

Version 1.3.2018

**Title: Predicting treatment response in Chronic Pancreatitis using Quantitative Sensory Testing**

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## Predicting treatment response in Chronic Pancreatitis using Quantitative Sensory Testing

### Objective:

Endoscopic therapy or surgery for treatment of pain is typically offered to chronic pancreatitis (CP) patients with pancreatic ductal strictures and/or stones. However, clinical pain symptoms correlate poorly with pancreatic ductal morphology, response to endoscopic or surgical therapy is unpredictable, and the rationale for invasive therapies is often questioned.

Quantitative sensory testing (QST) can map the pain system; the technique is based on the rationale that different neural pathways and networks can be explored using standardized stimulation and simultaneous recording of the evoked pain response by psychophysical and/or objective methods. We hypothesize that endoscopic or decompressive surgical therapy is most effective for patients with local sensitization without systemic or abnormal activation of the central pain system. Our objective is to distinguish phenotypes characterized by segmental sensitization of the pancreatic viscerotome (T10), and systemic sensitization with pathological central pain processing including augmented temporal summation and impaired descending pain inhibition.

### Aims:

- Aim 1) Investigate the association between QST profiles and demographic and clinical characteristics including depression and anxiety questionnaires in patients with suspected or definite CP.
- Aim 2) Investigate if the QST profile of the individual patient can be used to predict the clinical outcome of endoscopic or surgical treatment in patients with suspected or definite CP.
- Aim 3) Investigate the temporal evolution and association of QST profiles and clinical pain scores after endoscopic or surgical treatment in patients with suspected or definite CP.

### Background

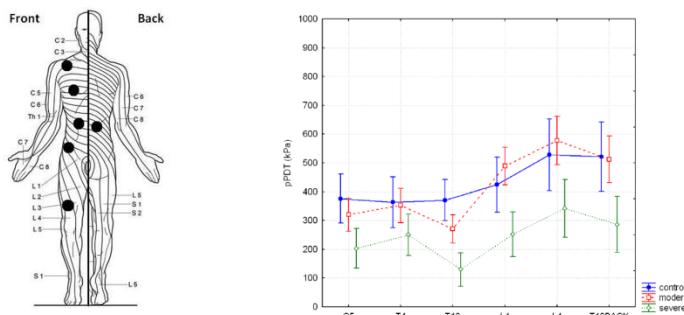
Treatment of pain in patients with CP is challenging and different treatments are offered to patients based on tradition and knowledge from other pain syndromes. In some patients, treatment is based on pathogenesis and when obvious duct changes, stones and strictures are present (large duct disease), surgery and endoscopic procedures with and without extracorporeal shock wave lithotripsy (ESWL) has been used successfully (Löhr et al. 2017). These procedures are to some extent mechanism based, as they aim to improve the flow of pancreatic juice or reduce inflammation. However, recent studies have *not* found a relation between the micro- or macrostructure and the pain intensity and therefore the pathophysiological evidence can be questioned (Frøkjær et al. 2013; Wilcox et al. 2015). It should also be noted that the marked placebo effect of the different treatment cannot be neglected and future research should aim to identify individual responders and if possible (such as in endoscopic procedures with stent placement) to include a sham arm in the studies. On the other hand, the many case reports and observational studies of pain improvement after invasive procedures cannot be neglected. Furthermore, evidence from studies in somatic tissues with peripheral nerve injury and painful polyneuropathy, also suggest that primary afferent input is critical for maintaining the neuropathic pain (Haroutounian 2014), and as such this provides a mechanistic rationale for treatment in patients with duct obstruction.

The *Nijmegen Aalborg Screening QST Paradigm (NASQ)* has been developed in collaboration between groups in Holland and Denmark to replace cumbersome and highly technological methods for visceral pain stimulation with a simpler paradigm that can be used at bedside. The method uses in its original design quantitative sensory testing (QST) with tetanic electrical and pressure stimulation at different dermatomes in order to unravel the pain system. Furthermore, it includes assessment of descending inhibition with pressure stimulation before and after a “conditioning stimulus” with the hand immersed into ice water (conditioned pain modulation, CPM). In order to detect changes in the pain system with NASQ we have previously used postoperative pain as a model, as the painful event (the surgery) is planned and controlled, and therefore the changes in the nociceptive system can be followed

systematically. After surgery, it has been shown that the initial changes in pain processing (using the NASQ) in the days after surgery can predict who will develop chronic postsurgical pain (Wilder-Smith 2015). For example, we recently showed that early postoperative hyperalgesia to pressure stimulation in the first days after surgery was an independent risk factor for development of chronic pain (van Helmond et al. In preparation 2016).

In CP, we have used NASQ to detect differences in generalised sensitization (overall difference between the blue and green curves in figure 1) as well as changes in the sensation between different dermatomes (for example the hyperalgesia at T10 in figure 1) together with assessment of CPM. Hence, we have showed that patient with increased sympathetic drive have increased pain to QST in general (Buscher et al. 2010), and the degree of generalised sensitization correspond with the MANNHEIM severity index (the more diseased, the more pain) as well as response to splanchnicectomy (Bouwense et al. 2011; Bouwense et al. 2013). The methods have also been used to guide treatment, as selective sensitization at the pancreatic dermatome (T10) rather than generalized sensitization was shown to predict the effect of pregabalin (Olesen et al. 2013). We have also shown that patients with CP suffer from deficient descending inhibition as reflected in CPM. Drugs such as tapentadol and venlafaxine may potentiate this mechanism in patients with neuropathy (Yarnitski et al. 2012; Niesters et al. 2015). We therefore believe that these drugs are helpful in many patients with pain due to pancreatitis, where a large fraction is thought to have neuropathic pain (Drewes et al. 2008).

Notably, QST profiles from CP patients have been reported only in Europeans to date: no data exist at this time on CP patients in the United States.



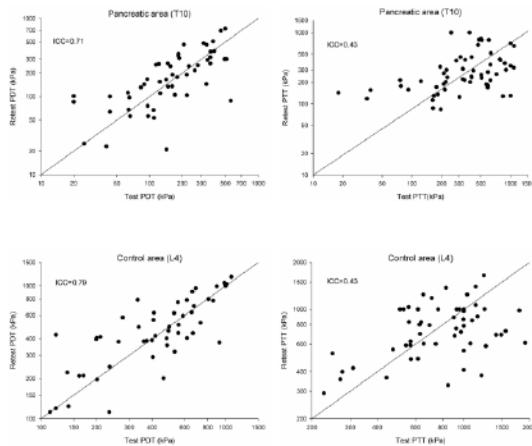
*Figure 1. The different dermatomes tested (left) and a profiling of controls and patients with different degree of sensitization to pressure pain stimulation (right)*

**Methodological aspects:** The pressure and electrical stimulations were previously shown to be reproducible in patients with CP (figure 2) whereas the CPM was not (Olesen et al. 2012). On the other hand, this is an inherent problem with all methods to evoke descending inhibition (even in healthy volunteers) and is not restricted to CP. As many patients are reluctant towards the electrical stimulation and the methods also are technically more demanding, we compared in a pilot study pain assessment between electrical and pressure stimulation at different dermatomes. As can be seen in figure 3 there is limited gain using electrical stimulation as compared with pressure when the pain tolerance thresholds are used. In the newest version of NASQ we also added pinprick stimulation with the possibility to address “temporal summation”. This is a method that corresponds to “wind-up” in preclinical studies and is suitable to study central sensitization. When temporal summation is used in patients with a sensitized pain system they show increased pain response to repeated stimuli at the same intensity delivered with a frequency above 0.3 Hz. Temporal summation has also been shown to reflect central sensitization in patients with pain due to CP (Dimcevski et al. 2007). We therefore suggest that the modified NASQ will consist of the following:

- 1) the mechanical pain with the pressure device at the different dermatomes shown in figure 1
- 2) temporal summation with the standardized pin-prick instrument
- 3) assessment of CPM with pressure (same device as 1) before and after immersion of the hand in ice-water.

This is doable in about 20 min after training, but to ensure reasonable repeatability it needs to be in the hand of few persons. The QST shall be supported by questionnaires to -

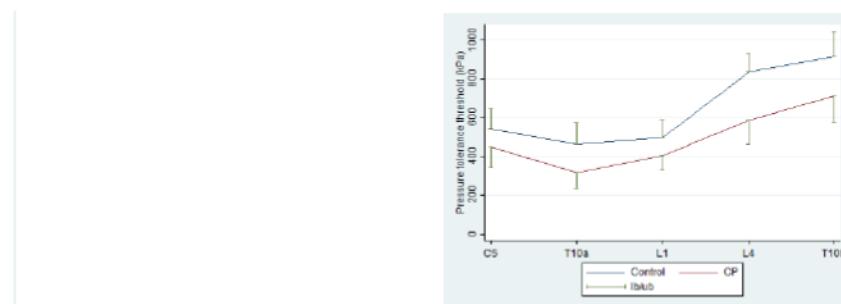
- 4) assess depression (using e.g., Hospital Anxiety and Depression Scale, Bjelland et al. 2002) and
- 5) situational catastrophizing after the cold water test (Grosen et al. 2016).



*Figure 2. Reproducibility of pressure pain at the pain detection threshold (PDT, left) and pain tolerance threshold (PTT, right) – for details, see Olesen et al. 2012*

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*Figure 3. Recent pilot studies comparing the pain profile in controls and patients between different dermatomes to electrical (left) and pressure (right) stimulations.*

### Significance:

The study may allow us to phenotype patients based on their QST findings in order to better understand and treat the pain syndromes that occur in the setting of CP. It may also allow us to predict the response of phenotyped patients to endoscopic and surgical interventions for CP. We would anticipate further clinical trials with this technique to more accurately understand these pain syndromes and elucidate patterns in other populations.

### Study Participants:

- 1) Subjects with no pancreatic disease and no abdominal pain, or patients with a diagnosis of functional dyspepsia.

#### *Inclusion Criteria:*

- Subjects are 18 years or older in age
- Subjects must be able to read and understand the study information.
- Personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
- Subject is willing and able to comply with the scheduled visits, questionnaires, treatment plan, and other study procedures.

***Exclusion criteria:***

- Subjects with evidence or history of medical or surgical disease of importance for this study as judged by investigator.
- Subjects suffering from painful conditions that make them unable to distinguish the pain associated with CP from chronic pain of other origins.
- Subjects with known pregnancy at the time of enrolment.
- Subjects who have previously undergone surgical intervention on their pancreas.

**2) Suspected CPs**

***Inclusion Criteria***

- Subjects are 18 years or older in age
- Subjects with a) Indeterminate CP (Cambridge 1 or 2 on CT scan or MRI/MRCP) who have abdominal pain without prior history of AP, or b) those with acute (AP) or recurrent acute pancreatitis (RAP) who have recovered from their attack(s) of AP, whose imaging studies are either normal or show changes consistent with Cambridge classification of 1 or 2, and they have ongoing abdominal pain. Both diabetic and non-diabetic subjects will be allowed to enter the study.
- Subjects must be able to read and understand the study information.
- Subjects must suffer from abdominal pain suspected to be pancreatic origin with an intensity above 3 on the visual analogue scale (VAS, where 0=no pain and 10= intolerable pain), and meet the criteria for chronic pain (pain  $\geq$  3 days per week for at least 3 months).
- Personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
- Subjects willing and able to comply with the scheduled visits, questionnaires, and other study procedures.

***Exclusion Criteria***

- Subjects with evidence or history of medical or surgical disease of importance for this study as judged by investigator.
- Subjects suffering from painful conditions other than pancreatitis or SOD type 1 or 2 that make them unable to distinguish the pain associated with pancreatitis or SOD from chronic pain of other origins.
- Subjects with known pregnancy at the time of enrolment.
- Subjects who have previously undergone surgical intervention on their pancreas.

**3) Definite Chronic Pancreatitis -**

***Inclusion Criteria***

- Subjects are 18 years or older in age
- Subjects will have a prior confirmed diagnosis of CP on CT scan or MRI/MRCP according to Cambridge Classification (grade 3 or 4). Both diabetic and non-diabetic subjects will be allowed to enter the study.
- Subjects must be able to read and understand the study information.
- Personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
- Subjects willing and able to comply with the scheduled visits, questionnaires, and other study procedures.

***Exclusion Criteria***

- Subjects with evidence or history of medical or surgical disease of importance for this study as judged by investigator.
- Subjects suffering from painful conditions other than pancreatitis or SOD type 1 or 2 that make them unable to distinguish the pain associated with pancreatitis or SOD from chronic pain of other origins.
- Subjects with known pregnancy at the time of enrolment.
- Subjects who have previously undergone surgical intervention on their pancreas.

**4) Sphincter of Oddi Dysfunction (SOD) Type 1 or Type 2**

***Inclusion Criteria***

- Subjects are 18 years or older in age
- Subjects have prior diagnosis of Type 1 or Type 2 Sphincter of Oddi Dysfunction (subjects with biliary pain accompanied by biochemical features of transient biliary tract obstruction including elevated transaminases, alkaline phosphatase, or conjugated bilirubin; may also be accompanied by biliary or pancreatic ductal dilation on imaging)
- Subjects must be able to read and understand the study information.
- Personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
- Subjects willing and able to comply with the scheduled visits, questionnaires, and other study procedures.

***Exclusion Criteria***

- Subjects with evidence or history of medical or surgical disease of importance for this study as judged by investigator.
- Subjects suffering from painful conditions other than pancreatitis or SOD that make them unable to distinguish the pain associated with pancreatitis or SOD from chronic pain of other origins.
- Subjects with known pregnancy at the time of enrolment.
- Subjects who have previously undergone surgical intervention on their pancreas.

\*\*Note: Women who become pregnant during the course of the study can no longer participate in QST testing.

**Study Procedures:**

**Baseline Testing:**

All subjects will complete a basic questionnaire at baseline with assistance of a study coordinator or physician investigator which will collect information on demographics, pain characteristics, and information related to their pancreatic health. Subjects will also complete questionnaires on quality of life

(PROMIS Global health Scale and EORTC-QLQ-C30), pain (modified brief pain inventory-short form (mBPI-sf)), psychological impact of pain (Hospital Anxiety and Depression Scale (HADS)) and situational catastrophizing (PCS). It will take approximately 30-60 minutes for subjects to complete the baseline questionnaires.

All subjects will also undergo QST testing at baseline. The procedures are described below in the section entitled “Experimental endpoints (quantitative sensory testing – QST).”

**Followup Testing:**

As part of their regular medical care, some subjects may undergo Endoscopic Ultrasound (EUS), Endoscopic Retrograde Cholangiopancreatography (ERCP), Extracorporeal Shock Wave Lithotripsy (ESWL), surgery, laboratory and imaging studies, and medical treatment. We will review medical records to collect data on these variables prior to enrolment and during the course of the study.

Follow-up testing will be limited to subjects who undergo endoscopic treatment or surgery for the pancreatitis or for SOD. These subjects will fill out a pain diary for 7 days prior to their intervention, as well as for seven days before each follow-up research visit at 1 month, 3 month, and 6 months post-intervention. The pain diary is designed to assess pain intensity and dynamics over time, and is based on a 0-10 NRS rating scale. Both the median and maximal pain for the last 24 hours is registered. It will take approximately 5 minutes per day for subjects to complete the pain diary. These subjects will also undergo QST testing at each follow-up visit at 1 month, 3 months, and 6 months. Lastly, these subjects will fill out the same baseline questionnaires (PROMIS, EORTC-QLQ-C30, mBPI-sf, HADS, PCS), and additionally the Patient’s Global Impression of Change (PGIC) questionnaire for assessment of change in symptoms over time.

**Study Timeline:** Study procedures at baseline and during follow-up and which groups of study subjects will complete individual procedures

	<b>Baseline</b>	<b>Follow-up day 30 post- intervention</b>	<b>Follow-up day 90 post- intervention</b>	<b>Follow-up day 180 post- intervention</b>
QST Testing	All Subjects	Subjects who underwent invasive intervention	Subjects who underwent Invasive intervention	Subjects who underwent invasive intervention
Standardized Patient Questionnaires (PROMIS, EORTC, HADS, BPIsf, PCS)	All Subjects	Subjects who underwent invasive intervention (Add PGIC)	Subjects who underwent invasive intervention (Add PGIC)	Subjects who underwent invasive intervention (Add PGIC)
Pain Diary for 7 days prior		Subjects who underwent invasive intervention	Subjects who underwent invasive intervention	Subjects who underwent invasive intervention
Personal medical history	All Subjects	Collect changes from subjects who	Collect changes from subjects who	Collect changes from subjects who

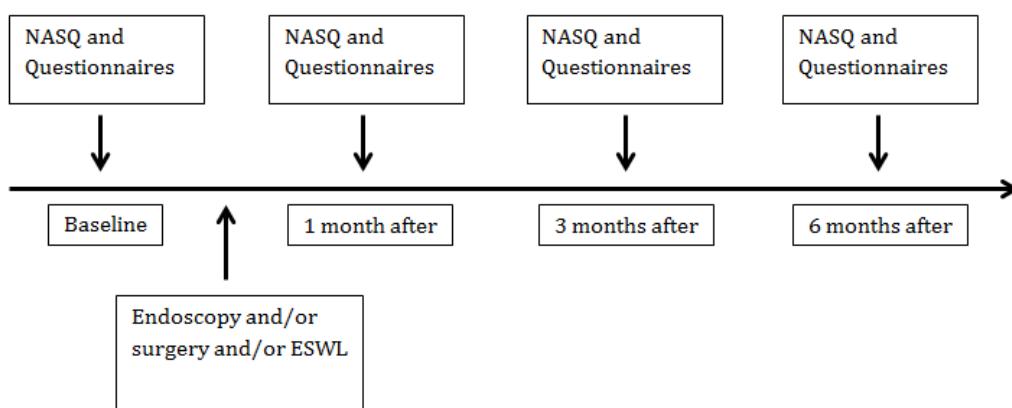
		underwent invasive intervention	underwent invasive intervention	underwent invasive intervention
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\***Intervention: endoscopic therapy or surgery**

### Study Timeline:

After informed consent the QST profile (NASQ in the figure) will be performed as seen in Figure xx. Follow-up QST testing as described above will only be performed in subjects who undergo endoscopic therapy or surgery.

Figure 4: Study timeline



### Experimental endpoints (quantitative sensory testing - QST)

*Repetitive pinprick stimulation (temporal summation):* Recording of temporal summation to repetitive pinprick stimulations in the pancreatic and control area (midline volar site of dominant forearm) will be employed using a 8mN PinPrick device (Pin-Prick Stimulatoren, MRC Systems GmbH, Heidelberg, Germany). Pain ratings using a 0-10 NRS scale will be obtained after a single application, and after the last application in a series of ten repetitive stimuli with an inter-stimulus interval of 1 second. For accurate timing of the stimuli the procedure is guided by an auditory signal using a metronome. The difference between the last and the first scores of the ten stimuli will be recorded as the temporal summation score.

*Muscle pressure stimulation:* The pressure pain detection threshold (PDT) and pain tolerance threshold (PTT) will be determined for the following skin dermatomes: C5 (clavicula), T10 ventral (upper epigastric area – pancreatic viscerotome), T10 back (pancreatic viscerotome), L1 (anterior superior iliac crest) and L4 (the quadriceps 15 cm above the patella). All lateralized pressure stimulations are applied on the subject's dominant side. An electronic pressure algometer (Algometer Type II, SBMEDIC Electronics, Solna, Sweden) with a probe surface area of 1 cm<sup>2</sup> is used for the pressure stimulations. Pressure will be increased in two sessions at a rate of 30 kPa per second until the PDT or PTT is reached and subjects will be instructed to press a button at this point. The assessment parameter is the pressure at the predefined sensory threshold measured in kPa.

*Bone pressure stimulation:* The same pressure algometer as described above will be used to mechanical stimulation on the right tibia bone, but with a specially designed probe of 3.1 mm<sup>2</sup> (Aalborg University, Denmark). The device has been used in previous studies and proven its reliability and validity<sup>20,21</sup>. Pressure will be applied at the tibial bone on the dominant site 10 cm distal to the lowest border of patella with a pressure rate at 30 kPa per second. Pain thresholds are determined as for muscle pain.

*Cold pressor test:* The dominant hand is immersed in an ice-chilled water bucket (2.0°C ± 0.3°C). The subject will be told to remove the hand from the water after 2 minutes of immersion or sooner if the pain is intolerable. The subjects rate the pain intensity for every 10 seconds during the cold pressor test using a 0-10 NRS rating scale. If the subject withdraws their hand sooner than two minutes, due to intolerable pain, the VAS will be considered to be 10 for the remaining period of time and the time for withdrawal of the hand will be noted.

*Conditioned pain modulation (CPM):* CPM is a clinically measurable form of descending pain modulation that can be induced experimentally by a conditioning stimulus (the cold pressor test) and quantified by applying a “test-pain” (pressure stimulation on the non-dominant quadriceps musculature 4 cm above the patella) before and after the conditioning stimulus<sup>22</sup>. The difference in pressure stimulus intensity (PTT) before and after the cold pressor test provides a quantitative index of the CPM capacity in the individual subject. The techniques used for pressure stimulation and cold pressor test described above will be combined to measure CPM.

QST testing will be performed at the GI clinic or Digestive Disorders Center or the GI lab at UPMC-Presbyterian and UPMC-Shadyside Hospital by the clinical research coordinator or a physician investigator.

#### **Device:**

Recording of temporal summation to repetitive pinprick stimulations in the pancreatic and control area (midline volar site of dominant forearm) will be employed using a 256 nm Von Frey Hair (Pin-Prick Stimulatoren, MRC Systems GmbH, Heidelberg, Germany).

The pressure pain detection threshold (PDT) and pain tolerance threshold (PTT) will be determined for the following skin dermatomes: C5 (clavicular), T10 ventral (upper epigastric area – pancreatic viscerotome), T10 back (pancreatic viscerotome), L1 (anterior superior iliac crest) and L4 (the quadriceps 15 cm above the patella), with an electronic pressure algometer (Algometer Type II, SBMEDIC Electronics, Solna, Sweden) with a probe surface area of 1 cm<sup>2</sup> is used for the pressure stimulations. Bone pressure stimulation will be measured with a probe of 3.1 mm<sup>2</sup> (Aalborg University, Denmark). The device has been used in previous studies and proven its reliability and validity<sup>20,21</sup>.

#### **Questionnaires to be used in the study:**

Hospital Anxiety and Depression Scale (HADS)

PROMIS Global Health Scale (PGHS)

Modified Brief Pain Inventory – short form (mBPI-sf)

Pain Catastrophizing Scale (PCS)

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)

Patient's Global Impression of Change (PGIC)

#### **Clinical Outcomes:**

The primary clinical endpoint will be:

- QST profile of subjects with Definite or Suspected CP, SOD, Functional Dyspepsia, and controls

The secondary clinical endpoint will be:

- In subjects undergoing endoscopic or surgical treatment - The absolute and percentage change from baseline in ratings of average pain in the past week at day 90 using a daily pain diary based on a 0-10 numerical rating scale (NRS). A percentage change of  $\geq 30\%$  is considered clinically significant.

### **Sample Size:**

#### **Sample size determination and statistical methods**

This is an explorative pilot study and therefore no formal power calculation has been conducted.

We plan to enroll a total of 500 subjects in the study, of whom at least 60 will be undergoing endotherapy, and at least 100 will be controls. The analysis of clinical and experimental endpoints will be by per-protocol, meaning that only subjects completing the experimental setup are included. The predictive value of the QST profiles will be analyzed using logistic regression and machine learning. Mixed models will be used to analyze the changes in clinical and experimental endpoints over time and subsequent analyses directed at the secondary clinical and experimental endpoints are analyzed using appropriate statistics.

### **Patient Recruitment**

Subject with Definite or Suspected CP, SOD type 1 or 2, or Functional Dyspepsia:

1. Subjects who are receiving care in the Digestive Disorders Center at UPMC Presbyterian-Montefiore Hospital or GI clinic at UPMC Shadyside Hospital for Definite or Suspected CP, or SOD type 1 or 2, or Functional Dyspepsia, will be pre-screened for potential enrolment by the study team. The study team provides clinical care to these subjects. If no exclusion criteria are present, and the subject meets the inclusion criteria, the study team will discuss the study with the subject for potential recruitment, and obtain informed consent.
2. Subjects who are receiving care as in-patients at UPMC Presbyterian-Montefiore Hospital or at UPMC Shadyside Hospital for Definite or Suspected CP, or SOD type 1 or 2 will be pre-screened for potential enrolment by the study team. The study team provides clinical care to these subjects. If no exclusion criteria are present, and the subject meets the inclusion criteria, the study team will discuss the study with the subject for potential recruitment, and obtain informed consent.
3. Physicians and other health care professionals at UPMC Hospitals, and in the area will be made aware of this study at the University of Pittsburgh by means of various internal communications. Referring physician will discuss about the study with subjects who may be potentially eligible, and if they are interested will provide their information to the study team to contact. The referring physicians may also ask the interested subject to contact the study team to discuss more about the study and potential recruitment. If an interested subject contacts the study team, the clinical research coordinator or physician investigator will schedule a study visit for the subject at the Digestive Disorders Center Pancreas Clinic at UPMC Presbyterian-Montefiore Hospital or GI clinic at UPMC Shadyside Hospital to undergo screening for eligibility. The study team will discuss the study with the subject for potential recruitment, and obtain informed consent. If the subject meets the inclusion criteria and no exclusion criteria are present, the subject will be enrolled in the study.
4. Subjects will be identified through the Clinical + Translational Science Institute (CTSI), via the Research Patient Registry. This is a voluntary database of individuals who have consented to be contacted for potential participation in research studies. The Registry's novel software matches participants, based on their demographics and ICD-9/10 codes and/or health preferences, with studies for which they may be eligible.

Controls:

1. Controls with no pancreas disease and no abdominal pain, or who have functional dyspepsia may be recruited through various tools, such as advertisements (e.g. brochures, university wide advertisements), the CTSI research patient registry, as well as approaching subjects who come in for preventive services (e.g. screening colonoscopy) to the GI lab, or for evaluation for other unrelated conditions (gastroesophageal reflux, dysphagia, etc) to the GI clinic or Digestive Disorders Center.

A prepared script will be read to the responders to advertisement to prescreen them for eligibility. If the subject agrees to participate, the coordinator will obtain a waiver to document the informed consent, and then ask questions regarding potential eligibility. If the subject is eligible, the research coordinator will schedule a study visit to sign an informed consent and undergo a more thorough screening evaluation to determine if the subject meets additional criteria to participate in the study. During the study visit the coordinator will review the study with the subject in detail, answer any questions, and if the subject is eligible, complete research related procedures. Prior to any research procedure, an informed consent will be obtained by the PI or physician investigator.

Subjects who are coming for screening colonoscopy or those with unrelated conditions identified from the Digestive Disorders Clinic will be pre-screened for potential enrolment by the study team. If no exclusion criteria are present, and the subject meets the inclusion criteria, the PI or Physician Investigator will discuss the study with the subject for potential recruitment. The PI or physician investigator and Clinical Research Coordinator will discuss with the subject about the study, answer any questions. The PI or physician investigator will obtain informed consent.

Subjects will be given as much time as needed to make a decision about study participation. They are encouraged to take the consent form home with them and to discuss their decision with their friends, family, personal care physician, etc. prior to deciding about participating in the trial. They are also informed by the study staff that their decisions will not affect their future care, and that their participation is entirely voluntary, and that they may withdraw from participation at any time.

Eligible subjects will have the study explained to them in detail, and they will be provided with the informed consent form. Any and all questions will be answered by the Principal investigator, other physician investigator(s) who are part of the study or study coordinator. Study enrolment will be initiated only after subjects have had all questions answered and have signed the informed consent form.

## **Consent**

The consent process will be carried out as a joint effort among the study coordinator, PI or physician who is listed as an investigator on the study and the subject's physician (if applicable). If the subject is eligible for the study and has no exclusion criteria, the physician investigator and the clinical research coordinator will discuss with the subject about participation in the study and answer questions that the subject has about the study. The PI or physician investigator will obtain informed consent. Once all questions are satisfactorily addressed, the participant signs the consent form along with the investigator and a copy of the consent form is given to the participant.

The potential participant will be address in a private room and the most current IRB-approved informed consent form is reviewed point by point. All aspects of the clinical study will be explained to the subject, including but not limited to the nature of participation. In addition, the subject is informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.

## **Data Safety**

**Data and Safety Monitoring Plan (DSMP):**

Overall safety of research participants and adverse events will be continuously monitored by the Principal Investigator, study investigators and research staff. All suspected adverse events should be reported immediately to the Principal Investigator. Overall safety and study-wide adverse events will be reviewed by the local Data Safety and Monitoring Team consisting of the Principal Investigator, research staff and study investigators. Reportable Events will be submitted to the University of Pittsburgh Institutional Review Board per its reporting guidelines.

**Local DSMB:**

A local Data Safety and Monitoring Board (DSMB) will be responsible for meeting every 6 months to evaluate the progress of the research study, including assessment of data quality and subject recruitment. They will also monitor any suspected adverse events that are reported related to the devices and will assess to determine if the study design needs to be refined. They will also review the procedures designed to protect the privacy of the research subjects and confidentiality of the research data. The results of the DSMB meeting will be submitted to the IRB at the time of the annual renewal.

**Data Safety:**

All data entered into a local computer will be password protected. Care will be taken to ensure that the personal information in a subject's medical record and research records will be kept private. To protect subject privacy, the study staff will use a study number and initials rather than name on any photocopies of study records, and on any records that are sent outside of the local research institution(s) for review or testing. If information from this study is published in scientific journals or presented at scientific meetings, the subject's name and other personal information will not be used. Any breach in subject confidentiality will be reviewed at the DSMB and reported to the IRB per its guidelines.

All data will be keyed into the web accessible RedCap database by the assigned staff. Only study IDs will be used for data entry.

This information is explained to the study participants in the informed consent as follows: If you agree to participate in the study, you can change your mind up until the end of the study. When study researchers receive written instructions from you, they will destroy your records and all information that identifies you. After the study ends, you will not be able to withdraw your records because the data storage facility will not know which records are yours.

Data obtained as part of this study will be stored securely for secondary analyses.