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### Authors

Hendifar, Andrew E  
Petzel, Maria QB  
Zimmers, Teresa A  
et al.

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## Pancreas Cancer-Associated Weight Loss

ANDREW E. HENDIFAR,<sup>a</sup> MARIA Q.B. PETZEL,<sup>b</sup> TERESA A. ZIMMERS,<sup>c</sup> CRYSTAL S. DENLINGER,<sup>d</sup> LYNN M. MATRISIAN,<sup>e</sup> VINCENT J. PICOZZI,<sup>f</sup> LOLA RAHIB,<sup>e</sup> ON BEHALF OF THE PRECISION PROMISE CONSORTIUM

<sup>a</sup>Cedars-Sinai Medical Center, Los Angeles, California, USA; <sup>b</sup>MD Anderson Cancer Center, Houston, Texas, USA; <sup>c</sup>Indiana University, Simon Cancer Center, Indianapolis, Indiana, USA; <sup>d</sup>Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA; <sup>e</sup>Pancreatic Cancer Action Network, Manhattan Beach, California, USA; <sup>f</sup>Virginia Mason Medical Center, Seattle, Washington, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Pancreatic cancer • Weight loss • Cachexia • Anorexia • Malabsorption • Supportive care

### ABSTRACT

Unintentional weight loss in patients with pancreatic cancer is highly prevalent and contributes to low therapeutic tolerance, reduced quality of life, and overall mortality. Weight loss in pancreatic cancer can be due to anorexia, malabsorption, and/or cachexia. Proper supportive care can stabilize or reverse weight loss in patients and improve outcomes. We review the literature on supportive care relevant to pancreatic cancer patients, and offer

evidence-based recommendations that include expert nutritional assessment, counseling, supportive measures to ensure adequate caloric intake, pancreatic enzyme supplementation, nutritional supplement replacement, orexigenic agents, and exercise. Pancreatic Cancer Action Network-supported initiatives will spearhead the dissemination and adoption of these best supportive care practices. *The Oncologist* 2019;24:691–701

**Implications for Practice:** Weight loss in pancreatic cancer patients is endemic, as 85% of pancreatic cancer patients meet the classic definition of cancer cachexia. Despite its significant prevalence and associated morbidity, there is no established approach to this disease entity. It is believed that this is due to an important knowledge gap in understanding the underlying biology and lack of optimal treatment approaches. This article reviews the literature regarding pancreas cancer-associated weight loss and establishes a new framework from which to view this complex clinical problem. An improved approach and understanding will help educate clinicians, improve clinical care, and provide more clarity for future clinical investigation.

### PREVALENCE, CLASSIFICATION, AND SIGNIFICANCE

Weight loss (WL) is highly prevalent among patients with pancreatic cancer (PC) [1, 2], as up to 85% of patients present with WL at diagnosis [3]. Nearly 50% of those with early-stage and locally advanced disease exhibit preoperative WL [4], and 80% will develop progressive WL after diagnosis. There are no approved medical treatments for PC-associated weight loss (PAWL), and commonly used orexigenic agents that stimulate appetite have no definite benefit [5]. Therefore, progressive WL is one of the most distressing and intractable features of PC [6].

Assessment of clinically significant WL in PC is complex and hindered by a lack of standardized definitions and therapeutic strategies [7–9]. The etiologies can be categorized as due to anorexia, malabsorption, and/or cachexia (Fig. 1). Clinically impactful WL in PC is frequently described as cachexia, and classification systems for WL in cancer patients are usually concerned with cancer cachexia. Cachexia is a

multifactorial syndrome characterized by progressive involuntary WL, loss of skeletal muscle mass with or without adipose loss, and systemic inflammation [10]. Despite an international consensus statement in 2011 regarding cachexia [10], definitions of clinically important WL in cancer patients remain unclear and heterogeneous [11].

WL in PC patients has predictive and prognostic implications. WL and cachexia predict poor outcomes in all PC stages [4, 9, 12, 13]. Most patients with PC will die with cachexia, and it's estimated that ~30% will die of cachexia [6, 9–11]. Decreased lean body mass and/or weight are predictors for toxicity [14, 15], mortality [16], postoperative infections, length of hospitalization, and therapeutic intensity [4, 9, 14, 16–21]. WL also correlates with shorter progression-free survival (PFS) and overall survival (OS), decreased response to chemotherapy, lower quality of life (QOL), and declining performance status [3, 10]. In addition,

Correspondence: Andrew E. Hendifar, M.D., Cedars-Sinai Medical Center, 8700 Beverly Blvd., Suite 1042 AC, Los Angeles, California 90048, USA. Telephone: 310-423-2217; e-mail: andrew.hendifar@cshs.org Received May 3, 2018; accepted for publication October 18, 2018; published Online First on December 27, 2018. <http://dx.doi.org/10.1634/theoncologist.2018-0266>

Existing definitions of clinically important weight loss and cachexia in cancer patients remain heterogeneous [7–9,11]. Progressive, lethal weight loss in patients with PC is variously referred to in literature and diagnostic guidelines as malnutrition, frailty, wasting, atrophy, sarcopenia, or cachexia. However, terminology that refers to nutritional status or skeletal muscle alone is inadequate to capture both the phenotype and its mechanisms. Although patients with PC often suffer anorexia and malabsorption, adipose and skeletal muscle loss is also due to active, catabolic processes compounded by disuse atrophy. These conditions cannot be reversed solely by adequate nutrition [10].

**Anorexia:** Loss of the desire to eat or loss of appetite.

**Cachexia:** Presence of one of the following:

- unintentional weight loss of >5% over 6 months,
- body mass index (BMI) of <20 kg/m<sup>2</sup> with unintentional weight loss of >2%;
- sarcopenia (skeletal muscle index <7.26 kg/m<sup>2</sup> for men and <5.45kg/m<sup>2</sup> for women) with unintentional weight loss of >2% [10].

**Malabsorption:** Abnormality in absorption of nutrients due to disruption of flow of pancreatic enzymes.

**Malnutrition:** Identification of 2 or more of the following 6 characteristics are recommended for diagnosis: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation, diminished functional status measured by hand-grip strength [55].

**Sarcopenia:** In the consensus definition of cancer cachexia, sarcopenia is defined as skeletal muscle index <7.26 kg/m<sup>2</sup> for men and <5.45kg/m<sup>2</sup> for women [10]

**Sarcopenic Obesity:** This refers to sarcopenia present in cancer patients who are obese. Patients who are both obese and sarcopenic have reduced survival in cancer [6] and most other conditions.

**Weight loss:** Historically there has been no standardized definition for clinically significant weight loss [148]. Limitations of using weight loss as a surrogate marker for malnutrition is that reported weight loss often does not take into account the amount of time over which the loss has occurred, nor does it account for the type of tissue loss [149].

**Figure 1.** Definitions and classifications.

Abbreviation: PC, pancreatic cancer.

obesity is a known risk factor for the development of PC [22–25], and its presence at the time of diagnosis is an independent predictor of survival [26]. Patients with low muscle mass and high body mass index (BMI), a condition now described as sarcopenic obesity, exhibit worse outcomes in PC and many other diseases [6, 27, 28].

Optimal approaches to the diagnosis and management of PC weight loss and cachexia are understudied and poorly understood; however, nutritional intervention can improve QOL and OS in advanced PC [29–31]. Recognizing and treating malnutrition in advanced cancer early in the treatment process is essential for improving outcomes [28, 32]. Furthermore, nutritional support in PC is complicated and influenced by many factors including tumor response, diabetes, pain management, altered physiology, and other comorbidities. In this review, we highlight the etiology, assessment, and management of PAWL, provide best supportive care recommendations based on current knowledge (Fig. 2), and bring attention to the gaps.

#### SUPPORTIVE CARE WORKING GROUP CONSENSUS PROCESS

The Supportive Care Working Group (SCWG) was formed to establish best supportive care practices across the Precision Promise Consortium (PPC) and to help foster supportive care research. The SCWG consists of scientists, physicians, and a dietician with expertise in pancreatic cancer, nutrition, exercise, cachexia, survivorship, and palliative care. The SCWG compiled all evidence by searching PubMed articles (from 1977 to 2017) on PAWL and other relevant topics. Keywords searched included weight loss, cachexia, anorexia, malabsorption, sarcopenia, pancreatic exocrine insufficiency,

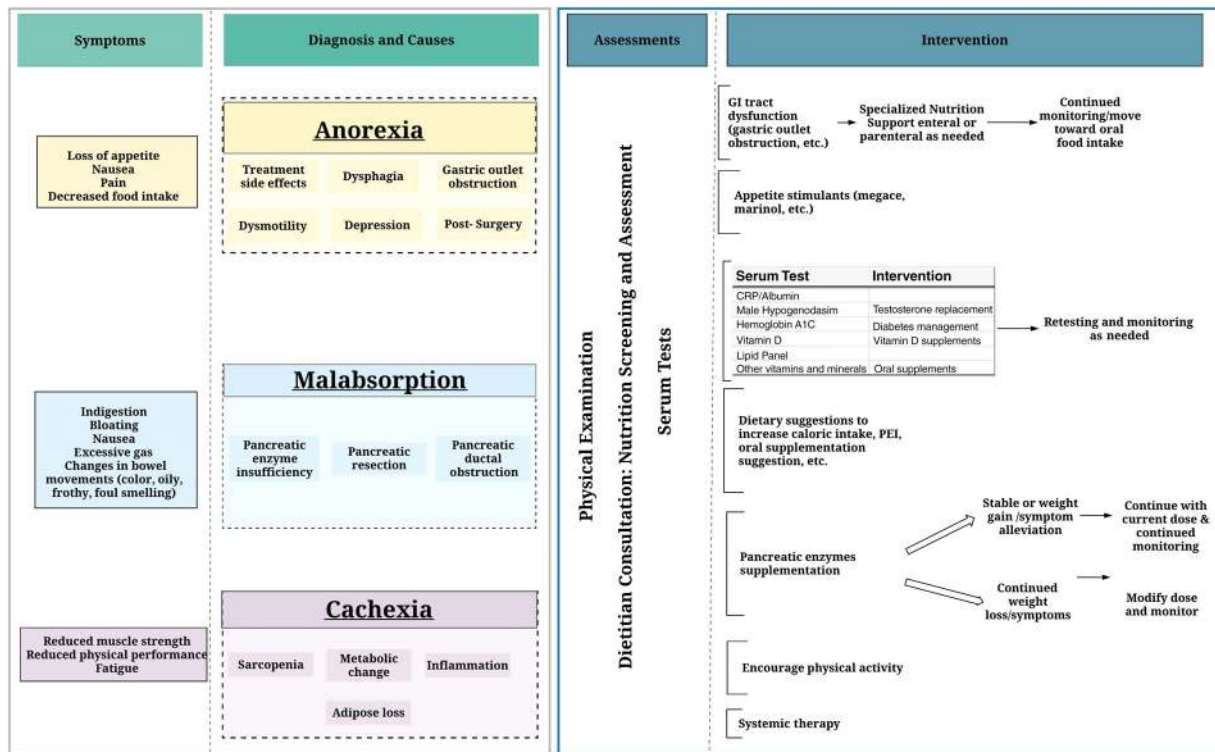
malabsorption, pancreatic enzyme replacement therapy, nutrition, and exercise. The group convened quarterly over an 18-month period and corresponded via teleconference bimonthly. The group initially presented the evidence and consensus to the PPC and Steering Committee (SC) in January 2017. The feedback was considered by the SCWG, integrated, and presented back to the PPC and SC in August 2017. Additional feedback was integrated, and the final consensus is presented here.

#### PATHOGENESIS (CAUSES OF PAWL)

We recommend categorizing PAWL into three causes: anorexia, malabsorption/pancreatic exocrine insufficiency, and cachexia/sarcopenia.

##### Anorexia

Anorexia is defined as loss of the desire to eat and is mediated by the inability of the hypothalamus to respond to energy deficit signals [28]. Pain, fatigue, depression, dysmotility, constipation, chemosensory disturbances (changes in smell and taste), vomiting, early satiety, and loss of appetite all contribute to anorexia [10, 33–36]. An important aspect of anorexia is the negative social impact including changes in social encounters and relationships and a sense of helplessness, anxiety, and distress [37, 38]. Patients commonly report distress related to dietary intake and gut symptoms including difficulties with gas, belching, bloating, pain/discomfort, and diarrhea leading to WL [39]. Additionally, current chemotherapy regimens, including gemcitabine/nab-paclitaxel [40], FOLFIRINOX [41], and nanoliposomal irinotecan/5FU [42], can cause nausea, vomiting, indigestion,



**Figure 2.** Clinically significant weight loss (see Table 1 for interpretation). Abbreviations: CRP, c-reactive protein; GI, gastrointestinal; PEI, pancreatic exocrine insufficiency.

diarrhea, and mouth sores [43] and thus contribute to lower food intake and reduced nutrition.

**Malabsorption/Pancreatic Exocrine Insufficiency**

Pancreatic exocrine insufficiency (PEI), a common complication of PC, occurs when the pancreas is unable to maintain normal digestive function (secretion of proteases, lipase, and amylase), resulting in malabsorption and malnutrition. PEI negatively impacts QOL [44, 45] and is associated with poor survival [44–46]. Additionally, markers of malabsorption and exocrine secretion impairment, such as fecal elastase-1, are strongly correlated with poor survival in PC [46].

Symptoms of malabsorption include increased abdominal bloating or discomfort, excessive gas causing burping or flatulence, indigestion, nausea, delayed gastric emptying/early satiety, changes in bowel movements—increased frequency, light color, floating, frothy, oily, and/or foul smelling, and WL despite intake meeting estimated caloric needs.

**Cachexia and Sarcopenia**

Cachexia results from a complex interaction between tumor, host, and therapy [34, 47] characterized by progressive wasting of skeletal muscle mass and to a lesser extent adipose tissue, occurring even before WL becomes apparent (precachexia) [28, 48]. Preclinical models indicate that chemotherapy and targeted agents can cause cachexia through mitogen-activated protein kinase-dependent muscle atrophy, mitochondrial depletion, and muscle weakness leading to disuse atrophy [49]. Despite the high prevalence and potential for mortality, PC-associated cachexia is diagnosed and treated in a minority of patients [5], as there is no established treatment [50]. The stages of cachexia occur across a

spectrum starting with “precachexia” characterized by WL <5%, then “cachexia” associated with systemic inflammation, and ending with “refractory cachexia defined by a loss of body reserves and rapidly deteriorating nutritional status [10]. Not all patients will progress through all the stages, and no predictive biomarkers have been identified to distinguish patients who will progress [10].

WL is our current measure of cachexia. However, advances in body composition assessment techniques indicate skeletal muscle and adipose tissue may behave independently during WL [51]. In obese patients with cancer, muscle wasting is common and obscured [51]; 40% of PC patients who were found overweight/obese at the time of diagnosis exhibited muscle wasting [6]. Consequently, sarcopenic obesity is linked to functional status, survival, chemotherapy toxicity, and poor outcomes following surgery [52, 53].

**ASSESSMENT OF PAWL**

The morbidity and mortality associated with PAWL compels a comprehensive approach to its assessment and management and should be tailored to each individual. We recommend that all patients be screened for WL, receive clinical and nutritional screening, be assessed for PEI, and receive serum testing. Body composition measurements should be considered in the research setting.

**Screening for WL**

It is important that clinicians assess and record the weight of a patient at presentation and prior to diagnosis. A quick review of WL history can illuminate the extent of PAWL. Assessment of WL over time is one of the standardized

**Table 1.** Interpretation of adult weight loss

| Time     | Weight loss for moderate (nonsevere) malnutrition | Weight loss for severe malnutrition |
|----------|---|-------------------------------------|
| 1 week   | 1%–2%   | >2%                                 |
| 1 month  | 5%  | >5%                                 |
| 3 months | 7.5%  | >7.5%                               |
| 6 months | 10%   | >10%                                |
| 1 year   | 20%   | >20%                                |

Adapted from [55] with permission.

diagnostic characteristics used to identify and document adult malnutrition as recommended by the Academy of Nutrition and Dietetics [54] and the American Society for Parenteral and Enteral Nutrition. Any patient who demonstrates moderate or severe WL and/or evidence of malnutrition or malnutrition risk by these criteria should be directed to a registered dietitian for a more extensive assessment and intervention as described below. The consensus guidelines for interpretation of WL in adults is outlined in Table 1 [55].

### Nutrition Screening and Clinical Assessment

Nutrition screening using a validated tool allows for identification and referral of at-risk patients to a registered dietitian for complete nutrition assessment and intervention. Screening should be completed on all patients before the start of treatment and at regular intervals such as weekly during radiotherapy, with each chemotherapy visit, and at each surveillance visit [54, 56, 57].

Two nutritional screening tools have been vetted for both inpatient and outpatient use: the malnutrition screening tool (MST) and the patient-generated subjective global assessment (PG-SGA). The MST is a quick, valid, and reliable screening tool. It consists of two questions regarding appetite and recent unintentional WL and has demonstrated high sensitivity and specificity for identification of individuals with or at risk of malnutrition [58]. The PG-SGA is a valid and reliable assessment tool to identify and triage malnourished patients with cancer in both the inpatient and outpatient setting. The abridged PG-SGA forgoes the physical examination used in the PG-SGA and is a practical, informative, and valid tool for use in the outpatient oncology setting for detecting malnutrition [59].

We recommend that patients are screened using one of these tools; those deemed to be at risk for malnutrition should then be referred to a registered dietitian for nutrition assessment. The services of a registered dietitian are important for the early identification of malnutrition and anticipation of nutritional impact on symptoms to help patients maintain weight, stay on their intended treatment, and maintain or improve QOL over the course of their disease.

A full nutrition assessment involves the following elements: obtaining a food history, evaluation of anthropometric measurements, review of medical history, biochemical data, medical tests and procedures, and completion of a nutrition-focused physical assessment [60]. Routine assessment of food intake should include patient estimate of overall food intake and 24-hour food recall [34]. An oncology-

focused assessment also involves reviewing the oncologic treatment plan with the goal to determine current and anticipated nutrition issues [54, 57, 61]. This information is all assimilated and used to formulate a plan to address existing and potential influences on malnutrition.

### Assessment for PEI

Although there are several tests to diagnose pancreatic exocrine insufficiency, their clinical application and use is variable [62, 63]. Definitive identification of PEI in PC patients is challenging; thus, PEI is usually a clinical diagnosis. Direct measures of gastric and duodenal contents such as a secretin-cerulein or secretin-pancreozymin tests are expensive, invasive, and only available at specialized centers [64]. Other tests such as fecal fat test, fecal elastase, and coefficient of fat absorption (CFA) are more clinically available but may be cumbersome [64–66]. Steatorrhea is classically defined as at least 7 grams of fecal fat over 24 hours, in the context of a 72-hour stool test while on 100 grams of fat daily [67]. However, the stool collection and associated diet is inconvenient and difficult for patients. Therefore, fecal elastase measurements are often used to diagnose PEI [67–69]. Fecal elastase is less sensitive (72%) than CFA collection but quite specific (90%). In PC patients, studies have shown a prevalence of PEI varying from 50%–89% when defined by low fecal elastase [46, 70, 71]. Expert opinion is that fecal elastase is appropriate for unresectable patients but is insufficiently sensitive to detect mild-moderate PEI and unsuitable for postpancreaticoduodenectomy patients [72]. Regardless, in standard PC care, these tests are not routinely performed and the diagnosis is established clinically and based on patients' history and reported symptoms (unintentional WL, change in stool, bloating after meals, etc.). Patients should be clinically assessed for PEI upon diagnosis, at the start of treatment, and on a regular basis throughout the course of their treatment.

### Serum Tests

There is no widely adopted serologic evaluation of patients with PAWL. However, WL in cancer patients has been associated with markers of inflammation, low levels of serum testosterone in men, and vitamin deficiencies. A more comprehensive serologic evaluation of patients who present with PAWL will likely improve supportive care.

Measuring serum inflammation in PC patients with a Glasgow Prognostic Score (GPS) has shown prognostic significance in several studies [73, 74], and is predictive of surgical outcomes [75, 76]. The GPS and other markers of inflammation are consistently associated with WL and cachexia in cancer patients [77, 78]. GPS is usually scored 0, 1, or 2 by providing 1 point each for c-reactive protein (CRP) >10 and Albumin <3.5. The GPS was recently studied as a predictive factor for response to a novel therapeutic in advanced PC [79]. Recent studies have also suggested that CRP:Albumin ratio and neutrophil:lymphocyte ratio also have prognostic validity [80, 81]. In routine practice, this score could help identify patients at high risk for PAWL and cachexia and could promote early intervention.

Male hypogonadism (MH) is a common complication in advanced cancer [82] and prominent in cancer patients

[83] with cachexia [84], occurring in more than 70% of these patients [85]. Hypogonadism in cancer cachexia is associated with decreased strength, poor nutritional status [86], decreased performance status, depression, and decreased survival [87, 88]. In a randomized study in cancer patients with fatigue and MH, testosterone replacement improved fatigue and performance status but not QOL [89]. Despite the high prevalence of MH in cancer patients and associated morbidity and mortality, there are no established guidelines for the diagnosis and management of MH in this population [90]. Consensus from the supportive care literature supports the practical application of testosterone replacement in symptomatic patients with MH [91].

There has been little published material regarding serum assessment for vitamin and mineral deficiencies in patients with PC. Most available literature is related to the post-pancreatic resection setting [92] or in the broader topic of PEI from all causes (chronic pancreatitis and cystic fibrosis included) [62]. After resection, reported nutritional deficiencies include fat-soluble vitamins A, D, and E, vitamins B12 and B6, iron, zinc, selenium, biotin, and copper. None of these can be considered diagnostic of malnutrition; however, vitamin D deficiency has been reported in patients with PC and may contribute to poor outcomes [93–95]. These findings were concluded from retrospective analysis, and it is not clear whether vitamin D supplementation improves outcomes. We recommend that vitamin D deficiency should be evaluated and supplemented per physician discretion.

### Body Composition Measurements

Muscle volumes can be measured and sarcopenia diagnosed using several modalities: computed tomography (CT) or magnetic resonance imaging (MRI); appendicular skeletal muscle index obtained from dual energy x-ray absorptiometry (DEXA); mid-upper-arm muscle area by anthropometry; and whole-body fat-free mass index determined by bioimpedance analysis [10, 96–98]. As CT is commonly used in the diagnosis and treatment of PC, this modality has been used to estimate sarcopenia radiographically by total psoas muscle area and radiodensity [96]. However, psoas muscle measurements do not reflect whole-body muscle; thus, measurements of a whole-body slice at the level of lumbar vertebrae are superior [99]. Morphometric analysis of diagnostic CT or MRI slices can be used to calculate whole-body skeletal muscle and adipose tissue, to assess muscle quality, and to detect presence of myosteatosis. Currently, this can be done using dedicated commercial software such as Sliceomatic or ImageJ. Skeletal muscle and adipose tissue can behave independently during cancer progression and therapy [51, 100], and there may be value in measuring these separate compartments in the research setting.

## INTERVENTION FOR PAWL

### Role of the Registered Dietitian

Dietitians play a central role in the successful management of PAWL. Nutrition interventions for PAWL have improved weight [30], QOL, and outcomes [29, 60, 101]. Dietitians can

provide essential dietary suggestions, identify PEI, and provide recommendations for oral nutritional supplementation and specialized nutrition support [102]. Dietitians may also provide more detailed advice on diet and pancreatic enzyme supplementation for management of symptoms of PEI [103–106].

### Pancreatic Enzyme Replacement Therapy

Pancreatic enzyme replacement therapy (PERT) has demonstrated benefit for PC patients with PEI. Two randomized controlled trials have evaluated the impact of PERT among patients with PEI due to chronic pancreatitis or surgery. These studies demonstrated an increase in fat absorption, reduced stool frequency, improved stool consistency [107–109], and symptom improvement [109]. A previous double-blinded trial of 21 patients with unresectable PC with obstructive jaundice in whom a biliary stent was placed showed that patients randomized to PERT had improved fat absorption and that WL was prevented compared with those who were randomized to placebo [110].

In a retrospective, nonrandomized study of 66 unresectable PC patients receiving PERT with nutritional counseling and palliative care or standard palliative care without PERT, median survival of patients receiving PERT was longer than that of those with standard palliative care (301 days vs. 89 days) [111]. More recently, a randomized study showed an increase in OS in patients randomized to taking enzymes but did not reach statistical significance because of a low enrollment rate [112]. Additionally, a prospective study of unresectable patient receiving chemotherapy showed improved changes in BMI and increased OS of patients who received PERT compared with historical controls [113].

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These clinical trials evaluating PERT used doses ranging from 40,000 to 72,000 units of lipase for meals and 20,000–36,000 units of lipase per snack. The maximum effective dose is unclear, guidelines vary, and dosing recommendations for PC are not currently indicated on U.S. Food and Drug Administration labels. Enzymes may be dosed based on body weight, fat content of diet, clinical symptoms, degree of steatorrhea present, or general per meal/snack guidelines. The recommended starting dose per meal is 500 lipase units per kg; dosing should be modified as appropriate and should be tailored to individuals as needed to reflect variations in meal sizes and fat content of the diet, clinical symptoms, and the degree of steatorrhea present. Dosages should not exceed 10,000 lipase units per kilogram body weight per day with a maximum of 2,500 lipase units per kilogram per meal [64]. Patients should be instructed to take enzymes at the start of the meal, and if taking multiple capsules, pills should be taken

at intervals at the start and then throughout the meal [114]. A study using the Pancreatic Cancer Action Network's Patient Registry indicated that in patients taking PERT appropriately, symptoms such as a feeling of indigestion and WL were significantly improved [115].

### Oral Nutrition Supplements

If patients show signs of deficiency, have prolonged inadequate intake, or have prolonged malabsorption, clinicians should consider evaluation for deficiencies including vitamins A, D, E, B12, and B6 as well as iron, zinc, selenium, biotin, and copper. Supplements should be recommended for replacement of known deficiencies in the diet or serum levels. Serum values may be rechecked approximately 3 months after attempted repletion. For individuals with inadequate intake of calories and/or protein, nutrition supplement drinks may be recommended as part of the nutrition care plan. Unfortunately, there have been few studies investigating the vitamin deficiencies associated with PEI and the benefit of oral nutrition supplements.

### Specialized Nutrition Support

Specialized Nutrition Support (SNS) is the use of enteral or parenteral nutrition. Both American and European guidelines for nutrition support recommend against routine use of SNS for oncology patients [116, 117]. However SNS may be necessary for patients with a dysfunction of the gastrointestinal tract such as gastric outlet obstruction or who are severely malnourished and will be undergoing major surgery [116–118]. If SNS is needed, enteral feeding is preferred because of lower risk of infections or other complications [119, 120]. In randomized studies, enteral feeding has shown benefit over other forms of artificial nutrition in patients following a pancreaticoduodenectomy [121].

Parenteral nutrition may improve weight [122] and maintain or improve performance status in selected patients, but it is not routinely recommended. Careful evaluation should be employed to identify those patients who would benefit and to avoid indiscriminate use of artificial nutrition [123], especially in cases of futile care and at end of life. Benefits may be limited to the perioperative setting for patients who are unable to tolerate oral nutrition, although there is a need for more explicit criteria for use [121, 124].

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### Pharmacologic Interventions

Advances in the understanding of etiology of cachexia are leading to pharmaceutical interventions aimed at targets

upstream (inhibiting systemic inflammation) or downstream (blocking catabolic pathways, stimulating anabolic pathways, and reducing anorexia) [51].

Appetite stimulants are frequently prescribed for patients with PAWL. Progestogens, such as megestrol acetate and corticosteroids, are used as orexigenics [5, 125–127]. Their mechanism of action is also through inhibition of cytokines (including interleukin-6 and tumor necrosis factor) and de-repression of appetite. Anecdotal evidence suggests cannabis improves appetite and food intake in patients with PAWL, and synthetic delta-9-tetrahydrocannabinol, dronabinol, is approved for use in acquired immunodeficiency syndrome-related cachexia and emesis from chemotherapy. However, insufficient data exist for prescribing cannabis for cachexia [128], and a randomized study in advanced cancer patients demonstrated superiority of megestrol acetate over dronabinol [129]. Novel agents for appetite stimulation include ghrelin and ghrelin mimetics, notably anamorelin, for which significant increase in lean body mass was observed in non-small cell lung cancer patients from two phase III trials [130, 131].

Nonsteroidal anti-inflammatory (NSAID) agents, thalidomide, and omega-3 fatty acids modulate cytokine production, thereby inhibiting inflammation. Previous studies of these agents have not shown conclusive benefit, and their routine use is not recommended. Agents targeting the cytokine activin and the related muscle growth inhibitor myostatin have also been evaluated, without report of benefit to date (NCT01433263 and NCT01505530). Newer therapies include monoclonal antibodies against cytokines, including interleukin-1 alpha (NCT03207724) [132]. Combination therapy with NSAID, nutritional supplementation, dietary consultation, and exercise showed benefit in a multicenter, randomized phase II trial of patients with lung or pancreatic cancer, and has now moved to phase III (MENAC, NCT02330926). Investigations of many novel agents are ongoing; however, there are currently no standard systemic therapies for PAWL or PC cachexia [133].

### Exercise

Physical activity (PA) and exercise could benefit patients with PAWL. In cancer patients, PA has been shown to improve health-related QOL and symptom burden. PA resulted in improved treatment tolerance [134, 135] and is associated with improved PFS and OS [136], suggesting that the benefit of PA is not confined to disease-free survivors.

Gradual resistance training and aerobic exercise can also maintain and restore lean muscle mass [137]. In addition, prescribed exercise resulted in improved appetite and general well-being in patients with advanced cancer receiving palliative care [138].

PA interventions have been deemed safe and feasible in PC patients [139] and may attenuate cachexia by modulating insulin sensitivity and inflammation [140–142]. Progressive postoperative exercise programs have also been demonstrated to be feasible, resulting in lower levels of fatigue and pain and improved perception of general health [143]. In advanced disease, a home-based walking intervention was associated with increased endurance

*OVERALL: Measures to optimize appetite, nutritional intake, micronutrients, and anabolic potential, while reducing disuse and catabolism should be implemented as thoughtfully and aggressively as anti-tumor therapy.*

**Dietitian Consultation:** All patients with weight loss and/or evidence of malnutrition risk should be directed to a registered dietitian for extended evaluation and treatment. Assessment of food intake should include patient estimate of overall food intake and 24-hour food recall.

**Pancreatic Enzyme Supplementation:** All patients with evidence or suspicion of pancreatic exocrine insufficiency should be initiated on pancreatic enzymes. The recommended starting dose per meal is 500 lipase units per kg and should be modified as needed based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet. Half of the prescribed individualized dose for a full meal should be taken with snacks. Maximum dose per meal should not exceed 2,500 lipase units per kg of body weight. Patient education should include guidance to take capsules at the start and throughout the meal/snack.

**Exercise:** Patients should be counseled to avoid inactivity. Physical activity goals should be tailored to each individual and in consultation with physical therapists. In general, patients should strive to engage in at least 150 minutes of moderate intensity aerobic exercise and 2 sessions of resistance training per week.

**Oral Nutrition Supplements:** Vitamin and minerals deficiencies should be treated by oral supplements as necessary.

**Systemic Therapy:** Appetite stimulants and non-steroidal anti-inflammatory drugs should be considered.

**Figure 3.** Consensus recommendations for pancreatic cancer-associated weight loss.

and improved symptom burden, with patients increasing their average duration of moderate-intensity exercise [144]. Given the potential for high symptom burden and poor survival outcomes in PC, Groupe Cooperateur Multi-disciplinaire en Oncologie has initiated a large randomized trial of adapted physical activity in PC [139]. This study will formally evaluate the benefits of aerobic and resistance exercises on fatigue and health-related QOL, but also investigate the effects of intervention on nutritional status, insulin resistance, cancer treatment tolerance, and survival.

One hundred fifty minutes per week of moderate-intensity aerobic exercise and at least two sessions of resistance training per week is the recommended physical activity for cancer patients and survivors [145–147]. The optimal form and duration of exercise is unclear, and recommendations should be tailored to an individual's current fitness level, treatment-related late/long-term toxicities, and comorbidities. Referral to physical therapy or other exercise professionals to guide initiation and engagement in physical activity may improve success and thus should be considered for all patients [145–147].

### Consensus Statement and Recommendation (Fig. 3)

Slowing WL in patients with PC should improve quality and length of life both directly through maintaining function and indirectly through enhancing treatment delivery and response. In many cases, favorable response to therapy will translate to overall improvement in symptoms and QOL. We recommend all patients who have significant WL and/or evidence of malnutrition be directed to a registered dietitian for a more extensive evaluation. As needed, patients should be provided pancreatic enzyme

replacement therapy, correction of hormonal and micronutrient deficiencies, and oral nutrition supplementation. Appetite stimulants should be considered. Patients should be warned against inactivity, and moderate-intensity exercise should be encouraged and supported. Measures to optimize appetite, nutritional intake, micronutrients, and anabolic potential, while reducing disuse and catabolism, should be implemented and integrated as part of treatment planning as thoughtfully and aggressively as antitumor therapy.

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Margaret Tempero (University of California, San Francisco); Hedy Kindler, Principal Investigator (University of Chicago); Thomas George, Principal Investigator; Jose Trevino (University of Florida); Robert Vonderheide, Principal Investigator; Gregory Beatty (University of Pennsylvania); Vincent Picozzi, Principal Investigator; Margaret Mandel-son (Virginia Mason Medical Center); Andrea Wang-Gillam, Principal Investigator; William Hawkins (Washington University); and the Precision Promise Steering Committee (Julie Fleshman, Pancreatic Cancer Action Network; Manuel Hidalgo, Dana Farber Cancer Institute; Sunil Hingorani, Fred Hutchinson Cancer Research Center; Anirban Maitra, MD Anderson Cancer Center; Victoria Manax, Pancreatic Cancer Action Network; Lynn Matrisian, Pancreatic Cancer Action Network; Vincent Picozzi, Virginia Mason Medical Center; Diane Simeone, Perlmutter Cancer Center/NYU Langone Health).

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## AUTHOR CONTRIBUTIONS

**Conception/design:** Andrew E. Hendifar, Maria Q.B. Petzel, Teresa A. Zimmers, Crystal S. Denlinger, Lynn M. Matrisian, Vincent J. Picozzi, Lola Rahib

**Collection and/or assembly of data:** Andrew E. Hendifar, Maria Q.B. Petzel, Teresa A. Zimmers, Crystal S. Denlinger, Lynn M. Matrisian, Vincent J. Picozzi, Lola Rahib

**Data analysis and interpretation:** Andrew E. Hendifar, Maria Q.B. Petzel, Teresa A. Zimmers, Crystal S. Denlinger, Lynn M. Matrisian, Vincent J. Picozzi, Lola Rahib

**Manuscript writing:** Andrew E. Hendifar, Maria Q.B. Petzel, Teresa A. Zimmers, Crystal S. Denlinger, Lynn M. Matrisian, Vincent J. Picozzi, Lola Rahib

**Final approval of manuscript:** Andrew E. Hendifar, Maria Q.B. Petzel, Teresa A. Zimmers, Crystal S. Denlinger, Lynn M. Matrisian, Vincent J. Picozzi, Lola Rahib

## DISCLOSURES

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