. Inclusion and exclusion criteria are described in detail in Tables 3 and 4. These are designed to mirror real-world clinical practices to evaluate the temporal evolution of pain in CP, hence the permissive inclusion and exclusion criteria.

Painful CP patients include subjects with a definitive CP diagnosis according to the M-ANNHEIM criteria with chronic abdominal pain.[13] Painful CP is further subcategorized into current painful CP (pain at consultation) and previous painful CP (no pain at consultation) to differentiate between previous painful CP and painless CP patients.

Painless CP patients include subjects with a definitive CP diagnosis, with the absence of abdominal pain compatible with a pancreatic origin throughout the patient's life.

Controls include subjects with no pancreas-associated diseases, chronic painful disorder(s), or treatment with analgesics (for the last 3 months). Intermittent use or over-the-counter analgesics, such as paracetamol/acetaminophen or nonsteroid anti-inflammatory drugs, is not an exclusion criterion. Data from these subjects will help to identify and inform the distribution of subjective/objective assessment parameters in a nonpancreatic and nonchronic pain disease(s) group for the cross-sectional analyses in substudy 2.

Study Procedures

Table 5 outlines the data to be collected in the case report form (CRF) for each subject at baseline and follow-up. The CRF was developed by a working group within the International Pancreatic Pain Consortium.[9] Subjective pain assessment parameters include the following questionnaires: the Short-Form Comprehensive Pain Assessment Tool (SF-COMPAT),[14] Brief Pain Inventory (BPI),[15] Hospital Anxiety and Depression Scale (HADS),[16,17] Pain Catastrophizing Scale (PCS),[18] Pittsburgh Sleep Quality Index (PSQI),[19] and the European Organization For Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30).[20,21] All questionnaires are validated in English, Spanish, and Danish. SF-COMPAT will also be validated in Telugu, Bengali, and Hindi. Trained study personnel will help with potential language barriers.

Objective pain assessment parameters include P-QST, neurophysiological measurements, imaging, and blood samples. Our study group has widely used and validated the P-QST and neurophysiological measurements for use in CP patients.[9,22–24]

As part of the routine clinical diagnostic workup, most patients with painful CP have a computed tomography (CT) scan of the pancreas to identify complications such as pancreatic duct stones or strictures and pseudocysts amendable to endoscopic or surgical interventions. Advanced image analyses based on radiomic features have shown that they can be used to differentiate between stages of the disease and will be integrated into the model.[25] The CT scans from all sites will be analyzed by specialists at the radiological department at Aalborg University Hospital.

Blood samples (1 × 10 mL ethylenediaminetetraacetic acid [EDTA] plasma and 1 × 10 mL serum) will be drawn at baseline. Blood samples will be analyzed at the local institutions; however, methods are standardized to allow comparability.

TABLE 3. Inclusion Criteria of Patients With Chronic Pancreatitis and Controls

	Chronic Pancreatitis	
Inclusion criteria (general)	• Definitive diagnosis of chronic pancreatitis with a typical clinical history according to the M-ANNHEIM criteria (13) • ≥18 y of age • The patients must be able to read and understand the consent forms • Patients should be capable of complying with scheduled visits and assessment procedures; hence, follow specific instructions	
	Painful Chronic Pancreatitis	**Painless Chronic Pancreatitis**
Inclusion criteria (group specific)	• Chronic abdominal pain characteristics for CP with a mean pain intensity >3 on the 0–10 VAS scale and meet the criteria for chronic pain (pain ≥3 days per week for ≥3 months)	• Absence of abdominal pain compatible with pancreatic pain throughout the patient's life
Inclusion criteria (study specific, substudy 3)	• Patients starting new pain-relieving therapy (medical/endoscopic/surgical) at baseline assessment or within the first 2 weeks of enrollment; titration of pain medication is allowed during the study period, but no additional new treatments can be started • CP patients with current pain, as defined above	
	Controls	
Inclusion criteria (controls)	• No pancreas-associated diseases • No chronic painful disorder(s) or treatment with analgesics for the last 3 months (intermittent use or over-the-counter analgesics, such as paracetamol or nonsteroid anti-inflammatory drugs, is not an exclusion criterion)	

VAS indicates visual analog scale.

FOLLOW-UP ASSESSMENT PARAMETERS

Subjects enrolled in the longitudinal prediction study (substudy 3) are scheduled for a new treatment. Three months after enrollment, changes in pain characteristics will be assessed using subjective and objective pain assessment parameters collected at baseline and follow-up (including the Patient's Global Impression of Change[26]). The primary goal of the longitudinal follow-up study (substudy 4) is to investigate the temporal evolution of pain and disease progression in CP. Subjects will be followed up every 6 months for 4 years, as potential alterations in pain patterns require an extended period to manifest.[27] Changes in pain characteristics will be captured utilizing subjective and objective pain assessment parameters collected from baseline and biannually for 4 years.

Assessment Parameters

Table 6 summarizes the patient and disease characteristics registered at baseline. Table 7 provides a comprehensive overview of the subjective and objective pain assessment parameters.

Clinical and technical data quality assurance liaisons at Aalborg University Hospital will ensure data quality and consistency across sites.

OUTCOME

Primary and secondary outcomes for the four substudies are outlined in Table 1. The endpoints of substudy 1 and 2 are explorative in nature. The primary endpoint of substudy 3 is a change in the mean SF-COMPAT score observed from baseline to 3 months after initiation of a new pain-relieving therapy. CP is a highly heterogeneous disease, and pain is very complex to assess[28,29]; therefore, sensitive parameters to assess pain in CP and CP progression may be characterized by multiple outcomes for substudy 4.

STATISTICAL CONSIDERATIONS

The statistical analysis plan will be thoroughly revised and finalized before any statistical analysis is initiated to ensure transparency and accuracy. The following sections outline the general statistical principles guiding the study, followed by specific plans for each substudy. Appropriate statistical methods will be thoroughly considered to account for nonignorable missingness, missing data, and dropout.[30] To control for the heterogeneity between patients/disease characteristics from different countries, we will aspire to an optimal balance between Asian and Caucasian sites.

TABLE 4. Exclusion Criteria of Patients With Chronic Pancreatitis and Controls

- Previous major abdominal surgery, where scars and nerve lesions can interfere with the P-QST procedures
- Severe chronic pain due to other diseases
- Substudy 3: Patients who need a change of pain-relieving therapy in the 3-month observation period are excluded and transitioned into substudy 4

P-QST indicates quantitative sensory testing for pain in chronic pancreatitis.

TABLE 5. Study Activities at Baseline Assessment and Follow-up

	Baseline Test Panel		Follow-up				
	Basic	Advanced	3 Months	6 Months	12 Months	18 Months	24 Months
Subjective parameters							
Patient and disease characteristics	X	X					
SF-COMPAT	X	X	X	X	X	X	X
BPI	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X
PCS	X	X	X	X	X	X	X
PSQI	X	X	X	X	X	X	X
EORTC-QLQ-C30	X	X	X	X	X	X	X
PGIC			X				
Objective parameters							
P-QST	X	X	X	X	X	X	X
Blood samples	X	X					
CT scans*†	X	X					
Neurophysiological measurements		X					

*As part of the routine clinical diagnostic workup, most patients with painful CP have a computed tomography (CT) scan of the pancreas to identify complications such as pancreatic duct stones or strictures and pseudocysts amendable to endoscopic or surgical interventions.

†Not applicable at all sites.

BPI indicates Brief Pain Inventory; CT, computed tomography; EORTC-QLQ-C30, European Organization For Research and Treatment of Cancer Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PGIC, Patient's Global Impression of Change; PSQI, Pittsburgh Sleep Quality Index; P-QST, quantitative sensory testing for pain in CP; SF-COMPAT, Short-Form Comprehensive Pain Assessment Tool.

TABLE 6. Summary of Baseline Data Collection for the Individualized Treatment for Pain in Chronic Pancreatitis (INPAIN) Study

Patient Characteristics
- Age
- Sex
- Anthropometrics
- Race
- Ethnicity
- Alcohol consumption
- Smoking history
- Comorbidities, according to the Charlson Comorbidity Index[28]
- Socioeconomic status

Disease Characteristics
- Symptoms
- Age at diagnosis and duration
- History of acute pancreatitis
- Risk factors (TIGAR-O version 2 short-form classification)[29]
- Treating physician-defined etiology
- Predisposition to pancreatic diseases
- Metabolic complications
- Details of treatment:
  - Analgesics: weak analgesics (paracetamol/acetaminophen and/or nonsteroid anti-inflammatory drugs), weak opioids (eg, tramadol), strong opioids (eg, morphine), adjuvant analgesics (eg, gabapentinoids antidepressants, and/or cannabinoids), and/or antioxidants
  - Endoscopic pancreatic duct decompression
  - Pancreatic surgery
- Scheduled for a new pain-relieving therapy

Substudies 1 and 2 (Cross-sectional)

The outcomes of substudy 1 and 2 are explorative in nature. Descriptive statistics and groupwise comparisons will be used as appropriate. Given the exploratory nature of these substudies, conducting a power calculation is not deemed feasible. However, for substudy 2, a minimum of 150 participants (50 painful CP patients, 50 painless CP patients, and 50 control subjects) was decided by a working group of the International Pancreatic Pain Consortium based on experience from previous studies with similar sample sizes where relevant group differences were observed.[9,10,17,22,29,31]

Substudy 3 (Prediction)

The primary endpoint of substudy 3 is a change in the mean SF-COMPAT score from baseline to 3 months after initiation of a new pain-relieving therapy, where a reduction of 30% will be considered a clinically relevant pain-relieving effect and used to define a treatment responder. This information is used to train AI models and used as a cutoff point for effectful pain treatment. The predictive model for substudy 3 will be trained using various machine learning techniques (eg, support vector machine, decision tree, random forest). Deep learning algorithms will also be included as part of an AI-driven approach. Internal cross-validation will be employed to optimize model parameters and ensure high generalizability across diverse patient populations. A meaningful test training split will be employed, depending on the data set. Feature selection techniques will be applied to identify the most informative predictors. This will aid in a better understanding of the variables that predict an optimal treatment strategy for pain. Using the best features, a prediction model will recommend the best treatment for a given patient based on prior knowledge of baseline characteristics and previous treatment outcomes for a given modality of care. This approach will facilitate the prediction of treatment response and aid in identifying personalized therapeutic strategies. As treatment modalities may vary across different

TABLE 7. Methodology of Pain Assessment Subjectively and Objectively

Subjective Pain Assessment Parameters		Method	Assessment Parameters	Substudy
SF-COMPAT[14]	Relevant aspects of pain in CP, based on five pain dimensions: 1) Pain severity 2) Pain pattern 3) Factors provoking pain 4) Widespread pain 5) Qualitative pain describing	A total score based on the pain dimension scores will be generated	2, 3, 4	
BPI[15]	Subjective pain intensity and interference in chronic pain, encompassing: 1) Pain localization 2) Treatment/medication details	It comprises 11 measures rated on a scale from 0 to 10, embracing pain within the last 24 hours and daily functions. This results in a pain severity and interference score.	2, 3, 4	
HADS[16]	Assesses the severity of anxiety/depression in individuals with CP	It encompasses 14 measurement points rated on a 4-point Likert scale, calculating 2 subscores: one for anxiety and one for depression. A score of >7 is considered abnormal.*	2, 3, 4	
PCS[18]	It encompasses CP patients' catastrophic thoughts regarding pain. Further assessing three types of cognition, each independently clinically significant: 1) Rumination 2) Magnification 3) Helplessness	It is consisted of a total score, and each type of cognition is assessed independently, where the following is clinically significant: Rumination: ≥11 Magnification: ≥5 Helplessness: ≥13	2, 3, 4	
PSQI[19]	Assesses the patient's sleep-related difficulties and overall sleep quality	It is consisted of 19 individual aspects of sleep, categorized into seven components, ultimately generating a single global PSQI score	2, 3, 4	
EORTC-QLQ-C30[20,21]	Assesses patients' quality of life as well as physical and social function as an overall measure of patient-reported outcomes	It comprises 30 measurement points, generating single-item and multi-item scores on a scale from 0 to 100	2, 3, 4	
PGIC[26]	Assesses the experiences of treatment change	11-point rating scale	3	
Objective Pain Assessment Parameters				
P-QST[30†]		Assesses sensitization of pain processing from the pancreas to the central nervous system	Categories pain into three pain phenotypes: 1) Predominantly 2) Segmental 3) Widespread	2, 3, 4

(Continued on next page)

TABLE 7. *(Continued)*

Subjective Pain Assessment Parameters		Method	Assessment Parameters	Substudy
Pin-prick test	Rate the pain sensitization after one pinprick stimulus and after a train of 10 stimuli on two test areas: 1) The dominant forearm 2) Anterior TH10 dermatome	Rated on the VAS score (0, no pain; 10, worst pain imaginable)	2, 3, 4	
Pain pressure test	Patient's pain detection- and tolerance threshold (PDT and PTT) are measured at five specific locations: 1) C5 (the clavicle) 2 TH10 (the back) 3) TH10 (the abdomen) 4) L1 (the anterior superior iliac spine) 5) L4 (straight thigh)	The imposed pressure (measured in kPa) at the PDT and PTT	2, 3, 4	
Cold pressor test	The patient's hand is immersed in cold water (approximately 2°C) for 120 seconds. At 40, 80, and 120 seconds, the patient is asked to rate the pain sensation using a VAS score.	The assessment parameters are the cold pressor endurance time (seconds) and the evoked pain responses (VAS)	2, 3, 4	
Conditioned pain modulation (CPM)	The patient's PTT is assessed at 15 cm above the patella in the L4 dermatome on the nondominant side before and after the cold pressor test is performed	The CPM effect is calculated as follows: $\text{CPM} = \frac{PTT\ (L4\ after) - PTT\ (L4\ before)}{PTT\ (L4\ before)}$	2, 3, 4	
Neurophysiological measurements		While performing the P-QST, EEG and ECG are measured before and after the cold pressor test	Several EEG and ECG parameters are measured as explorative outcomes to investigate the temporal evolution of central pain processing and autonomic responses	2, 3
Imaging		CT abdomen — pancreas specific	Advanced analyses based on radiomic features	2, 3, 4
Blood samples		1 × 10 mL EDTA plasma 1 × 10 mL serum	Immunological signatures (cytokines, chemokines, and adhesion molecules) and genetics	3

*The HADS score does not establish a clinical diagnosis but indicates a risk for an anxiety or depressive disorder. The cutoff score of 8 and above will be used to define abnormality as it has been used in previous studies and will be used to define the presence of anxiety or depression in this study.[16,31]

†The P-QST is the overall method and encompasses the pin-prick, pain pressure, and cold pressor tests.

BPI indicates Brief Pain Inventory; CP, chronic pancreatitis; CPM, conditioned pain modulation; CT, computed tomography; ECG, electrocardiography; EDTA, ethylenediaminetetraacetic acid; EEG, electroencephalogram; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PGIC, Patient's Global Impression of Change; PDT, pain detection threshold; P-QST, quantitative sensory testing for pain in chronic pancreatitis; PSQI, Pittsburgh Sleep Quality Index; PTT, pain tolerance threshold; SF-COMPAT, Short-Form Comprehensive Pain Assessment Tool; VAS, visual analog scale.

countries, reflecting real-world clinical practices, the model will be designed to accommodate these variations during the 3-month testing period. For substudy 3, we have previously found meaningful features and clinical predictors with an accuracy of 72% with 200 patients.[32] This was achieved by training AI models on feature-rich data sets and selecting the best parameters for a reduced set of 10 features, allowing for much better generalizability while still taking advantage of the computational strengths of feature selection using machine learning. With at least 200 patients and assuming a false detection rate of 5%, it will be possible to detect an accuracy of at least 22% above (clustering), that is, 72%, with a power of 99.8%.

Substudy 4 (Longitudinal)

The primary endpoint of substudy 4 is the mean SF-COMPAT score from baseline to 4 years. Analyses of longitudinal data will be performed using linear or generalized linear mixed models. Trajectories in pain parameters will be characterized by graphical analyses (eg, Sankey diagrams). We determined a total sample size of 400 participants, 350 patients with painful CP and 50 patients with painless CP based on previous studies and CP-specific cohort studies.[9,10,22,29,31,33,34] The relationship and temporal evolution of pain in CP patients will be depicted through joint modeling techniques.[35,36]

CONTINGENCY PLAN

Participating institutions may be modified as the INPAIN study progresses. A working group of the International Pancreatic Pain Consortium will consider the inclusion of new institutions upon request. If necessary, a working group will consider modifications to the CRFs as the study progresses to embrace real-world data and cultural differences.

DISCUSSION

The INPAIN study is the first international, prospective, longitudinal cohort study that (1) phenotypes pain through subjective and objective investigations, (2) predicts the optimal pain treatment on an individual patient level, and (3) assesses the temporal evolution of pain in CP. The INPAIN study, facilitated by the International Pancreatic Pain Consortium,[9] has established the necessary research infrastructure to conduct multiple clinical as well as translational studies. It serves to transfer complicated knowledge between centers, aiming to develop novel treatment strategies and improve methods for monitoring disease progression. The study will ultimately create a bedside test panel with the most sensitive parameters to assess pain in CP. This will help clinicians determine which patients are most likely to respond positively to specific pain-relieving therapies. Finally, the techniques may lead to spin-offs into other diseases and increase our general understanding of chronic pain.

A significant strength of this study is the comprehensive design, which includes optimized technical equipment, validated questionnaires in several languages, prediction of treatment effects, AI, and longitudinal studies. Incorporating cutting-edge methodologies enhances the study's ability to capture nuanced information. The longitudinal aspect of this study has the potential to give valuable insight into the natural history of CP. Its broad geographical scope, involving 15 different institutions worldwide, part of the International Pancreatic Pain Consortium,[9] enhances the generalizability of the study's findings and brings a wealth of expertise and resources to the study. As the AI models depend on the quality of and representativeness of the training data, quality assurance is performed thoroughly for all patients.

CONCLUSION

In conclusion, the successful completion of the INPAIN study will establish the first international, longitudinal research cohort conducting a comprehensive subjective and objective assessment of painful CP, which will have a major impact on future treatment strategies.

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