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# A multicenter study of total pancreatectomy with islet autotransplantation (TPIAT): POST (Prospective Observational Study of TPIAT)

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ABSTRACT

*Background/objectives:* Total pancreatectomy with islet autotransplantation (TPIAT) is considered for managing chronic pancreatitis in selected patients when medical and endoscopic interventions have not provided adequate relief from debilitating pain. Although more centers are performing TPIAT, we lack large, multi-center studies to guide decisions about selecting candidates for and timing of TPIAT.

*Methods:* Multiple centers across the United States (9 to date) performing TPIAT are prospectively enrolling patients undergoing TPIAT for chronic pancreatitis into the Prospective Observational Study of TPIAT (POST), a NIDDK funded study with a goal of accruing 450 TPIAT recipients. Baseline data include participant phenotype, pancreatitis history, and medical/psychological comorbidities from medical records, participant interview, and participant self-report (Medical Outcomes Survey Short Form-12, EQ-5D, andPROMIS inventories for pain interference, depression, and anxiety). Outcome measures are collected to at least 1 year after TPIAT, including the same participant questionnaires, visual analog pain scale, pain interference scores, opioid requirements, insulin requirements, islet graft function, and hemoglobin A1c. Health resource utilization data are collected for a cost-effectiveness analysis. Biorepository specimens including urine, serum/plasma, genetic material (saliva and blood), and pancreas tissue are collected for future study.

*Conclusions:* This ongoing multicenter research study will enroll and follow TPIAT recipients, aiming to evaluate patient selection and timing for TPIAT to optimize pain relief, quality of life, and diabetes outcomes, and to measure the procedure's cost-effectiveness. A biorepository is also established for future ancillary studies.



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## Introduction

Chronic pancreatitis (CP) and recurrent acute pancreatitis (RAP) represent a spectrum of disease in which patients suffer from episodic and progressive inflammation and fibrotic replacement of the exocrine and endocrine pancreas [1]. Affected patients often suffer from abdominal pain which can be severe and difficult to treat, ultimately resulting in impaired quality of life, inability to attend work or school, and increased health care utilization with repeated emergency department visits or hospitalizations [2–8]. First-line therapies for CP and RAP include low-fat diet, pancreatic enzyme therapies to reduce pancreatic stimulation, comprehensive pain management, and endoscopic retrograde cholangiopancreatography (ERCP) for endoscopic sphincterotomy and stent placement [9–12]. When medical and endoscopic therapies fail in patients with debilitating pain and consequent life disruption, surgical therapy is considered including ductal drainage or parenchymal resection procedures, depending on pancreatic duct and tissue morphology. In some patients, particularly those with diffuse small duct disease or with genetic pancreatitis or those who have failed lesser surgeries, total pancreatectomy with islet autotransplantation (TPIAT) may be considered [13].

In TPIAT, the goal of pancreatectomy is to relieve pain and restore quality of life, while islet autotransplantation is intended to reduce the burden of post-surgical diabetes [14]. Centers performing TPIAT have individually reported improvements in health-related quality of life, reduction in pain symptoms, and reduction in opioid use [13,15–17]. Despite pain symptom improvement, however, about half of patients may require opioid analgesics 1 year after surgery, and about 25% 5 years after TPIAT [13,15]. In one single-center analysis, about 15% of patients reported pain burden at 1–3 years after TPIAT similar to what they experienced before TPIAT [13]. Preliminary data suggest that poor outcomes might be associated with specific risk factors such as past alcohol abuse disorder or prolonged opioid use, while children may have greater chance of pain relief and insulin independence [18–20]. Diabetes outcomes vary greatly, ranging from full insulin independence soon after TPIAT in 30–50% of patients, to complete failure of the islet graft either due to low islet mass available for isolation or poor survival of the transplanted islets [13,19,21–23].

With increasing utilization of TPIAT as a therapy for CP and RAP, larger collaborative studies of carefully phenotyped and followed TPIAT recipients are critical to identify patient, disease, and surgical characteristics that may guide selection of candidates likely to benefit from TPIAT, avoid TPIAT surgery for those unlikely to benefit, and to determine the optimal timing of TPIAT. The variability in approach to TPIAT from different centers represents an obstacle to performing high quality comparative effectiveness studies that can guide management and ensure optimal patient outcomes. This was identified as a key research gap by experts convening at the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored workshop to define research priorities in TPIAT in July 2014 [24,25]. To address these critical research gaps, a multicenter research consortium was formed under a 5-year grant from the NIH (grant R01DK109124, PI M. Bellin) to prospectively collect data about pain, quality of life, glycemic control, and cost-effectiveness in patients undergoing total pancreatectomy or completion pancreatectomy with islet autotransplant (TPIAT), under a study protocol entitled: Advancing Treatment for Pancreatitis: a Prospective Observational Study of TPIAT (**POST**). The specific aims of the POST study are to determine patient and disease characteristics and timing of intervention associated with optimal pain and quality of life outcomes (SA 1), to determine patient and disease characteristics and timing of intervention associated with optimal diabetes outcomes (SA 2), and to assess the cost-effectiveness of TPIAT (SA 3).

## Methods

### *Participating centers*

The current POST consortium members include the University of Minnesota, Baylor Medical Center, Medical University of South Carolina, Cincinnati Children's Hospital, John Hopkins Medical Institutions, Dartmouth-Hitchcock Medical Center, University of Chicago, University of Pittsburgh Medical Center, and The Ohio State University Wexner Medical Center, with additional membership anticipated. Member sites and contact information are listed on the study website at www.tpiat.study, and the study is registered on ClinicalTrials.gov (NCT03260387).

All sites submit data to a data and coordinating center (DCC) at the University of Minnesota Division of Biostatistics that includes a biostatistician, study manager, and database manager. The DCC maintains a secure, regulatory-compliant web site that is used to enter study data, to post reports for use by enrollment site coordinators and investigators, and to download paper case report forms (CRFs) and other study documents (e.g., the manual of procedures). Data is double entered from CRFs into the electronic data-capture system by participating sites.

### *Study aims and participant eligibility*

The study's aims are to identify characteristics associated with favorable pain, quality of life, and diabetes outcomes and to measure the cost-effectiveness of TPIAT (Table 1). To address these aims, 450 participants of any age, who are undergoing TPIAT to manage CP or RAP, are eligible for enrollment. Patients who undergo TPIAT for a diagnosis other than CP or RAP (i.e. tumor or trauma) are excluded, as are patients having a primary partial pancreatectomy (distal or Whipple/pancreatic head resection) with IAT, due to potential impact of the residual pancreas on pain and diabetes outcomes. By design, the study does not define CP or RAP, except that participants must meet the clinical criteria to undergo TPIAT as established by the participating center. The rationale for this approach is that the study is intended to encompass the current full spectrum of patients undergoing this procedure in the U.S., to determine which patients are likely to benefit from surgery. Baseline CRFs capture the symptoms and procedures that lead to the diagnosis of CP or RAP, as well as prior clinical course and treatments performed.

### *Study assessments*

Participants are assessed before surgery (within 3 months) and postoperatively at 6 months, 1 year, and then yearly until the end of the study (up to 4 years). Recruitment is planned such that each participant will have $\geq$1 year of follow-up by the end of the grant period. To optimize retention of participants, many of whom live far from the treating center, follow-up visits are performed face-to-face or remotely by telephone interview, with lab measurements obtained at a local clinic when follow up occurs remotely. Key baseline characteristics collected from participant interview and medical records include demographics; etiology of pancreatitis; disease duration; prior medical, endoscopic, and surgical

**Table 1**
Specific Aims of the Prospective Observational Study of Total Pancreatectomy with Islet Autotransplant (POST) study.

| Aim# | Aim as stated in the study protocol |
|---|---|
| 1 | The primary aim of this study is to determine (1a) whether patient and disease characteristics are associated with favorable pain and health-related quality-of-life outcomes (HRQOL) after TPIAT; (1b) the optimal timing of the TPIAT intervention to resolve pain and improve HRQOL; and (1c) in a subset of patients, the impact of central sensitization on pain resolution. |
| 2 | To determine (2a) whether patient and disease characteristics are associated with favorable glycemic outcomes from the IAT procedure; and (2b) the optimal timing of TPIAT to obtain post-surgical insulin independence. |
| 3 | To determine the cost-effectiveness of TPIAT. |

treatments for pancreatitis; analgesic dosage; complications of pancreatitis; psychiatric diagnoses; health-care utilization related to pancreatitis (procedures and hospitalizations); and details of perioperative management including the surgical procedure and approach, islet dose transplanted, and surgical complications. Participants are asked to complete questionnaires before surgery including the Medical Outcomes Survey Short Form-12 (SF-12), EQ-5D, visual analog pain scores, and NIH PROMIS instruments for depression, anxiety, and pain interference. Pediatric and adult versions of the PROMIS instrument are administered depending on participant age (<18 or ≥18 years). Labratory measurements collected include fasting glucose, C-peptide, and hemoglobin A1c as well as liver enzymes and fat soluble vitamin levels. These labs were agreed upon by consortium members as consistent with recommended best care for a TPIAT recipient. Serum, plasma, buffy coat, saliva, urine, and when feasible a small pancreatic biopsy (300 mcg x 1–2 biopsies) are collected for biorepository storage for future ancillary studies. A subset of participants at the University of Minnesota will undergo quantitative sensory testing (QST) with thermal stimuli using the PATHWAY Model AST (Medoc, Yishai, Israel) on a pancreatic and peripheral dermatome as well as a conditional pain modulation protocol to assess measures of central sensitization before surgery.

After surgery, participant use of opioid and non-opioid analgesics, insulin and other anti-diabetic medications, and pancreatic enzymes are collected at each visit by interview. Data describing health resource utilization, including hospital admissions, outpatient visits, and procedures, is collected from both participant interview and medical records. At each follow up interview (6 months, 1 year, yearly), participants again complete quality of life and pain assessment questionnaires. Labs are collected consistent with recommended standard clinical practice including fasting glucose, fasting C-peptide, hemoglobin A1c, liver panel, and fat soluble vitamin levels (A, D, and E). If the participant is seen face-to-face for the 1 year follow-up, serum, plasma, and urine are collected for the biorepository. Table 2 summarizes study outcomes.

### *Statistical power*

The accrual goal is 450 participants across all centers; allowing for loss to follow-up, we compute power assuming retention of at least 400 participants at 1 year for the primary analyses. With up to 10 predictors per analysis, the design has 80% power to detect $R^2 = 0.04$ for those predictors (equivalent to Pearson's $r = 0.20$) and 90% power to detect $R^2 = 0.05$ (equivalent to Pearson's $r = 0.22$). In analyses considering individual predictors for binary outcomes, we will have 80% power to detect an odds ratio (OR) of 0.74–0.77 (equivalently 1.30 to 1.35) depending on the overall rate of the binary outcome, and 90% power to detect an odds ratio (OR) of 0.71–0.74 (equivalently 1.35 to 1.40).

### *Analyses for specific aims 1 and 2: risk modeling for pain remission, quality of life, and diabetes outcomes*

For each primary outcome describing HRQOL and pain, we will devise a likely-to-benefit score computed from patient and disease characteristics including timing (time from diagnosis of pancreatitis to surgery), and allowing the effect of other characteristics to depend on timing (i.e., including timing-by-X interactions) so that a higher score indicates the patient is more likely to benefit. For each primary outcome measure, regression analysis (linear or logistic, as appropriate) will be performed to model how the primary outcome is related to the predictors. For the primary outcome measure of insulin independence, logistic regression analysis will be performed to model the primary outcome as a function of predictors, in the same manner as just described.

### *Analyses for specific aim 3: cost-effectiveness*

To address the cost-effectiveness of TPIAT, we will compare costs of TPIAT with the extrapolated costs of continued medical management without TPIAT using the participant's costs in the 18 months before surgery to estimate the cost of continued medical care. We make the assumption that participants would continue in the same state of impaired health if not treated with TPIAT. Baseline costs will be determined by the healthcare utilization experience related to pancreatitis abstracted from the participant's electronic medical record during the 18 months before TPIAT, converted to Medicare billing codes and then to U.S. dollars using Medicare unit costs. Utilization includes medications (opioids, pancreatic enzymes, and diabetes medications), inpatient admissions and procedures (diagnostic related groups, and number and length of stay), emergency department use, office visits, diagnostic tests, and outpatient procedures (endoscopic retrograde cholangiopancreatography, endoscopic or percutaneous celiac plexus block, feeding tube or central venous line/port placement, imaging and non-TPIAT surgery). The same utilization data will be collected at each study visit to assess costs after surgery. Because participants will have variable durations of follow up depending on time of enrollment, for the purpose of this analyses, we will include participants with at least 2 years of follow-up ($n = 375$). To hold constant the time period, costs will be rolled up and converted to expenditures per month, adjusted for inflation by the Personal Health Care Expenditure deflator [26] possibly modified by the personal consumption expenditure price index [27]. Quality adjusted life years (QALY) assessment is performed using the 5-question EQ-5D at baseline and at each follow-up visit, and evaluated using the standard American weights [28]. Both expenditures and QALYs will be discounted at a 3% rate per the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine [29].

Incremental cost effectiveness ratios (ICERs) will be constructed using the baseline costs and quality of life (QOL) weights to represent the counterfactual natural history of the disease

**Table 2**
Key outcome measures in POST.

| Outcomes (category) | Primary outcomes | Secondary outcomes |
|---|---|---|
| Pain resolution | * Visual analog pain scale | * Opioid use (any)<br>* Opioid dose in daily morphine equivalents<br>* Pain interference score |
| Health related quality of life | * SF-12 physical component summary (PCS) score<br>* SF-12 mental component summary (MCS) score | * SF-12 subscales<br>* Number of hospitalizations<br>* Number of ED visits<br>* Disability (working/attending school) |
| Diabetes and glycemic control | * Insulin independence (no insulin required with HbA1c $\leq$ 6.5%) | * Insulin dose<br>* Fasting C-peptide<br>* Hemoglobin A1c<br>* Graft function (fasting C-peptide $\geq$0.3 ng/mL)<br>* Severe hypoglycemia |
| Cost-Effectiveness | * Composite analysis of health utilization and EQ-5D | |
| Other | | * Nutritional measures<br>* Pre-specified events of interest including abdominal surgery, GI complications |

assuming no TPIAT intervention during the 2 year follow-up period. This is a conservative assumption because we believe that cost would likely have increased over this period without intervention, as aging and chronicity would affect the disease's course. To measure the effect of intervention, the QOL weights will be determined by the average QOL over the 2 years of follow up. Sensitivity analysis (one-way, threshold, and probabilistic) will be conducted and cost-effectiveness acceptability curves will be calculated.

## Discussion

When medical and endoscopic therapies fail to treat intractable pain and disability in chronic pancreatitis, surgical therapy including TPIAT may be considered. The goal of TP is to relieve the underlying cause of debilitating pain, while the IAT is undertaken to reduce the burden of post-pancreatectomy diabetes. Patient selection and surgical timing have not been well established to date. The field of TPIAT is growing, reflected in more centers performing the procedure and more procedures performed over the past decade. Yet much remains unknown about how to optimize pain, quality of life, and diabetes outcomes using this procedure [21,30–36]. Questions remain around patient selection, risk for persistent pain and disability, diabetes risks, and optimal timing of surgery. Thus, it is critically important to advance the field of TPIAT through well-executed large-volume multi-center research, to understand which patients will benefit from the procedure, and when and how to intervene. The POST study is designed to address these gaps in the research.

The most critical outcome of TPIAT is success or failure at reducing pain burden and improving quality of life. The current study's measures of pain burden include changes in visual analog pain scores, pain interference scores, and daily opioid requirements. The SF-12 is used as a standard measure of health-related quality of life. Single-center studies suggest improvements in pain burden, reduced opioid use, and improvement in physical and mental component summary scores overall, but with a proportion of patients reporting high persistent pain burden or opioid use. Factors that may influence success of the surgery that will be measured include but are not limited to duration of pancreatitis, type of medical and endoscopic interventions performed before surgery as well as opioid use and duration before surgery, because long disease or high opioid use may contribute to central sensitization and opioid-induced hyperalgesia that could limit the benefit of TPIAT [37–39]. Also, medical and psychological comorbidities including gastroparesis, depression, and anxiety have been suggested as potential risk factors for poor outcomes. All such measures require better systematic assessment in a large cohort that incorporates the diversity of multiple treating centers. Cost-effectiveness analysis will also be undertaken to compute the cost-to-benefit ratio of TPIAT compared to continued non-surgical care.

While risk of post-operative diabetes does not necessarily dictate surgical candidacy, patients and providers benefit from an accurate assessment of post-procedure diabetes risk. The best predictor of diabetes outcomes is islet mass transplanted, which is not known before the pancreatectomy. Risk modeling in the large POST cohort, incorporating patient characteristics such as disease etiology, disease duration and severity, number and type of interventions prior to TPIAT, morphologic features on imaging, anthropometric measures, and baseline metabolic labs will help to provide more accurate risk assessment for individual patients and guide informed decisions about timing of a TPIAT intervention. Ultimately, physicians offering TPIAT want to find the right balance between not intervening too early (when TPIAT is not necessary) versus intervening too late (when risk is high for persistent chronic pain and diabetes).

The POST study is an observational study protocol. Laboratory assessments and data abstracted from medical records are designed to coincide with standard of care in this population, with additional information provided by standard interview and participant-completed questionnaires. An initiative towards a standardization of approach and management of TPIAT patients will allow comparative effectiveness studies to be conducted. More cumbersome metabolic testing that may be suitable for research is not included in the standard protocol, although some centers are performing mixed meal tolerance testing with Boost HP in addition to the standard fasting C-peptide and glucose. Because of the specialized equipment and procedures required to assess central sensitization, quantitative sensory testing is not performed for all study participants, but will be performed in a subset. Biorepository specimens will be maintained for pancreas tissue, blood, urine, and genetic material that can serve as the basis for ancillary studies. This may include future research on genetic testing in different domains including phenotypes of pancreatitis, diabetes risk, or markers of opioid drug metabolism or risk for substance abuse disorders.

In conclusion, the POST study consortium is conducting the first large, prospective multicenter study of TPIAT. The study's aims are to provide predictive models to guide patient selection and timing of TPIAT to optimize pain relief, quality of life, and diabetes outcomes, as well as to provide a cost-effectiveness analysis of TPIAT.

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## References

[1] Machicado JD, Yadav D. Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. Dig Dis Sci 2017;62(7):1683–91.
[2] Mullady DK, Yadav D, Amann ST, O'Connell MR, Barmada MM, Elta GH, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut 2011;60(1):77–84.
[3] Pezzilli R, Morselli Labate AM, Fantini L, Gullo L, Corinaldesi R. Quality of life and clinical indicators for chronic pancreatitis patients in a 2-year follow-up study. Pancreas 2007;34(Journal Article):191–6.
[4] Fitzsimmons D, Kahl S, Butturini G, vanWyk M, et al. Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. Am J Gastroenterol 2005;100(Journal Article):918–26.
[5] Wehler M, Reulbach U, Nichterlein R, Lange K, Fischer B, Farnbacher M, et al. Health-related quality of life in chronic pancreatitis: a psychometric assessment. Scand J Gastroenterol 2003;38(10):1083–9.
[6] Schwarzenberg SJ, Bellin M, Husain SZ, Ahuja M, Barth B, Davis H, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. J Pediatr 2015;166(4), e1. 890–896.
[7] Machicado JD, Amann ST, Anderson MA, Abberbock J, Sherman S, Conwell DL, et al. Quality of life in chronic pancreatitis is determined by constant pain, disability/unemployment, current smoking, and associated Co-Morbidities. Am J Gastroenterol 2017;112(4):633–42.
[8] Uc A, Andersen DK, Bellin MD, Bruce JI, Drewes AM, Engelhardt JF, et al. Chronic pancreatitis in the 21st century - research challenges and opportunities: summary of a National Institute of diabetes and digestive and Kidney diseases workshop. Pancreas 2016;45(10):1365–75.
[9] Chauhan S, Forsmark CE. Pain management in chronic pancreatitis: a treatment algorithm. Best Pract Res Clin Gastroenterol 2010;24(3):323–35.
[10] Olesen SS, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology 2011;141(2):536–43.
[11] Issa Y, van Santvoort HC, van Goor H, Cahen DL, Bruno MJ, Boermeester MA. Surgical and endoscopic treatment of pain in chronic pancreatitis: a multidisciplinary update. Dig Surg 2013;30(1):35–50.
[12] Drewes AM, Bouwense SAW, Campbell CM, Ceyhan GO, Delhaye M, Demir IE, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology 2017;17(5):720–31.
[13] Sutherland DE, Radosevich DM, Bellin MD, Hering BJ, Beilman GJ, Dunn TB, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg 2012;214(4):409–24.
[14] Kirchner VA, Dunn TB, Beilman GJ, Chinnakotla S, Pruett TL, Wilhelm JJ, et al. Total pancreatectomy with islet autotransplantation for acute recurrent and chronic pancreatitis. Curr Treat Options Gastroenterol 2017;15(4):548–61.
[15] Wilson GC, Sutton JM, Abbott DE, Smith MT, Lowy AM, Matthews JB, et al. Long-term outcomes after total pancreatectomy and islet cell autotransplantation: is it a durable operation? Ann Surg 2014;260(4):659–65. discussion 65–67.
[16] Chinnakotla S, Radosevich DM, Dunn TB, Bellin MD, Freeman ML, Schwarzenberg SJ, et al. Long-term outcomes of total pancreatectomy and islet auto transplantation for hereditary/genetic pancreatitis. J Am Coll Surg 2014;218(4):530–43.
[17] Morgan K, Owczarski SM, Borckardt J, Madan A, Nishimura M, Adams DB. Pain control and quality of life after pancreatectomy with islet autotransplantation for chronic pancreatitis. J Gastrointest Surg 2012;16(1):129–33. discussion 33–34.
[18] Chinnakotla S, Bellin MD, Schwarzenberg SJ, Radosevich DM, Cook M, Dunn TB, et al. Total pancreatectomy and islet autotransplantation in children for chronic pancreatitis: indication, surgical techniques, postoperative management, and long-term outcomes. Ann Surg 2014;260(1):56–64.
[19] Chinnakotla S, Beilman GJ, Dunn TB, Bellin MD, Freeman ML, Radosevich DM, et al. Factors predicting outcomes after a total pancreatectomy and islet autotransplantation lessons learned from over 500 cases. Ann Surg 2015;262(4):610–22.
[20] Dunderdale J, McAuliffe JC, McNeal SF, Bryant SM, Yancey BD, Flowers G, et al. Should pancreatectomy with islet cell autotransplantation in patients with chronic alcoholic pancreatitis be abandoned? J Am Coll Surg 2013;216(4):591–6. discussion 6–8.
[21] Savari O, Golab K, Wang LJ, Schenck L, Grose R, Tibudan M, et al. Preservation of Beta cell function after pancreatic islet autotransplantation: university of chicago experience. Am Surg 2015;81(4):421–7.
[22] Kesseli SJ, Wagar M, Jung MK, Smith KD, Lin YK, Walsh RM, et al. Long-Term glycemic control in adult patients undergoing remote vs. Local total pancreatectomy with islet autotransplantation. Am J Gastroenterol 2017;112(4):643–9.
[23] Wang H, Desai KD, Dong H, Owzarski S, Romagnuolo J, Morgan KA, et al. Prior surgery determines islet yield and insulin requirement in patients with chronic pancreatitis. Transplantation 2013;95(8):1051–7.
[24] Bellin MD, Gelrud A, Arreaza-Rubin G, Dunn TB, Humar A, Morgan KA, et al. Total pancreatectomy with islet autotransplantation: summary of an NIDDK workshop. Ann Surg 2015;261(1):21–9.
[25] Bellin MD, Gelrud A, Arreaza-Rubin G, Dunn TB, Humar A, Morgan KA, et al. Total pancreatectomy with islet autotransplantation: summary of a National Institute of Diabetes and Digestive and Kidney diseases workshop. Pancreas 2014;43(8):1163–71.
[26] Grosse SD, Zuvekas SH. The price is right: on adjusting health expenditures for inflation. Centers for Disease Control and Prevention: Mimeo; 2015.
[27] Quality AfHRa. Medical expenditure panel Survey (MEPS). Using appropriate price indicies for analysis of health care expenditures or income across multiple years. 2015. Available from: http://meps.ahrq.gov/about_meps/Price_Index.shtml.
[28] Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43(3):203–20.
[29] Neumann Peter J, Sanders Gillian D, Russell Louise B, Siegel Joanna E, Ganiats TG, editors. Cost-effectiveness in health and medicine. second ed. New York: Oxford University Press; 2017.
[30] Witkowski P, Savari O, Matthews JB. Islet autotransplantation and total pancreatectomy. Adv Surg 2014;48:223–33.
[31] Kesseli SJ, Smith KA, Gardner TB. Total pancreatectomy with islet autologous transplantation: the cure for chronic pancreatitis? Clin Transl Gastroenterol 2015;6, e73.
[32] Takita M, Lara LF, Naziruddin B, Shahbazov R, Lawrence MC, Kim PT, et al. Effect of the duration of chronic pancreatitis on pancreas islet yield and metabolic outcome following islet autotransplantation. J Gastrointest Surg 2015;19(7):1236–46.
[33] Morgan KA, Borckardt J, Balliet W, Owczarski SM, Adams DB. How are select chronic pancreatitis patients selected for total pancreatectomy with islet autotransplantation? Are there psychometric predictors? J Am Coll Surg 2015;220(4):693–8.
[34] Zureikat AH, Nguyen T, Boone BA, Wijkstrom M, Hogg ME, Humar A, et al. Robotic total pancreatectomy with or without autologous islet cell transplantation: replication of an open technique through a minimal access approach. Surg Endosc 2015;29(1):176–83.
[35] Bottino R, Bertera S, Grupillo M, Melvin PR, Humar A, Mazariegos G, et al. Isolation of human islets for autologous islet transplantation in children and adolescents with chronic pancreatitis. J Transplant 2012, 642787.
[36] Makary M, Cooper M, Desai N, Jiam N, Warren D, Sun Z, et al., editors. Laparoscopic total pancreatectomy with islet autotransplantation for chronic pancreatitis. Salt Lake City, UT: Society of American Gastrointestinal and Endoscopic Surgeons; 2014.
[37] Bouwense SA, Ahmed Ali U, ten Broek RP, Issa Y, van Eijck CH, Wilder-Smith OH, et al. Altered central pain processing after pancreatic surgery for chronic pancreatitis. Br J Surg 2013;100(13):1797–804.
[38] Pasricha PJ. Unraveling the mystery of pain in chronic pancreatitis. Nat Rev Gastroenterol Hepatol 2012;9(3):140–51.
[39] Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006;104(3):570–87.