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# Total Pancreatectomy and Islet Autotransplantation in Chronic Pancreatitis: Recommendations from *PancreasFest*

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## Abstract

**Description—**Total pancreatectomy with islet autotransplantation (TPIAT) is a surgical procedure used to treat severe complications of chronic pancreatitis or very high risk of pancreatic cancer while reducing the risk of severe diabetes mellitus. However, clear guidance on indications, contraindications, evaluation, timing, and follow-up are lacking.

**Methods—**A working group reviewed the medical, psychological, and surgical options and supporting literature related to TPIAT for a consensus meeting during *PancreasFest*.

**Results—**Five major areas requiring clinical evaluation and management were addressed: These included: 1) indications for TPIAT; 2) contraindications for TPIAT; 3) optimal timing of the procedure; 4) need for a multi-disciplinary team and the roles of the members; 5) life-long management issues following TPIAP including diabetes monitoring and nutrition evaluation.

**Conclusions—**TPIAT is an effective method of managing the disabling complications of chronic pancreatitis and risk of pancreatic cancer in very high risk patients. Careful evaluation and long-term management of candidate patients by qualified multidisciplinary teams is required. Multiple recommendations for further research were also identified.

## Rationale

Recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) (ICD 9 577.1) are related progressive inflammatory syndromes of the pancreas associated with complications that can be disabling and life threatening. In many cases, standard medical and endoscopic treatment is ineffective, while total pancreatectomy alone leads to brittle diabetes with hypoglycemia linked to loss of counter-regulatory pancreatic glucagon. An alternative is total pancreatectomy with islet autotransplantation (TPIAT). However, guidance on indications, contraindications, evaluation, timing, and follow-up related to TPIAT is lacking.

Recurrent acute pancreatitis is defined as more than one episode of acute pancreatitis. Each episode of acute pancreatitis can differ in severity, duration, and the degree of incapacitation from school or work. Furthermore, the frequency of recurrent acute pancreatitis can range from twice in a lifetime to multiple episodes per month.

Chronic pancreatitis can be defined as irreversible damage to the pancreas caused by pancreatic inflammation. Complications of CP include severe parenchymal damage with morphologic changes, including calcifications, and functional changes that are complicated by variable and progressive nutrient maldigestion, diabetes mellitus (pancreatogenic; Type 3c (1, 2)), pain syndromes, and increased risk of pancreatic ductal adenocarcinoma (PDAC) (3, 4). The rate of progression from early CP to end-stage CP varies from a few years to decades, and whereas a majority of patients eventually develop pancreatic exocrine failure and diabetes mellitus, only a subset develop constant pain, and fewer develop pancreatic cancer late in life. Thus, for both RAP and CP, there is variability and uncertainty in the

natural history of the disease for individual patients, and the impact can range from mild inconvenience to a severely disabling and intolerable condition (5, 6).

A common feature of CP is pain, which arises from multiple etiologies. Pain is highly variable among patients, and does not correlate well with severity of fibrosis or with impairment of exocrine or endocrine function. In the North American Pancreatitis Study 2 (NAPS2), about 40% of patients with CP diagnosed by imaging criteria had persistent pain (5, 6). Persistent pain, more than episodic pain regardless of severity, was associated with significantly higher morbidity, worse mental and physical quality of life, and disability for school or work (5, 6). Management of pain can be challenging, with concerns of opiate addiction and even suicide. Pain should be managed early, with optimal therapy targeting the etiology rather than only the symptoms (7). However, in some cases, standard treatment fails and guidance on selecting more invasive or aggressive therapies, the timing of procedures, and choosing appropriate options is lacking.

Chronic pancreatitis is an established risk factor for PDAC (8–11). The risk is independent of underlying etiology, but factors such as smoking (12, 13), diabetes (14–16), and genetics (11, 17) modify pancreatic cancer risk. While fear of cancer is a major issue for many patients with chronic pancreatitis, especially hereditary pancreatitis, screening remains challenging due to distortion of the tissue architecture by inflammation and fibrosis (18). In such cases, key questions remain unanswered, including when is the optimal time for treatments such as total pancreatectomy, and is TPIAT safe in patients at high risk for PDAC?

Over the past decade, there have been technical improvements and growing interest in the use of TPIAT as a surgical intervention and treatment for RAP, CP, and patients thought to be at high-risk for PDAC such as hereditary pancreatitis patients. The rational for TPIAT is that the offending tissue is removed to eliminate pancreatitis and its inflammation, pain, and cancer risk while preserving the islet cells to protect the patient from brittle Type 3c diabetes with loss of both insulin and the counter-regulatory hormone glucagon. While the initial reports and case series have been promising, it must be considered that: (A) the operation is irreversible; (B) there is a risk of serious and life-threatening complications; (C) pain relief is not always experienced; (D) protection from diabetes is often incomplete and of variable durability; (E) all patients will require life-long, full-dose pancreatic digestive enzyme replacement therapy; (F) significant post-surgical gastrointestinal motility dysfunction may occur, and (G) none of these patients could benefit from any future medial approaches for controlling pancreatic pain, cancer risk, or other complications.

Thus, the risk-benefit calculation is complicated. Since there are no consensus guidelines to help physicians and patients approach many of the critical questions and decisions surrounding TPIAT in the contest or RAP and CP, a working group was formed to address these issues.

## Guideline Focus

The *PancreasFest* working group framed the development of their discussion questions and guidance statements around three areas of concern: 1) Indications and contraindications for TPIAT; 2) Evaluation and timing of TPIAT; and 3) Following patients after TPIAT.

## Target Population

The clinical recommendations guide the evaluation and management of pediatric and adult patients who are potential candidates for TPIAT or who have undergone TPIAT and require ongoing care.

## Guideline Development Process

*PancreasFest* is an annual meeting that brings together physicians and scientists with interests in the pancreas: pancreatologists, endoscopists, surgeons, radiologists, molecular biologists, geneticists, epidemiologists, statisticians, systems biologists, and experts in biomarkers (typically 150+ attendees).

At *PancreasFest 2009*, an expert working group convened to identify the most important clinical questions related to TPIAT and prepared state-of-the-art lectures and case studies for presentation at *PancreasFest 2010*. At *PancreasFest 2011*, the group evaluated the current evidence supporting TPIAT and its management and developed specific discussion questions and guidance statements.

At *PancreasFest* 2012, the final process was guided by the Italian Consensus Guidelines for Chronic Pancreatitis (1, 19) . Conference attendees (Appendix) responded to the updated discussion questions and guidance statements and indicated their level of agreement based on a 5-point scale (Table 1) using digital voting devices.

## Evidence Review and Grading

Methods of developing consensus were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Grid to reach decisions on clinical practice guidelines (20) and the Surviving Sepsis Campaign report (21).

## Evidence and Modification

The discussion questions presented to attendees of *PancreasFest 2012* were followed by one or more guidance statements intended to provide a concise summary and, if indicated, a clinical recommendation. Conference attendees (Appendix A and B) discussed the initial questions and guidance statements of the working group, which were projected for the entire conference to see and revise in real-time. The conference participants then voted on the level of agreement with the statements, with the results tabulated and likewise projected for all to see in real-time. If there was less than 80% strong agreement, the statement was further discussed and modified in real time. Following the discussion, a second (final) vote was taken, and the results were again projected. The working group and audience were also invited to identify areas in which there are insufficient data and where further research is

recommended. Some conference participants (Appendix A) also reviewed the manuscript and provided critical comments or additional perspective to more accurately present the evidence.

## Clinical Recommendations

### Discussion Question 1: What are the indications for considering TPIAT to manage chronic pancreatitis?

**Guidance Statement 1—**The primary indication for TPIAT is to treat intractable pain in patients with impaired quality of life due to CP or RAP in whom medical, endoscopic, or prior surgical therapy have failed.

Evidence Level: 2a

Grade of recommendation: B

Level of Agreement: A 76%; B 19%; C 5%; D 0%; E 0%

**Evidence—**In patients with CP, pancreatectomy and islet autotransplantion should be considered in patients with intractable pain and seriously impaired quality of life due to pain. Patients with known genetic causes of chronic or recurrent pancreatitis should be given special consideration for TPIAT, as their disease is unlikely to remit. TP with IAT should be avoided if an established dysplastic or malignant lesion is suspected. Choice of TPIAT versus more conventional surgeries, such as partial resection and/or drainage, is challenging and must be individualized to the patient's anatomy, comorbidities, symptom burden, presence or absence of diabetes, and rate of progression of disease. Total pancreatectomy resects the diseased pancreatic parenchyma but when performed alone, results in brittle insulin-dependent pancreatogenic (type 3c) diabetes mellitus (T3cDM). Simultaneous islet autotransplantion minimizes the risk and severity of post-pancreatectomy diabetes. In IAT, the islets are isolated from the resected pancreas and infused back into the patient's liver, where they secrete insulin in response to ambient blood glucose without the need for any immunosuppression (22, 23). Islet autotransplant is performed at a small number of centers across the US at which facilities meet GMP standards and have expertise in islet isolation.

TPIAT improves quality of life, as measured by SF-36 medical outcomes survey (24–26). Most, but not all, patients report improved or resolved pain, and the proportion of patients requiring narcotics is reduced after TPIAT (25, 27–29). Performing IAT results in longer patient survival compared to TP alone, and despite the upfront cost for surgical admission and islet isolation, TPIAT has been demonstrated to be cost-neutral or cost-effective over a 16 year period, due to the reduction in pain and hospitalizations subsequent to TPIAT (30). Studies to date include retrospective analyses and prospective cohorts (26–29, 31–35).

Despite removing the original source of pain in patients with CP, pain persists or recurs in 10% to 20% of patients after TPIAT. Reasons may include central and peripheral sensitization (36–39), visceral hyperalgesia (40), opiate-induced hyperalgesia (41) and tolerance (42), neuropathic pain (43), myofascial syndromes (44), gastrointestinal dysmotility, narcotic bowel syndrome (45), chronic post-surgical pain (46, 47), and other

causes that may be difficult to diagnose or treat. Many of these persistent pain states are related to altered central nervous system processing of the original peripheral stimulus. Additionally, complex patients with comorbid mental illness, substance use disorders, or difficult to control pre-operative pain (chronic pain states) are at risk for persistent pain and require aggressive pre-operative preparation (48, 49) and pain control, meticulous multimodal perioperative pain management (50–52), psychological support, and structured rehabilitation post-operatively to maximize recovery.

Patients with hereditary pancreatitis or *PRSS1* gene mutations are at an elevated risk of pancreatic adenocarcinoma later in life. The risk of cancer is multifactorial, with smoking and diabetes increasing risk, and absence of these factors significantly reducing life-time risk (12, 14). Genetics also appears to play an important role in the development of pancreatic cancer, since some large hereditary pancreatitis families have no documented cases of PDAC, while in other families, the risk of cancer can be very high (Whitcomb, unpublished observations, 2013). Imaging-based surveillance for early cancer is difficult in CP because of the distortion of the pancreatic parenchyma. TPIAT has not been formally studied as a method to reduce risk of subsequent cancer. However, no post-TPIAT cases of cancer of pancreatic origin have been reported to occur in the liver in up to 35 years since the introduction of this procedure.

After IAT, endogenous islet function is present in the majority of patients: ~90% and 100% of patients at University of Minnesota and Leicester, respectively, were C-peptide positive following autologous islet transplant (25, 27). Approximately 30–40% of patients can withdraw entirely from insulin therapy after surgery by approximately 1 year but require lifelong monitoring for diabetes (25, 27, 29). These numbers may be somewhat better in pediatric patients and vary depending on the center and patient population and initial transplanted islet cell mass (53). While attrition of islet function does occur, including return to insulin dependence, islet function has been documented for >20 years after IAT (25).

TPIAT should be performed only after careful discussion between the patient, surgeon, and medical physicians, to ensure the patient is fully aware of surgical risks, including diabetes, lifelong need for pancreatic enzyme replacement therapy, gastrointestinal dysmotility syndromes, post-splenectomy complications and the comparative risks of alternate surgical procedures or therapies.

## Discussion Question 2.1: What are the psychosocial contraindications for TP or TPIAT ?

**Guidance Statement 2.1—**TPIAT should not be performed in patients with active alcoholism, active illicit substance use, or untreated/uncontrolled psychiatric illness that could be expected to impair the patient’s ability to adhere to complicated medical management (pain medication taper, pancreatic enzyme therapy, diabetes cares, and frequent clinic follow up). Patients with poor support networks have a relative contraindication due to the cost and complexity of managing diabetes and pancreatic enzyme replacement therapies.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 68%; B 26%; C 3%; D 3%; E 0%

### Q2.2: What are the medical contraindications for TPIAT?

**Guidance Statement 2.2—**TPIAT should not be performed in patients with specific medical conditions, including: C-peptide negative diabetes, type 1 diabetes, portal vein thrombosis, portal hypertension, significant liver disease, high-risk cardiopulmonary disease, or known pancreatic cancer.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 68%; B 29%; C 3%; D 0%; E 0%

**Evidence—**There are no studies that specifically evaluate contraindications to this procedure. However, TP and TPIAT are major surgical procedures, with potential operative complications, a prolonged surgical recovery, and an intensive post-operative regimen that includes management of diabetes mellitus and lifelong enzyme therapy for pancreatic exocrine insufficiency (23, 54). Adequate nutrition may be difficult to maintain after TPIAT. While abstinence from alcohol is considered mandatory before TPIAT, no guidelines exist as to how to determine the duration of abstinence and monitoring for abstinence. In the liver transplant literature, among patients with alcoholic liver disease, most centers require a 6-month period of abstinence and assessment by a substance use professional prior to transplantation listing (55). In addition, a recent study suggests that TPIAT for alcoholic pancreatitis resulted in failed isolations, lower yields, higher insulin requirements, lesser long-term QOL improvement (vs non-alcoholic CP), and no improvement in pain scores compared with non-alcoholic pancreatitis patients (56). However, this study was limited by inclusion of partial pancreatectomies (in about 35% of patients), and this experience has not been universal; many centers continue to consider otherwise appropriate candidates with history of alcoholism (in remission) for TPIAT while ensuring these patients have the mental health services required for optimal surgical recovery.

Because of the risk of post-operative complications and diabetes, TPIAT should be reserved for patients with intractable recurrent acute or chronic pancreatitis who have failed concerted prior treatment efforts to control recurrent pancreatitis or constant pain, and is not recommended for self-limited disease, such as a single episode of severe acute pancreatitis. Historically, most patients undergoing TPIAT have idiopathic or genetic disease; however, this procedure has been performed in patients with alcoholic CP (25). Portal vein thrombosis, portal hypertension, and significant liver disease (by liver biopsy) are contraindications to major pancreatic resective surgery in general and are specific contraindications to infusing the islets into the liver but are not contraindications to an alternative islet transplant site. The efficacies of alternate sites such as intraperitoneal or sub-serosa of the stomach are still being investigated (57).

Because functioning beta cells are necessary to perform islet autotransplantation, the IAT portion of the procedure is contraindicated in those with C-peptide negative diabetes

mellitus secondary to chronic pancreatitis or type 1 (autoimmune) diabetes mellitus. The value of IAT in patients with mild pancreatic diabetes mellitus (C-peptide positive) is still being investigated, but at least a subgroup of these patients appear to benefit from retained islet function with IAT (58).

### Discussion Question 3: What factors determine the optimal timing for TPIAT?

**Guidance Statement 3—**The severity, frequency, and duration of pain symptoms, narcotic requirements, disability/impaired quality of life, residual islet function, rate of disease progression, and age of the patient should be considered in timing of the procedure.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 80%; B 20%; C 0%; D 0%; E 0%

**Evidence—**The patient's report of pain, narcotic requirements, and impaired ability to function are the most significant factors considered in determining the need for and timing of TPIAT. Prolonged painful disease can result in central sensitization, in which the threshold for perceiving pain is altered by damage to the nociceptive neurons from repeated stimulation and chronic inflammation. Prolonged narcotic therapy has been associated with opioid-induced hyperalgesia and can make post-operative weaning of pain medications more difficult (59). These factors favor earlier intervention with TPIAT to avoid a chronic pain syndrome in patients for whom disease is unlikely to spontaneously remit, although one must balance the risk of complications of a major operation with the negative impact of prolonged pain and narcotic use for each patient individually.

Prolonged disease and prior surgical procedures, including partial pancreatectomy or lateral pancreaticojejunostomy, may compromise islet mass (25, 57). Because the method of islet isolation involves perfusion of the main pancreatic duct under pressure, many centers consider prior lateral pancreaticjejunostomy a relative contraindication to TP/IAT due to the reduction in islet yield. Earlier TPIAT favors better islet mass and lower risk of diabetes. However, because the risk of diabetes is at least 60%, TPIAT should not be used solely as a procedure to prevent diabetes in patients with chronic pancreatitis. In children, the assent of the patient (as age appropriate) should be obtained.

### Discussion Question 4: How should patients with painful CP or RAP and impaired QOL be evaluated for possible TPIAT?

**Guidance Statement 4.1—**Patients who meet the inclusion criteria (Guidance Statement 1) and who are not excluded (Guidance Statements 2.1, 2.2) should be evaluated by a multi-disciplinary team who will review alternative interventions, assess the likelihood of success in reducing pain and preventing or minimizing diabetes, follow the patient through the procedure and provide guidance for long term care.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 67%; B 27%; C 3%; D 0%; E 0%

**Guidance Statement 4.2—**Evaluation should include confirming that pancreatitis is the primary diagnosis, determining that the pain is of pancreatic origin, monitoring for the presence of diabetes (1), assessing beta-cell mass (1), and assessing the patency of the portal venous system, evaluating for liver disease, and determining immunization status.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 67%; B 33%; C 0%; D 0%; E 0%

**Evidence—**Prior to TPIAT, the diagnosis of pancreatitis should be established (24). This may be documented by a combination of: 1) histopathology positive for CP; 2) imaging and/or pancreatic function tests clearly indicating CP; 3) Documented genetic mutations SPINK1, CFTR, or PRSS1 positive familial pancreatitis with a compatible clinical picture; or 4) recurrent episodes of elevation in amylase and lipase. Other etiologies of abdominal pain should be ruled out (24). Medical physicians and surgeons should jointly agree that TPIAT is a reasonable treatment option using objective criteria.

A multi-disciplinary team is an important component of the preoperative, perioperative, and postoperative management. Patients and families should receive counseling about the risks and benefits of the procedure, including the risk of insulin-dependent diabetes, the need for pancreatic enzyme supplementation, the risks of infection with encapsulated bacteria associated with splenectomy, the likelihood of long-term pain relief, long-term outcomes, and comparison with other surgical options or therapeutic approaches (57, 60). Alternatives to TPIAT should be discussed with the patient. This discussion would precede obtaining consent.

Because diabetes mellitus is a frequent complication of chronic pancreatitis, patients should be assessed before surgery for diabetes with, at minimum, a fasting glucose and hemoglobin A1c, with diabetes diagnosed based on standard American Diabetes Association criteria (fasting glucose ≥126 mg/dL or hemoglobin A1c ≥6.5%) (61). Impairment in either fasting glucose (100 – 125 mg/dl) or hemoglobin A1c (5.7 – 6.4%) should be further evaluated by a standard 75 gram oral glucose tolerance test.

For the glucose tolerance test, serum glucose should be measured fasting and at both one and two hours following glucose ingestion. Per the American Diabetes Association (61), a diagnosis of diabetes mellitus should be made by a two-hour glucose measurement of ≥ 200 mg/dl, and an impaired glucose tolerance is defined by a two-hour glucose of 140–199 mg/dl. While there are no standard criteria for interpreting the one-hour glucose test, a level ≥ 200 mg/dl likely represents an early indication of impaired beta cell function in patients with pancreatic disease (62) Assessment of functional beta-cell mass should be considered as part of the evaluation and follow-up for TPIAT (1). Functional beta-cell mass can be

estimated from serum C-peptide levels determined during either oral glucose (63) or mixed meal tolerance testing (64). Intravenous glucose tolerance testing, arginine stimulation testing, or glucose-potentiated arginine testing for insulin or C-peptide responses can be performed in a research setting and may provide more sensitive measures of preoperative and post-transplant beta cell mass (65).

Because TPIAT often involves splenectomy, patients should undergo standard pre-splenectomy vaccinations well in advance of planned surgery (66). Evaluation for liver disease is recommended, including serum liver chemistries and imaging by CT or MRI, either of which will also permit assessment of the patency of the portal vein.

Evaluation should include psychiatric/psychologic/pain evaluation in patients who have ongoing psychiatric issues, those who are suspected of having substance abuse issues, and in those with a clinical course suggesting difficulty in managing pain regimens and who may benefit from optimal management of comorbid conditions, such as anxiety.

## Discussion Question 5: How should patients be followed after TPIAT?

**Guidance Statement 5.1—**Lifelong monitoring for diabetes mellitus shall be performed at least annually and should include self-monitored blood sugar, fasting blood glucose, and hemoglobin A1c. These patients may be followed for beta cell mass (C-peptide).

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 73%; B 27%; C 0%; D 0%; E 0%

**Guidance Statement 5.2—**Life-long pancreatic enzyme replacement therapy is mandatory. Nutritional monitoring should include assessment of steatorrhea, weight maintenance, and fat - soluble vitamin levels on an at least an annual basis.

Evidence Level: 1

Grade of recommendation: A

Level of Agreement: A 83%; B 13%; C 3%; D 0%; E 0%

**Guidance Statement 5.3—**A physician experienced in pain management should be a part of the patient’s care team following hospital discharge to assist with the tapering of narcotic medications.

Evidence Level: 5

Grade of recommendation: D

Level of Agreement: A 97%; B 3%; C 0%; D 0%; E 0%

**Evidence—**Because islet function can wane over time, insulin-independent patients must be monitored for the development of diabetes mellitus. Attrition of insulin independence occurs more frequently and more rapidly in those with lower islet mass transplanted, while it may be maintained for years in those with high islet mass (>5,000 IEQ/kg) (25). Monitoring for diabetes mellitus should include fasting glucose and hemoglobin A1c level at least annually and up to quarterly. Patients should have access to and perform home blood glucose monitoring. Stimulatory tests (oral glucose or mixed meal tolerance tests) with measurement of glucose and C-peptide levels may also be considered to monitor islet function over time.

All patients have surgically induced exocrine insufficiency and are at risk for malabsorption and fat-soluble vitamin deficiencies (67). While no randomized controlled trials have been conducted specific to TP, the benefit of pancreatic enzyme replacement therapy is clearly established by clinical studies in CP and other forms of pancreatic exocrine insufficiency (68, 69). Patients should be asked about stool frequency, stool consistency, flatulence, abdominal pain, and presence of fat mixed with stool during routine clinic visits, and patients should be weighed at each visit to monitor for weight loss and evidence of adequate digestive enzyme replacement therapy. Pediatric patients should have a weight and height recorded at each visit, with height and weight measures every 3 months. A physician experienced in pancreatic enzyme replacement therapy and nutrition management should be part of the patient's care team. Lab monitoring should include measurement of fat-soluble vitamin levels (A, D, E) as well as vitamin B12, albumin, and pre-albumin. Steatorrhea not responsive to increased pancreatic enzyme dose should raise consideration of small bowel bacterial overgrowth (70).

It is recommended that a DXA bone density scan be performed selectively, as patients with CP are at increased risk for osteopenia and osteoporosis due to their potential risk of malabsorption of calcium and vitamin D, particularly after after TPIAT (67, 71, 72).

Patients who undergo splenectomy as part of their procedure require appropriate precautions (66), including prompt evaluation for fever, ongoing vaccinations as recommended by the Center for Disease Control and Prevention for asplenic patients, and possible antibiotic prophylaxis in children. MedicAlert bracelets are recommended for splenectomy and diabetes.

For those patients on prolonged or frequent narcotics prior to surgery, an experienced pain management physician should be involved in the patient's postoperative care. In 10–20% of patients, pain may persist or recur after TPIAT due to centralization of pain, narcotic-induced hyperalgesia, or neuropathic causes (36, 41, 43). If pain abates and then recurs, alternate etiologies should be considered, including anastomotic or other ulcer, gastritis, bile reflux, motility disorders, constipation, bacterial overgrowth syndromes (70), or biliary anastomotic obstruction.

## Research Recommendations

Areas of potential research related to TPIAT were identified by the guideline coauthors and PancreasFest participants. These included additional research on mechanisms and

management of pain, psychological assessment and care of the TPIAT recipient, diabetes evaluation, and the role of cancer risk in selecting candidates for TPIAT, and are summarized below.

**Guidance Statement 1—**A better understanding of pain mechanisms in CP is needed, which could aid in selection of TPIAT candidates. In particular, diagnosing central sensitization or neuropathic pain syndromes may identify those patients who will continue to struggle with pain after TPIAT. Development of better risk models of pancreatic cancer in individual patients based on etiology of pancreatitis, family history/genetics, smoking, alcohol, diabetes and other risk factors would help better assess the benefit-risk ratio of TPIAT. While the primary indication for TPIAT remains pain relief, studies are needed to determine the impact and optimal timing of TPIAT for PDAC prevention and a comparison of outcome measures in patients treated with TPIAT compared to other surgical procedures or therapeutic interventions.

Risk of pancreatic adenocarcinoma is a major concern of many patients with chronic pancreatitis, but the individual risk, and the optimal timing of TPIAT, if the risk is high, is poorly defined. Better risk models of pancreatic cancer in individual patients based on etiology of pancreatitis, family history, genetics, smoking, alcohol, diabetes and the patient's age are needed. Tissue samples from patients undergoing TPIAP for any reason should be collected under standard protocols and processed for research studies.

**Guidance Statement 2.1—**Treatment with cognitive behavioral therapy should be studied to see if benefits seen in IBD can be achieved in CP. Research is needed to determine what constitutes a clear psychological contraindication to TPIAT (ie when psychiatric disease portends poor outcomes) and when potential psychosocial contraindications for TPIAT are treatable and reversible. Because children with hereditary disease are often considered as candidates for TPIAT, studies should include family dynamics in hereditary pancreatitis families surrounding TPIAT.

**Guidance Statement 2.2—**For patients in whom intraportal infusion of islets is contraindicated (due to hepatic disease), additional research is needed on the efficacy and safety of alternate sites for islet transplant.

**Guidance Statement 3.1—**A better understanding of when medical management will be futile is needed to facilitate more expedient utilization of TPIAT (when necessary), in order to preserve islet mass, reduce postoperative diabetes burden, and reduce risk of a neuropathic pain syndrome refractory to pancreatic resection. Better study of longitudinal use of stimulatory testing to follow beta cell mass or function before surgery would help in deciding timing of TPIAT, to balance risk of major surgery with likelihood of diabetes if surgery is delayed. Clinico-pathologic studies should be performed to determine factors that may predict optimum response to various surgical treatment of complicated chronic pancreatitis with good or marginal beta cell mass.

**Guidance Statement 4.1—**Studies need to be done to determine the minimal and optimal number of team members, the exact role on the team, the amount of effort, and benefit for centers of different sizes to optimize efficiency and effectiveness.

**Guidance Statement 4.2—**Future research should include pre-TPIAT assessment of central and peripheral nerve sensitization, and determine impact of pain sensitization on the temporal course and likelihood of pain remission after TPIAT. Better test to predict or determine the origin of pain, and the optimal treatment early in the disease course. Studies on pain coping, on objective, quantitative and qualitative sensory testing, and on pain genetics are needed. Standardized protocols for the collection, processing and utilization of pancreas tissue from each TPAIT should be instituted to facilitate pain research.

**Guidance Statement 5.1—**Continued research is needed on what measures of insulin and/or C-peptide responses are the most accurate, clinically meaningful, and feasible to obtain, in order to follow the function of transplanted islets over time. Identification of markers of impending islet decline (before hyperglycemia is present) would identify patients at high risk for return to insulin use and facilitate study of intervention therapies to sustain islet graft function.

**Guidance Statement 5.2—**Consensus on markers of nutritional status, threshold levels of success, frequency of evaluation and optimal methods of intervention are needed. There is a known increased risk of osteoporosis in chronic pancreatitis but the risk of osteopenia and osteoporosis after TPIAT are poorly defined. Future research should include determining, which patients need DXA assessment and frequency of such assessments, and appropriate therapies for osteoporosis or osteopenia when present after TPIAT.

**Guidance Statement 5.3—**Future research should include standardized pain measures before and after TPIAT, and consideration of which pharmacologic and non-pharmacologic approaches provide the greatest likelihood of pain resolution (and chance for withdrawal of narcotics).

## Summary

Total pancreatectomy and islet autotransplant is a potential treatment option for select patients with severe painful chronic or recurrent acute pancreatitis. Among the PancreasFest participants, there was high consensus (>90% agreement) that the indication for the procedure is intractable pain despite other appropriate treatment modalities in selected patients lacking psychosocial or medical contraindications, that candidates should be evaluated by a multidisciplinary team, and that assessment and follow up of TPIAT recipients needs to include careful consideration of pain assessment/pain management, diabetes risk, and potential nutritional deficiencies. Patient and disease characteristics are considered in determining timing of TPIAT. Thus, there remain numerous areas for potential future research in this emerging field.

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## Appendix: Consensus Development Participants

## A. Authors who participated in the guidance conference and critically reviewed the paper

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**Table 1**

Voting Options

| For each statement the audience was asked to vote on their level of agreement using the following options: | | |
|---|---|---|
| A: | Strong positive | (definitely) |
| B: | Weak positive | (probably) |
| C: | Uncertain or equivocal | (=) |
| D: | Weak negative | (probably not) |
| E: | Strong negative | (definitely not) |