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Pancreatic quantitative sensory testing to predict treatment response of endoscopic therapy or surgery for painful chronic pancreatitis with pancreatic duct obstruction: study protocol for an observational clinical trial

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ABSTRACT

Introduction Treatment for abdominal pain in patients with chronic pancreatitis (CP) remains challenging in the setting of central nervous system sensitisation, a phenomenon of remodelling and neuronal hyperexcitability resulting from persistent pain stimuli. This is suspected to render affected individuals less likely to respond to conventional therapies. Endotherapy or surgical decompression is offered to patients with pancreatic duct obstruction. However, the response to treatment is unpredictable. Pancreatic quantitative sensory testing (P-QST), an investigative technique of standardised stimulations to test the pain system in CP, has been used for phenotyping patients into three mutually exclusive groups: no central sensitisation, segmental sensitisation (pancreatic viscerotome) and widespread hyperalgesia suggestive of supraspinal central sensitisation. We will test the predictive capability of the pretreatment P-QST phenotype to predict the likelihood of pain improvement following invasive treatment for painful CP.

Methods and analysis This observational clinical trial will enrol 150 patients from the University of Pittsburgh, Johns Hopkins and Indiana University. Participants will undergo pretreatment phenotyping with P-QST. Treatment will be pancreatic endotherapy or surgery for clearance of painful pancreatic duct obstruction. Primary outcome: average pain score over the preceding 7 days measured by Numeric Rating Scale at 6 months postintervention. Secondary outcomes will include changes in opioid use during follow-up, and patient-reported outcomes in pain and quality of life at 3, 6 and 12 months after the intervention. Exploratory outcomes will include creation of a model for individualised prediction of response to invasive treatment.

Ethics and dissemination The trial will evaluate the ability of P-QST to predict response to invasive treatment for painful CP and develop a predictive model for individualised prediction of treatment response for widespread use. This trial was approved by the University of Pittsburgh Institutional Review Board. Data and results will be reported and disseminated in conjunction with National Institutes of Health policies.

Trial registration number NCT04996628.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre observational clinical trial that will evaluate the predictive capability of pretreatment pancreatic quantitative sensory testing (P-QST) for pain improvement in patients with painful chronic pancreatitis undergoing invasive treatments to relieve pancreatic duct obstruction.
⇒ All participants will undergo P-QST prior to invasive therapy to determine pain phenotype.
⇒ Pain phenotype in combination with demographic and clinical variables and neuroinflammatory markers will be used to develop a prediction model to determine the probability of individual response to treatment.
⇒ Response to treatment will be determined by Numeric Rating Scale at 6 months following initial invasive treatment compared with baseline result.
⇒ This study will be performed at three US tertiary care centres, a limitation that can be addressed in the future by international dissemination and validation of these results.

INTRODUCTION

Chronic pancreatitis (CP) is a debilitating fibroinflammatory disease of the pancreas that manifests with abdominal pain in over 80% of patients during the course of their disease.[1] There is no cure for CP, and therefore, treatment options remain limited to symptom

control primarily for pain. Pancreatic ductal obstruction due to stones and/or strictures is believed to be one important determinant of pain, and therefore, patients with evidence of ductal obstruction on imaging may be offered invasive treatment (endotherapy or decompressive surgery) to relieve intraductal hypertension thought to be the source of pain.[2 3] Successful decompression of the pancreatic duct results in improvement of pain for some patients; however, in clinical practice, it is difficult to know which patients who are undergoing invasive treatment will benefit from the procedure.[4] The variable and unpredictable nature of improvement after successful ductal decompression suggests the role of previously unaccounted factors.[5 6] Pain in CP is multifactorial and includes neuropathic and inflammatory components as well as central sensitisation, a phenomenon of increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input, ultimately resulting in altered pain processing.[7] To date, there has been no diagnostic test capable of identifying this phenomenon for evaluation in clinical settings, although it has been a suspected contributor in those cases where successful ductal decompression results in incomplete pain relief. Pancreatic quantitative sensory testing (P-QST) is a minimally invasive technique of standardised stimulations that can be used to characterise nociception in the setting of CP and has the potential to be used as a predictive tool to stratify treatment response for painful CP by identifying characteristics of segmental and widespread central nervous system hyperalgesia as a proxy for central sensitisation.[8 9]

Though this is its first use in a large, appropriately powered predictive study, P-QST has previously been used to phenotype CP patients with pain in cross-sectional studies, and the presence of widespread hyperalgesia has been shown to associate with pain severity and frequency.[9] Published pilot data in 48 subjects who underwent P-QST phenotyping prior to endoscopic or surgical therapy for painful CP showed an increased density of widespread hyperalgesia in those patients who had limited improvement or worsening of pain at 6 months after intervention.[10] The study outlined here is designed to provide more definitive evidence for the predictive capability of P-QST. The presence of widespread hyperalgesia alone is, however, unlikely to be the sole predictor of pain response to pancreatic ductal decompression. Other known and suspected biological, demographic, and psychological factors also impact pain outcomes in CP patients. Previous studies have even identified biomarker signatures of pain severity and response to pharmacological interventions and have been used as predictors for surgical/invasive outcomes.[10–13] The assessment of P-QST phenotype for evidence of central sensitisation has the potential to identify those patients for whom this phenomenon plays a significant role in their pain experience. On its own or combined with other clinical factors, P-QST phenotype has the potential to change patient selection processes for invasive therapies if it can serve as a predictor of likelihood of reducing pain. However, a lack of standardised definitions of pain response in prior studies, variable patient selection and interventions have made it difficult to identify reliable predictors of outcome to therapy. No model—even in the absence of assessment for central sensitisation—is currently available clinically to predict pain response for individual patients.

METHODS

The study protocol is reported in accordance with the Transparent Reporting of a Multiariable Prediction Model for Individual Prognosis or Diagnosis guidelines (figure 1).[14]

Study hypothesis and aim

The hypothesis of the study is that patients with painful CP who have evidence of widespread hyperalgesia suggestive of supraspinal central sensitisation are less likely to experience pain relief following technically successful invasive treatments to alleviate ductal obstruction than those who do not. Building on this, we hypothesise that the pretreatment P-QST phenotype can be used to predict the likelihood of alleviating pain following invasive treatment for painful CP at 6 months after achieving successful intervention. As the P-QST phenotype is unlikely to be the sole predictor of the outcome to therapy, we further hypothesise that the combination of P-QST phenotype with relevant patient, disease and treatment-related covariates, as well as biochemical inflammatory marker data will allow us to create a model for likelihood of individual response to invasive treatment for relief of pain from ductal obstruction.

Study design and setting

This is a multicentre observational clinical trial that will evaluate the predictive capability of pretreatment P-QST for pain improvement in patients with painful CP who are undergoing invasive treatments (endoscopic therapy or surgical drainage procedure) to relieve pancreatic duct obstruction. P-QST phenotype, demographic and clinical variables and neuroinflammatory markers will be used to develop a prediction model to determine the probability of an individuals' response to treatment. The study will be conducted across three tertiary care centres: The University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania, Johns Hopkins University in Baltimore, Maryland and Indiana University Medical Center in Indianapolis, Indiana, all in the USA.

Patient and public involvement

This trial directly responds to named patient priorities about treatment for pain in CP.[15] Although design of this trial was performed by the scientific authorship team, patients will be directly involved in the execution of this trial as research study subjects and in dissemination of the results through advocacy. Patients and the public were not involved in the design of this study.

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	17
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	Describe eligibility criteria for participants.	7
	5c	Give details of treatments received, if relevant.	9
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	11
	6b	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	9
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	Explain how the study size was arrived at.	13
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	14
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	14
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	14
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	14
Risk groups	11	Provide details on how risk groups were created, if done.	N/A
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7
Model development	14a	Specify the number of participants and outcome events in each analysis.	14
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	N/A
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	N/A
	15b	Explain how to the use the prediction model.	14
Model performance	16	Report performance measures (with CIs) for the prediction model.	N/A
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	N/A
Implications	20	Discuss the potential clinical use of the model and implications for future research.	16
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	18
Funding	22	Give the source of funding and the role of the funders for the present study.	18

Figure 1 TRIPOD checklist: prediction model development. Completed for the Pancreatic Quantitative Sensory Testing (P-QST) Study. N/A, not available; TRIPOD, Transparent Reporting of a Multiariable Prediction Model for Individual Prognosis or Diagnosis.

Inclusion criteria

- Definite evidence of CP on cross-sectional imaging (meets Cambridge III or IV criteria)[16] with evidence of ductal obstruction and upstream dilation of the main pancreatic duct.
- Age ≥18 years.
- Abdominal pain (constant or intermittent) secondary to pancreatic pathology as determined by their treating pancreatologist.
- Patients who are undergoing decompressive invasive treatments (endotherapy or surgery) to relieve main pancreatic duct obstruction due to stones and/or strictures for management of pancreatic pain.
- Participants must be able to read, understand and personally sign the informed consent form and participate in the informed consent process.
- Participants should be willing to comply with all scheduled visits and study procedures as laid out in the study protocol.

Exclusion criteria

- Endoscopic therapy successfully accessing the pancreatic duct upstream of an obstruction within the preceding 12 months.
- Any prior pancreatic surgery.
- Plan for undergoing resective surgery (ie, Whipple procedure or pancreatectomy) as opposed to drainage surgery for pain management.
- Participants <18 years of age.
- Patients with abdominal pain that cannot be discerned as different from pancreatic pain.
- Suspected or established pancreatic malignancy.
- Peripheral sensory deficits from stroke or other cause.
- Known pregnancy.

Intervention

In this observational clinical trial, all participants will undergo P-QST testing and pain assessment at time of enrolment before they undergo clinically indicated invasive intervention with either endoscopic therapy or surgery (figures 1 and 2).

Baseline data collection

Assessment of pain at baseline will be performed using the following question accompanied by a Numerical Rating Scale (NRS): 'Please describe on a scale of 0–10 how intense your abdominal pain has been on average over the past 7 days (range 0–10 with 0=no pain, 10=worst pain Imaginable).' Patients with 7 or more days between enrolment and planned intervention will also complete a 7-day diary of average score on each day (0–10 NRS for abdominal pain). Information on opioid use (medication type, mean daily dose in milligrams of morphine equivalent (MME) calculated using conversion from the Centers for Disease Control and Prevention) will be assessed in the week prior to the intervention as able. Additional data collected at the time of enrolment will include demographics, CP characteristics including aetiology of disease, ongoing alcohol, tobacco or marijuana use, pain characteristics (duration, temporal nature, severity), duration and dose range of opioids, other analgesic use including neuromodulating agents, psychiatric and other comorbidities, details of invasive treatment (eg, endotherapy, surgery) and validated patient-reported outcome tools (Patient Reported Outcomes Measurement Information System [PROMIS]—Global Health, Nociceptive Pain, Neuropathic Pain), Pain Interference,[17] Hospital Anxiety and Depression Scale,[18] Pain Catastrophising Scale[19] and Comprehensive Pain Assessment Tool for Chronic Pancreatitis Short Form.[20]

P-QST phenotyping and scheduled intervention

Patients will undergo preprocedure P-QST testing using our published protocol.[8] Based on the previously published nomogram and phenotyping algorithm,[9] patients will be stratified into the following groups: widespread hyperalgesia (suggestive of spinal and supraspinal central sensitisation), segmental hyperalgesia (suggestive of sensitisation in the pancreatic viscerotome but not yet involving the supraspinal area) and no hyperalgesia (suggestive of normal pain processing). Patients will undergo scheduled invasive treatment as directed by their treating gastroenterologist after P-QST. The date of the first endoscopic therapy or surgery will be used to calculate the dates and timing of each follow-up window.

Sample collection

All patients will undergo blood and urine sample collection at baseline and at 6 months after intervention for evaluation of inflammatory cytokines. Expression of neuroinflammatory analytes will be assessed in serum

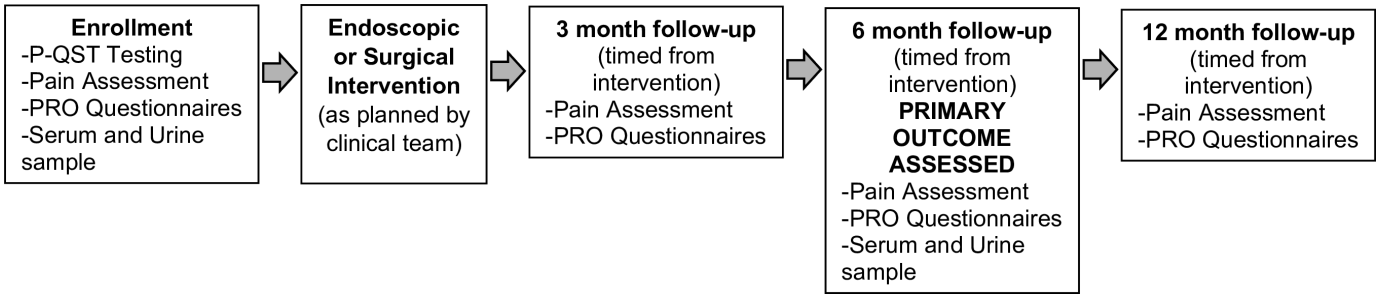

Figure 2 Flowsheet of overall study design. P-QST, Pancreatic Quantitative Sensory Testing; PRO, Patient-Reported Outcome Questionnaire.

samples via multiplex Meso Scale Discovery platform and validated ELISA kits to assess correlation with pain improvement after therapy. The intention is that if the analysis with serum is shown to have predictive capability of treatment response, the biorepository can be used to perform exploratory analyses with urine samples for minimally invasive testing that can be incorporated into a typical clinic visit. The multiplex assay includes standards to develop a calibration curve. Positive (known concentration of targets) and negative controls (diluent only) will also be included.

Clinically indicated invasive intervention

All enrolled patients will have definite CP and be scheduled to undergo decompressive invasive treatments (endoscopic therapy or surgery) to relieve main pancreatic duct obstruction due to stones and/or stricture for the management of pain. Endoscopic therapy will include endoscopic retrograde cholangiopancreatography (ERCP) with pancreatic duct stone removal, stent placement and/or stricture dilation. ERCP may be performed with or without intraductal lithotripsy or extracorporeal shockwave lithotripsy. A course of endotherapy may consist of several sessions lasting up to 1 year to achieve ductal clearance or stricture dilation. At every endoscopic session, an assessment will be made by the therapeutic endoscopist regarding degree of success of the procedure. Complete endoscopic success will be defined as no further evidence of stricture at the end of the intervention, or return of the pancreatic duct to a normal calibre at that location, or complete removal of obstructing stones. Partial endoscopic success will be defined as a decrease in the duct diameter from baseline (but not return to normal parameters as above) or partial removal of stones. The third option is 'none' which is defined as neither decrease in duct diameter from baseline nor any successful removal of stones. Surgery will include drainage procedures, such as Frey and Puestow operations.[21 22] Each surgical operator will be asked to report on the success of their attempt at relief of obstruction at the close of their procedure (yes/no/unknown). Technical success of all interventions will be recorded for all participants throughout the study and analysed as a covariate at end of the study. Although limits will not be placed on enrolment of patients undergoing either type of procedure, based on practice patterns at the enrolling institutions, we anticipate 80% of enrolled patients to undergo endotherapy and 20% surgery (either as primary form of treatment or after failed endotherapy). All pancreatic interventions undergone by study participants will be tracked within the study period.

Follow-up

The follow-up timeclock will begin at the time of first attempted treatment (either endotherapy or surgery as primary treatment), and patients will be followed up at 3, 6 and 12 months. At each follow-up time point, patients will complete 7 days of average daily pain NRS scores, an assessment of opioid use, patient-reported outcome tools and the Patient Global Impression of Change. Data on follow-up interventions (additional sessions of endotherapy or surgical procedures) will be collected throughout the follow-up period. Follow-up windows will be scheduled continuously in order to optimise retention rates throughout the study (3 months: ≥1 to <4 months, 6 months: ≥4 to <9 months, 12 months: ≥9 to 18 months).

Primary endpoint

The primary outcome of the study is the difference between average pain score at 6 months postprocedure in the group with widespread hyperalgesia and those without based on single-question NRS scale (average pain in the preceding 7 days prior to assessment (range 0–10)). As there is no standardised definition to assess pain response after medical or invasive treatment in patients with CP, and prior studies have used varying definitions,[4 5 23 24] we have elected to use follow-up pain score with covariate adjustment for baseline pain score rather than the 'change' in an outcome variable as it will provide better statistical power and specifically address the estimated difference in follow-up pain scores between the patients with and without widespread hyperalgesia. We will measure pain response at 6 months as the primary outcome to allow time for patients with more than one endotherapy sessions prior to 6-month assessment and for postsurgical pain (from incisions and inflammation) to improve prior to 6-month assessment.

Secondary endpoints

Secondary endpoints will include:

- Differences between P-QST phenotypes in mean scores from the 7 day pain diary at 3, 6 and 12 months after intervention (widespread vs other, and comparison across all groups; anticipate lower completion rate than single-question NRS).
- Differences between P-QST phenotypes in pain measurements with single-question NRS at 3 months (to assess for short-term pain relief) and 12 months (for more durable pain relief).
- Differences between groups in patterns of opioid use (assessed as both a binary variable (yes, no) and a continuous variable (measured in MMEs per day)) at enrolment 3, 6 and 12 months.
- Differences between groups in percentage of patients with ≥30% and ≥50% pain relief from baseline.
- Differences between groups in quality of life, anxiety, depression and pain interference (patient-reported outcomes (eg, PROMIS).
- Differences between groups in Patient Global Impression of Change scores.

Experimental endpoints

The additional experimental endpoints will be assessed following the completion of the study:

- Creation of a model for the likelihood of individual response to therapy based on demographic,

patient-centred, treatment-related and P-QST phenotype factors.
- Identification of neuroinflammatory biomarkers that associated with P-QST phenotype.
- Creation of an augmented model for likelihood of individual response to therapy based on demographic, patient-centred, treatment-related, P-QST phenotype and neuroinflammatory biomarker factors.

Sample size determination

Sample size calculations were performed by simulation in R (V.3.4.0). Assuming 30% prevalence of widespread hyperalgesia in the study population, an overall mean baseline NRS of 6 points and an SD in NRS of 2 points (based on our preliminary data), a sample size of 120 patients will have at least 91.7% power to detect a difference of 1 point on the primary endpoint of NRS at 6 months after intervention between patients with widespread hyperalgesia compared with those with segmental hyperalgesia or normal pain processing, with the adjustment for baseline NRS in the models. The previously published distribution of phenotypes in patients with painful CP were as follows: widespread hyperalgesia 24%, segmental hyperalgesia 30%, no hyperalgesia 46%. A larger difference between groups (eg, 2-point difference in response for patients with widespread hyperalgesia vs patients without widespread hyperalgesia) will result in an increase in power (to >99% in this instance). For our secondary endpoints, the sample size of 120 will have at least 88% power assuming that opioid use at follow-up is approximately 20% in patients without widespread hyperalgesia vs 50% in patients with hyperalgesia. To ensure that we have at least 120 patients with complete outcome data, we will recruit 150 patients to allow for up to 20% attrition.

Statistical analysis

The research question asked by this study is whether there is a significant difference in pain response for patients with widespread hyperalgesia versus without. The primary outcome variable of interest is average pain score on single question NRS pain score at 6 months postprocedure. The primary independent variable will be the presence of widespread hyperalgesia (yes/no) according to P-QST. Patients with segmental hyperalgesia or normal pain processing will be combined into the 'no' widespread hyperalgesia group. This question is appropriately answered by using a multivariable linear regression that allows estimation of the difference in pain response between these two groups with covariate adjustment including the baseline pain scores, centre, type of intervention (endoscopic or surgical) and ductal clearance achieved (yes/no) at 6 months—a linear regression is able to accommodate dichotomous variables as independent variables.

All secondary outcome measures will be evaluated by either linear (continuous) or logistic (categorical) regression in a similar manner. Sensitivity analyses for the primary and secondary outcomes will be performed using methods appropriate for different missing data mechanisms.

The analysis will serve as a foundation for creation of an individual model for prediction to therapy that will confirm what patient, disease and treatment-specific variables are independently likely to predict the primary outcome (NRS pain score at 6 months postprocedure), and what combination of variables provides the best predictive capability of response for an individual patient. To complete this analysis, standard and lasso regression models will be used to identify variables that are significantly correlated to the 6-month NRS pain score, and additional machine learning models including probabilistic graphical models will be incorporated to analyse this data.[25–29] The models resulting from this procedure will be compared with regression, support vector machine and random forest models. Analysis of secondary endpoints for pain will be similar.

Neuroinflammatory biomarker data will be assessed for each substance as both a continuous (level) and categorical (present, yes/no) data point for association with the primary outcome. In addition, logistic regression models will be developed for response to invasive therapy using all available clinical data from the model described above as well as the cytokine data collected from biological samples. Statistical analysis similar to the above-described model will be performed with the incorporated biomarker data for a more complete model. Data will be assessed from both baseline samples and 6-month follow-up samples. In the absence of a second (external) cohort, an assessment of accuracy of all models will be done using a nested cross-validation procedure.

Monitoring and safety

This is an observational study with minimal risk to its participants given the low risk of the study intervention and follow-up activities. Slight erythema at the sites of pressure stimulation where P-QST has been performed has been noted. Rarely can patients experience vagal symptoms when placing their hands into cold water. Patients are invited to participate and can decline participation without changing their clinical care. There is US$50 compensation offered to the patient at each study time point for their time and effort in completing study activities (total US$200 for all time points completed during the study). Overall safety and confidentiality of research participants will be continuously monitored by the principal investigator, study investigators and research staff. All suspected adverse events (including breaches in data security) will be reported immediately to the principal investigator at each site, and to the principal investigator of the overall study as soon as possible. Overall safety and study-wide adverse events will be reviewed by the PI, study coordinators and study staff at each institution on a monthly basis at each site. In addition, data safety monitoring will be added to the monthly phone call meetings

between all sites to ensure that these events are raised in a timely manner.

All P-QST testers will complete an in-person training session with study leadership and perform supervised testing on 20 patients prior to testing independently. An instructional video for intermittent refresher courses and technical consultation will be used for reinforcement and standardisation of testing techniques across centres. All testers will meet minimum standards for performing testing independently before their data will be included in the study. Data quality surveys for all sites will also be conducted. Centre effects were evaluated in our preliminary data, and no significant differences were seen between sites.[8] Repeatability results for pressure testing in similar QST protocols have previously been published.[30] The multicentre aspect of this work will facilitate enrolment from diverse minority groups and account for variations between geographic populations.

DISCUSSION

Abdominal pain is the main symptom of CP and is the major motivator for patients to seek high-risk, invasive procedures with unpredictable outcomes. The response is often suboptimal for patients, and many continue to require analgesic therapy—opioid and non-opioid—after treatment even when there is technical success at relieving ductal obstruction.[4] The P-QST trial introduces the opportunity to assess the effect of central sensitisation and associated cofactors in the pain experience of CP patients and importantly to evaluate the ability of P-QST phenotyping to predict the likelihood of response to invasive therapy.

Although the presence of central sensitisation alone is unlikely to predict the outcome to invasive therapy, this trial offers the potential to incorporate P-QST phenotype with other patient-related, treatment-related and biochemical factors to optimise the likelihood of using all of this information to predict response to therapy. Both endoscopic therapies and surgical therapies for ductal decompression are included in this trial, and importantly, the efficacy of achieving ductal decompression will be adjusted for in the final analyses.

This trial will bring several important innovations to the field to further advance the individualised approach to treatments for painful CP. This includes the novel application of sensory testing to predict treatment response to ductal decompression in this patient population, the use of machine learning tools to develop a predictive model for the likelihood of individual response to treatment and the generation of a biorepository combined with systematic phenotyping of patients with painful CP. Together, these efforts will also set the stage for future multicentre studies for the prediction of treatment response in painful CP.

In conclusion, the P-QST trial is an observational clinical trial investigating the ability of P-QST phenotyping to predict treatment response to invasive therapy for ductal decompression in painful CP.

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Competing interests AEP: Board Member, National Pancreas Foundation. VKS: Consultant to Abbvie, Ariel Precision Medicine, Horizon Therapeutics and Panafina; Medical Advisory Board participant to Organon; Scientific advisory board participant for Kyttaro, Origin Endoscopy and Solv Endoscopy; Equity holder in Kyttaro, Origin Endoscopy, Solv Endoscopy. The other authors have no financial or personal competing interests to declare.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Gardner TB, Kennedy AT, Gelrud A, *et al*. Chronic Pancreatitis and its effect on employment and health care experience:

results of a prospective American multicenter study. *Pancreas* 2010;39:498–501.
2 Drewes AM, Kempeneers MA, Andersen DK, *et al*. Controversies on the endoscopic and surgical management of pain in patients with chronic Pancreatitis: pros and cons *Gut* 2019;68:1343–51.
3 Drewes AM, Bouwense SAW, Campbell CM, *et al*. Guidelines for the understanding and management of pain in chronic Pancreatitis. *Pancreatology* 2017;17:720–31.
4 Issa Y, Kempeneers MA, Bruno MJ, *et al*. Effect of early surgery vs Endoscopy-first approach on pain in patients with chronic Pancreatitis: the ESCAPE randomized clinical trial. *JAMA* 2020;323:237–47.
5 Cahen DL, Gouma DJ, Nio Y, *et al*. Endoscopic versus surgical drainage of the Pancreatic duct in chronic Pancreatitis. *N Engl J Med* 2007;356:676–84.
6 Díte P, Ruzicka M, Zboril V, *et al*. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic Pancreatitis. *Endoscopy* 2003;35:553–8.
7 Merskey H, Bogduk N. *International Association for the Study of Pain. Task Force on Taxonomy. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*2nd ed. Seattle: IASP Press, 1994.
8 Phillips AE, Faghih M, Kuhlmann L, *et al*. A clinically feasible method for the assessment and characterization of pain in patients with chronic Pancreatitis. *Pancreatology* 2020;20:25–34.
9 Faghih M, Phillips AE, Kuhlmann L, *et al*. Pancreatic QST Differentiates chronic Pancreatitis patients into distinct pain phenotypes independent of psychiatric Comorbidities. *Clin Gastroenterol Hepatol* 2022;20:153–61.
10 Phillips AE, Faghih M, Singh VK, *et al*. Widespread hyperalgesia by Pancreatic quantitative sensory testing is associated with reduced pain response in chronic Pancreatitis. *Pancreas* 2023;52:e257–8.
11 Niculescu AB, Le-Niculescu H, Levey DF, *et al*. Towards precision medicine for pain: diagnostic biomarkers and Repurposed drugs. *Mol Psychiatry* 2019;24:501–22.
12 Vardanyan M, Melemedjian OK, Price TJ, *et al*. Reversal of Pancreatitis-induced pain by an orally available, small molecule Interleukin-6 receptor antagonist. *Pain* 2010;151:257–65.
13 Olesen SS, Graversen C, Bouwense SAW, *et al*. Quantitative sensory testing predicts Pregabalin efficacy in painful chronic Pancreatitis. *PLoS One* 2013;8:e57963.
14 Collins GS, Reitsma JB, Altman DG, *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 2015;350:g7594.
15 van Dijk SM, van Grinsven J, van Oostveen GJCB, *et al*. Patient input into future clinical research in acute and chronic Pancreatitis. *Lancet Gastroenterol Hepatol* 2018;3:452–3.
16 Sarner M, Cotton PB. Classification of Pancreatitis. *Gut* 1984;25:756–9.
17 Cella D, Riley W, Stone A, *et al*. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol* 2010;63:1179–94.
18 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
19 Sullivan MJL, Bishop SR, Pivik J. The pain Catastrophizing scale: development and validation. *Psychological Assessment* 1995;7:524–32.
20 Kuhlmann L, Teo K, Olesen SS, *et al*. Development of the comprehensive pain assessment tool short form for chronic Pancreatitis: validity and reliability testing. *Clin Gastroenterol Hepatol* 2022;20:e770–83.
21 Frey CF, Smith GJ. Description and rationale of a new operation for chronic Pancreatitis. *Pancreas* 1987;2:701–7.
22 PUESTOW CB, GILLESBY WJ. Retrograde surgical drainage of Pancreas for chronic relapsing Pancreatitis. *AMA Arch Surg* 1958;76:898–907.
23 Clarke B, Slivka A, Tomizawa Y, *et al*. Endoscopic therapy is effective for patients with chronic Pancreatitis. *Clin Gastroenterol Hepatol* 2012;10:795–802.
24 Ahmed Ali U, Nieuwenhuijs VB, van Eijck CH, *et al*. Clinical outcome in relation to timing of surgery in chronic Pancreatitis: a Nomogram to predict pain relief. *Arch Surg* 2012;147:925–32.
25 Sedgewick AJ, Buschur K, Shi I, *et al*. Mixed graphical models for integrative causal analysis with application to chronic lung disease diagnosis and prognosis. *Bioinformatics* 2019;35:1204–12.
26 Sedgewick AJ, Shi I, Donovan RM, *et al*. Learning mixed graphical models with separate Sparsity parameters and stability-based model selection. *BMC Bioinformatics* 2016;17 Suppl 5(Suppl 5):175.
27 Raghu VK, Ge X, Balajee A, *et al*. A pipeline for integrated theory and data-driven modeling of Genomic and clinical data. In: *2019 ACM BioKDD; 2019*. Anchorage, AK, 2019.
28 Manatakis DV, Raghu VK, Benos PV. piMGM: incorporating multi-source Priors in mixed graphical models for learning disease networks. *Bioinformatics* 2018;34:i848–56.
29 Raghu VK, Ramsey JD, Morris A, *et al*. Comparison of strategies for Scalable causal discovery of latent variable models from mixed data. In: *2017 ACM SIGKDD*. Halifax, Nova Scotia, Canada: Springer, 2017.
30 Olesen SS, van Goor H, Bouwense SAW, *et al*. Reliability of static and dynamic quantitative sensory testing in patients with painful chronic Pancreatitis. *Reg Anesth Pain Med* 2012;37:530–6.