GUT CANCER FOUNDATION

A guide for clinicians:

PANCREATIC ENZYME REPLACEMENT THERAPY

Gut Cancer Foundation

The Gut Cancer Foundation funds innovative research, is the voice of cancers of the digestive system, and provides vital information and education to improve and save the lives of all New Zealanders affected by cancers of the digestive system with pancreatic, liver, stomach, biliary, oesophageal, bowel and anal cancers.

The information in this booklet has been repurposed from our partners at Pancare Foundation Australia. We would like to extend our sincere gratitude to Pancare for generously sharing their patient support material and providing permission for us to adapt it to support Kiwis and whānau with pancreatic cancer in Aotearoa New Zealand.

This booklet has been reviewed for the New Zealand system by relevant specialists in the New Zealand medical sector.

Note to the Reader

The medical profession and research community are continually updating information about pancreatic cancer. We have taken care to ensure that the information in this handbook is reflective of the clinical best practice at the time of publication. Sponsoring organisations have not had input into the contents of this document.

This handbook is not a substitute for professional help or advice from medical practitioners. It is important to discuss any medical (physical, emotional and/or general) symptoms, questions or concerns with your health professional as soon as possible.

Gut Cancer Foundation excludes itself from all liability for any injury, loss or damage incurred by use of, or reliance on, the information provided in this booklet.

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Supporting you on your Cancer Journey

A cancer diagnosis can come as a terrible shock, but we are here to help you every step of the way and support you, your whānau and friends.

In this booklet, you will learn more about a recent diagnosis, your treatment options, working with your care team, managing symptoms, ways to nurture your health through diet, exercise and strengthening your emotional wellbeing and practical ways we can support you and your whānau.

Talk to our team

To discover more or talk further with our team,
visit www.gutcancer.org.nz,
email support@gutcancer.org.nz or call 0800 112 775

Your guide for using this handbook

This handbook contains key detail in colour coded boxes.

ADDITIONAL DETAILS

PATIENT STORIES

FREQUENTLY ASKED QUESTIONS

HELPFUL TIPS

Contents

What is pancreatic exocrine insufficiency?

Pancreatic exocrine insufficiency (PEI) is when the pancreas does not produce enough digestive enzymes, or when the amounts of enzymes secreted into the duodenum are insufficient.

PEI results in maldigestion, and sometimes malabsorption and malnutrition. It also increases the risk of death.[1] PEI can result when pancreatic function is affected due to disease or surgery – for example, from pancreatic cancer and associated surgeries, stomach cancer, diabetes and irritable bowel syndrome.

This booklet focuses on PEI in patients living with pancreatic cancer.

1 Layer P et al. (2019). Contribution of pancreatic enzyme replacement therapy to survival and quality of life in patients with pancreatic exocrine insufficiency, World J Gastroenterol 25(20): 2430–41. www.ncbi.nlm.nih.gov/pmc/articles/PMC6543241

Symptoms of PEI

Patients with PEI usually present with:

- abdominal pain
- diarrhoea
- steatorrhoea (fatty stools)
- weight loss
- bloating
- more frequent bowel movements
- malnutrition
- vitamin deficiency
- flatulence
- burping
- nausea.

Clinical consequences

If left untreated or undiagnosed, patients with PEI can have:

- malnutrition
- higher infection risk
- fat-soluble vitamin deficiency (A, D, E and K)
- higher fracture risk
- higher risk of cardiovascular events
- poor glycaemic control
- poor quality of life
- higher mortality.

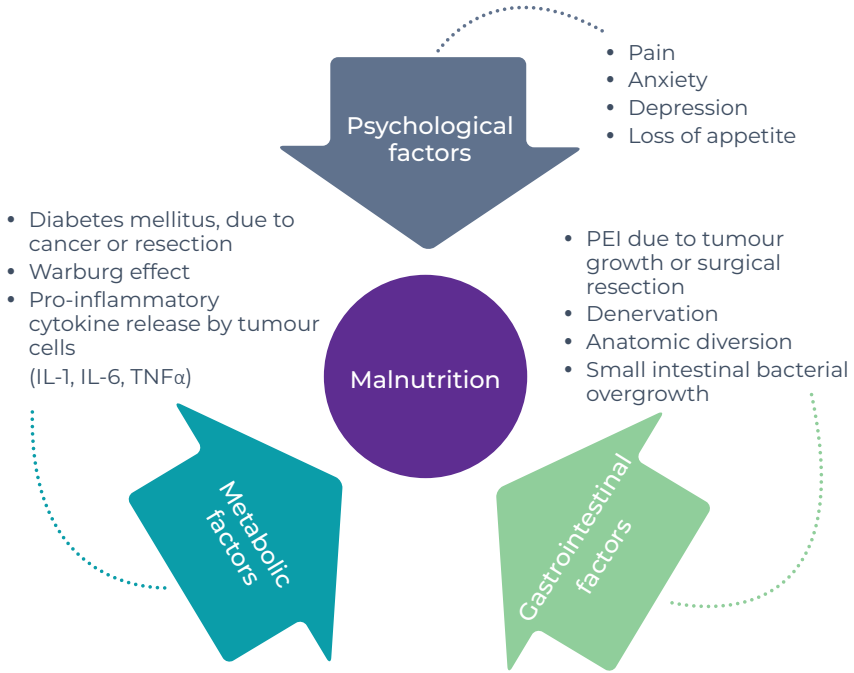
Note that the pancreas has a large exocrine reserve capacity, so clinical symptoms may not appear until this capacity is less than 10% of normal. This means that steatorrhoea and related symptoms may not appear until the patient's duodenal lipase falls to less than 5–10% of normal postprandial levels.

Malnutrition in patients with pancreatic cancer is associated with a number of contributing factors, including psychological, gastrointestinal and metabolic changes, which may also need to be considered when treating PEI *(see Figure 1)*.

Patients with PEI most commonly have fat maldigestion. This can result in steatorrhoea and unintentional weight loss. Levels of micronutrients, fat-soluble vitamins (especially vitamins A, D, E and K) and lipoproteins (forms of cholesterol) may be pathologically low, although patients may not present with clinical symptoms from this.

PEI can cause depletion of vitamin D, which may cause calcium deficiency and lead to hypocalcaemia (low calcium levels), hypophosphataemia (low phosphate levels) and osteomalacia (soft bones). Patients with PEI may present with bone pain and have an increased incidence of fractures.

Figure 1: Contribution of psychological, gastrointestinal and metabolic factors to pancreatic cancer malnutrition.



Source: Pezzilli et al.[2]

2 Pezzilli R et al. (2020). Pancreatic enzyme replacement therapy in pancreatic cancer, Cancers 12(2):275. https://doi.org/10.3390/cancers12020275

Patients may also have an increased risk of cardiovascular pathological events (eg. heart disease). This can result from low plasma levels of high-density lipoproteins, which protect against atherogenesis.

Fat-soluble vitamin deficiency can cause complications associated with vision, blood clotting, bone mineral density, immune and neurological function, and oxidative stress.

PEI has been associated with high morbidity and mortality – secondary to malnutrition-related complications – and an increased risk of cardiovascular events.

Diagnosing PEI

PEI is very common in patients with pancreatic cancer and should be considered when someone is diagnosed with pancreatic cancer.

It can be difficult to diagnose PEI accurately. All testing methods have advantages and disadvantages.

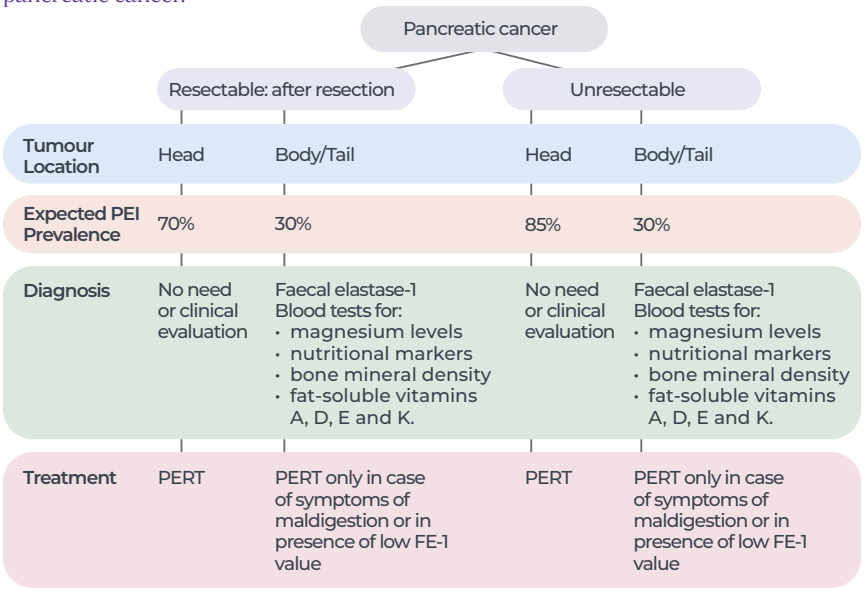
Figure 2 shows an approach to testing and treating PEI in patients with pancreatic cancer. The faecal elastase-1 (FE-1) test is a valuable test for diagnosing PEI, and should be your first choice of diagnostic test if PEI is suspected in a patient with body/tail pancreatic cancer *(see 'Indirect pancreatic function tests')*.

All patients with pancreatic cancer in the head of the pancreas should be assumed to have PEI. Such patients can start treatment without PEI testing. If someone has had a complete pancreatectomy, they will have associated PEI and no diagnostic tests are needed.

In addition to the FE-1 test, you should also perform blood tests for:

- magnesium levels
- nutritional markers
- bone mineral density
- fat-soluble vitamins A, D, E and K.

Figure 2: Clinical management algorithm for testing and treating PEI in patients with pancreatic cancer.



Source: Pezzilli et al.[3]

These tests can suggest if PEI is present, and should be part of investigations if the patient is suspected or known to have PEI.

The faecal elastase-1 (FE-1) test is an easy and popular choice for agnosing PEI.

Indirect pancreatic function tests

The 3-day faecal fat test is the gold standard indirect function test for diagnosing steatorrhoea, but it is unpopular with patients and laboratories, which limits its use. Also, it does not distinguish between pancreatic and nonpancreatic causes of diarrhoea and steatorrhoea.

The FE-1 test is more commonly used than the faecal fat test, as the levels of FE-1 correlate with the flow rate of pancreatic enzymes. The FE-1 test measures the amount of pancreatic exocrine elastase-1 enzyme in the stool. The test requires a single stool sample, making it a popular clinical choice. The specificity is about 93% (that is, 7% of patients with diarrhoea can have false-positive results).

3 Pezzilli R et al. (2020). Pancreatic enzyme replacement therapy in pancreatic cancer, Cancers 12(2):275. https://doi.org/10.3390/cancers12020275

In patients with:

- severe PEI, the FE-1 has 100% sensitivity
- moderate PEI, sensitivity is 77–100%
- mild PEI, sensitivity is 0–63%.

FE-1 levels can be further quantified by an enzyme-linked immunosorbent assay (ELISA) *(see 'Table 1')* to address any uncertainty in the diagnosis.

Table 1: Faecal elastase-1 (FE-1) levels are quantified with an ELISA

Detection	Diagnosis
<200 µg FE-1 per gram of stool	Mild PEI
<100 µg FE-1 per gram of stool	Severe PEI

ELISA = enzyme-linked immunosorbent assay; PEI = pancreatic enzyme insufficiency

Direct pancreatic function tests

Direct pancreatic function tests are the most specific and sensitive for detecting PEI, but they are generally too expensive and invasive for routine clinical use:

- The secretin-cholecystokinin (CCK) stimulation test is the gold standard, but it requires bicarbonate and enzymes to be collected through a duodenal tube.
- The endoscopic pancreatic function test (ePFT) is replacing the secretin-CCK test, but the sensitivity is only 85% and specificity 59% compared with the CCK test.

Imaging

CT scans with contrast often provide good results and are readily available. Some CT scans are followed by MRI, endoscopic ultrasound and/or secretin magnetic resonance cholangio-pancreatography (MRCP). An endoscopic retrograde cholangiopancreatography (ERCP) may be used occasionally, but this test involves significant risks.

Pancreatic enzyme replacement therapy for people living with upper gastrointestinal cancer

PEI is usually treated with pancreatic enzyme replacement therapy (PERT). PERT involves a pancreatic extract – which includes lipases, amylases and proteases – in microtablets or microspheres with a pH-sensitive enteric coating.

The microspheres mix with the chyme in the stomach, and are protected by the enteric coating. The enzymes then pass with the chyme from the stomach into the duodenum. The differing pH of the duodenum dissolves the enteric coating, and the enzymes are released in the duodenum to help digest the food.

Before surgery

Patients can have PEI as a result of the cancer itself. If a patient is showing symptoms of PEI while they await surgery, they may benefit from PERT.

"After I was diagnosed with pancreatic cancer, the surgeon put me on Creon® (a brand of pancreatic enzyme) while I was waiting for my surgery. I couldn't believe the difference it made to my upset stomach, eating and bowel habits."

After a total or distal pancreatectomy

Patients with any form of pancreatectomy will likely require PERT postoperatively. It is recommended to assess these patients and, when required, treat with PERT.

Continued monitoring of the patient's nutritional status is recommended, because PEI can manifest some time after surgery. PERT may not be required immediately, but may be needed in the weeks or months after surgery.

After a Whipple procedure

Patients with cancer in the head of the pancreas may require a pancreaticoduodenectomy – also known as a Whipple procedure. This procedure often results in PEI, which can take some time to develop.

Any patient who has had a pancreaticoduodenectomy should be assessed for PEI and given PERT when required. Patients should be monitored regularly, because PEI manifestation can be delayed.

Unresectable pancreatic cancer

Patients with unresectable pancreatic cancer are also likely to have their pancreatic function affected. This may come from blocked pancreatic ducts and/or diseased pancreatic tissue. These may both result in PEI, which should be treated with PERT to increase quality of life and reduce any negative effects of malabsorption.

After gastric surgery

After a gastrectomy, food can pass too quickly from the oesophagus to the small intestine. A gastrectomy can also result in the pancreas releasing fewer digestive enzymes. In these cases, PERT may be trialled, and continued if it helps relieve symptoms; but bear in mind there may be a placebo effect.[4]

The main treatment for PEI is PERT, which aims to deliver sufficient enzymes into the duodenum alongside the meal to aid digestion.

Recommendations for patients

Creon® is the brand of pancrelipase, or PERT, used most often in Australia. It comes in capsule form.

Creon is the only available product in New Zealand at this time; however, there may be alternate products available in the future.

Dosage

PEI severity varies from patient to patient, PERT dosage therefore needs to be individually adjusted to the lowest effective dose. The PERT dosage you prescribe should be initiated at the lowest recommended dose based on your patient's weight, and individualised based on:

- clinical symptoms
- degree of steatorrhea present
- fat content of the diet.

An Accredited Practicing Dietitian can assist with all these factors, and you should refer your patient to one. The Dietitians New Zealand website, www.dietitians.org.nz has a search tool to find an Accredited Practicing Dietitian in your area.

A dietitian should be involved with new patients and with setting starting doses for PERT after pancreatic surgery, as dosing needs to consider clinical symptoms and nutritional content of the meal, snack or fluid.

4 Lee A & Ward S (2019). Pancreatic exocrine insufficiency after total gastrectomy – a systematic review. JOP J Pancreas 20(5): 130–7.

To treat PEI, including after partial or complete pancreatectomy, 75,000 IU of lipase are generally required with each main meal. PERT doses should be individualised, but generally the required amount of lipase is 75,000 IU with each regular meal, and at least 25,000 IU with each small meal, snack or fluid. Adjust the amount to suit the meals' fat content.

Table 2 summarises the recommended starting doses for PERT, based on fat content in meals. Creon capsules come in the following doses:

- 10,000 IU
- 25,000 IU

Table 2: Recommended starting doses for Creon based on fat content in meal

Circumstance	Fat in meal (g)	Starting dose (IU)
After pancreatic surgery		
Main meals	30–40	75,000
Snacks	12–16	25,000

"What Creon has allowed me to do is eat what I want, when I want. It's important to understand how it works. Many people are unsure how to use it correctly.

My dietitian helped me to understand the correct dosage, when to take it and how to make it work best for me."

The efficacy of PERT may be influenced by factors such as the type of preparation, enzyme concentration and dosage schedule. If the patient has an inadequate response to therapy, doses could be increased 2 to 3-fold. Using adjuvant therapy to improve bioavailability of enzymes can also affect efficacy. If severe steatorrhoea continues even with adequate dosing of pancreatic enzyme, adjunctive acid suppression therapy is recommended. If patients remain unresponsive to therapy, other possible causes (eg bacterial overgrowth) should be considered.

Patients should not take more than 10,000 IU/kg body weight/day. So, for a 60-kilogram patient, they should not have more than 60 × 10,000 IU or 24 × 25,000 IU capsules per day.

Also see *'How to store and take pancreatic enzymes'*.

Timing of PERT

When to take PERT depends on the length of the meal. Meals or snacks that take more than 15–20 minutes to eat will need more than one dose:

- **Less than 15-minute meal:** take the full dose with the first few mouthfuls.
- **15–30-minute meal:** take half the dose at the start of the meal, then the other half in the middle.
- **30–45-minute meal:** take one-third of the dose at the start, one-third in the middle and the final one-third towards the end of the meal.

For longer meals, patients may need to increase the total PERT dose.

Longer meals – more than 15–20 minutes – may need additional dose(s) of PERT during the meal.

How to store and take pancreatic enzymes

Tips for taking and storing PERT:

- Store the PERT at room temperature and out of direct sunlight.
- Swallow the capsule whole with a glass of water – do not pull it apart, crush or chew it. The capsule is full of tiny beads (granules) that hold the enzymes *(see 'Figure 3')*. The capsule will be broken down in the stomach, which releases the beads containing the enzymes. The beads break open and the enzymes are activated in the small bowel.

- Crushing or chewing the capsule will break open the beads in the mouth, which is too early for them to be effective. These capsules are large, like a multivitamin, so your patient will need a big mouthful of water to get a capsule down without chewing it.
- Where capsules cannot be swallowed, Creon capsules can be carefully opened and the contents mixed into an acidic vehicle (eg apple puree) and swallowed without chewing.
- For patients with accelerated gastric emptying after gastric surgery the contents of the capsules can be sprinkled on food. This is acceptable for these patients because the stomach contents are emptied much faster than normal.
- Enzymes should be taken with meals or snacks that contain protein and/or fat. They are usually not needed for foods or fluids that contain no protein or fat, such as fruits, vegetables, juices, jellies, lollies, cordial, black or herbal tea, and soft drinks.
- High fat meals, including fried foods, fatty meats, pastries, take-away foods, cakes, biscuits, desserts, milk drinks and creamy pastas and soups, will require larger doses of PERT.
- Patients should take one or more capsules when they have a milk drink, smoothie or milky cup of coffee (such as a latte, cappuccino or flat white).
- Advise your patients not to take over-the-counter antacids that contain calcium or magnesium, such as Gaviscon® or Mylanta®, while taking PERT.
- Advise your patients to drink plenty of water every day if they are taking PERT.
- Do not take PERT or any medication if it is past the expiry date.
- If a patient forgets to take the PERT, they do not need to make up the dose.

Figure 3: Creon capsules

Source: CREON® image supplied by Viatris Inc.

Allergies and side effects

Pancrelipase capsules and granules are made from porcine (pig) products. There are no other options available in New Zealand. People who are allergic to pork should not be prescribed PERT. Ensure a dietitian referral has been made to explore dietary modifications to meet nutritional needs in the context of allergies to PERT.

People who cannot eat pork products due to religious or personal reasons (including vegan, vegetarian) should be made aware of the origin of pancrelipase, and they may choose to not take them.

Appropriate education and counselling should be offered in such cases.

Pancrelipase is a pig product –
there are no other options in New Zealand.

Other lifestyle changes

As well as prescribing PERT, PEI should be managed using other lifestyle changes, such as:

- eating smaller meals more frequently, rather than fewer large meals
- avoiding smoking and alcohol
- considering fat-soluble vitamin supplementation (vitamins A, D, E and K).

If a patient has problems swallowing large capsules, they can try:

- taking more, smaller-dose capsules
- opening them and sprinkling the granules on something soft and acidic that doesn't need to be chewed, such as apple sauce or pureed fruit.

Frequently asked questions

Who should prescribe PERT?

GPs, specialists and dietitians can evaluate patients with symptoms of PEI, order diagnostic tests and prescribe PERT. An Accredited Practising Dietitian should be involved and can advise patients about their diet after a pancreatic cancer diagnosis, and can discuss appropriate use and dosing of PERT.

How do I know whether my patient is taking the right dose of PERT?

Patients should be guided by their doctor and dietitian on starting doses for PERT *(see 'Dosage')*. If an appropriate dose is provided, the patient should see a change in stools (less pale, not floating, less odorous), a reduction in abdominal pain and gas, and weight gain (or reduced weight loss). Doses may need to be gradually increased until the patient's symptoms subside.

Note that a patient may need a higher dose for longer meals or meals that are high in fat. The website **Think PEI** (www.thinkpei.com.au/en-au) explains how PERT dosing can be optimised.

Acid suppression therapy, for example, with the administration of a proton pump inhibitor, may improve the effectiveness of PERT and should be considered where appropriate.[5]

Should my patient reduce the amount of fat in their diet if they have PEI?

No. If a patient is at risk of unwanted weight loss, they should not restrict the amount of fat they eat. Rather, they should be encouraged to increase their PERT dosage. Maintaining a healthy weight and preventing unintentional weight loss is important for any cancer patient. Referring your patient to an Accredited Practising Dietitian can assist with this.

5 Dominguez-Munoz et al. (2006). Optimising the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric coated pancreatic extracts. Gut 55(7): 1056–7. www.ncbi.nlm.nih.gov/pmc/articles/PMC1856339

Can my patient have too much PERT?

Yes. Patients should not take more than 10,000 IU/kg body weight/day. So, for a 60-kilogram patient, they should not take more than 60 × 10,000 IU or 24 × 25,000 IU capsules per day.

My patient's dosage isn't working any more. Why?

As a cancer patient's condition deteriorates, their natural pancreatic enzyme production may also deteriorate. They may need a higher PERT dosage to compensate. Referring your patient to an Accredited Practising Dietitian can help to determine why a dosage is no longer working.

Further information

- Refer to www.gutcancer.org.nz/apc-pert-guidelines-2015 for the Australasian guidelines for the management of pancreatic exocrine insufficiency, Australasian Pancreatic Club (2015)
- Refer to www.gutcancer.org.nz/PERT-Guide-for-health-professionals-May-2021 for a quick guide to pancreatic cancer and pancreatic enzyme replacement therapy (PERT), Pancreatic Cancer UK (2021)
- Think PEI – optimising management of pancreatic exocrine insufficiency (Viatris): www.thinkpei.com.au/en-au
- Dietitians New Zealand website search tool to find an Accredited Practicing Dietitian in your area: https://dietitians.org.nz

For your patients

- Visit www.gutcancer.org.nz/resources for
  - Webinar on Diet & Nutrition in Pancreatic Cancer
  - Pancreatic Enzyme Replacement Therapy (PERT) Patient Information flyer

A guide for clinicians: Pancreatic Enzyme Replacement Therapy.

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