Pancreatic Cancer UK

The Clatterbridge Cancer Centre NHS Foundation Trust

Pancreatic enzyme insufficiency (PEI) and pancreatic enzyme replacement therapy (PERT)

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Overview and learning outcomes

- **Role of the pancreas and role in digestion**
- **Pancreatic enzyme insufficiency (PEI)**

Causes

Signs and symptoms

Diagnosing PEI

Impact of PEI

- **Pancreatic enzyme replacement therapy (PERT)**

Groups that benefit from PERT

Impact of PERT

Pancreatic replacement therapy

Use tips and considerations with PERT

PERT and enteral feeding

Differential diagnosis

- **Case study**
- **Summary**

Poll one
What are the key roles of the pancreas?

Answer all that apply…

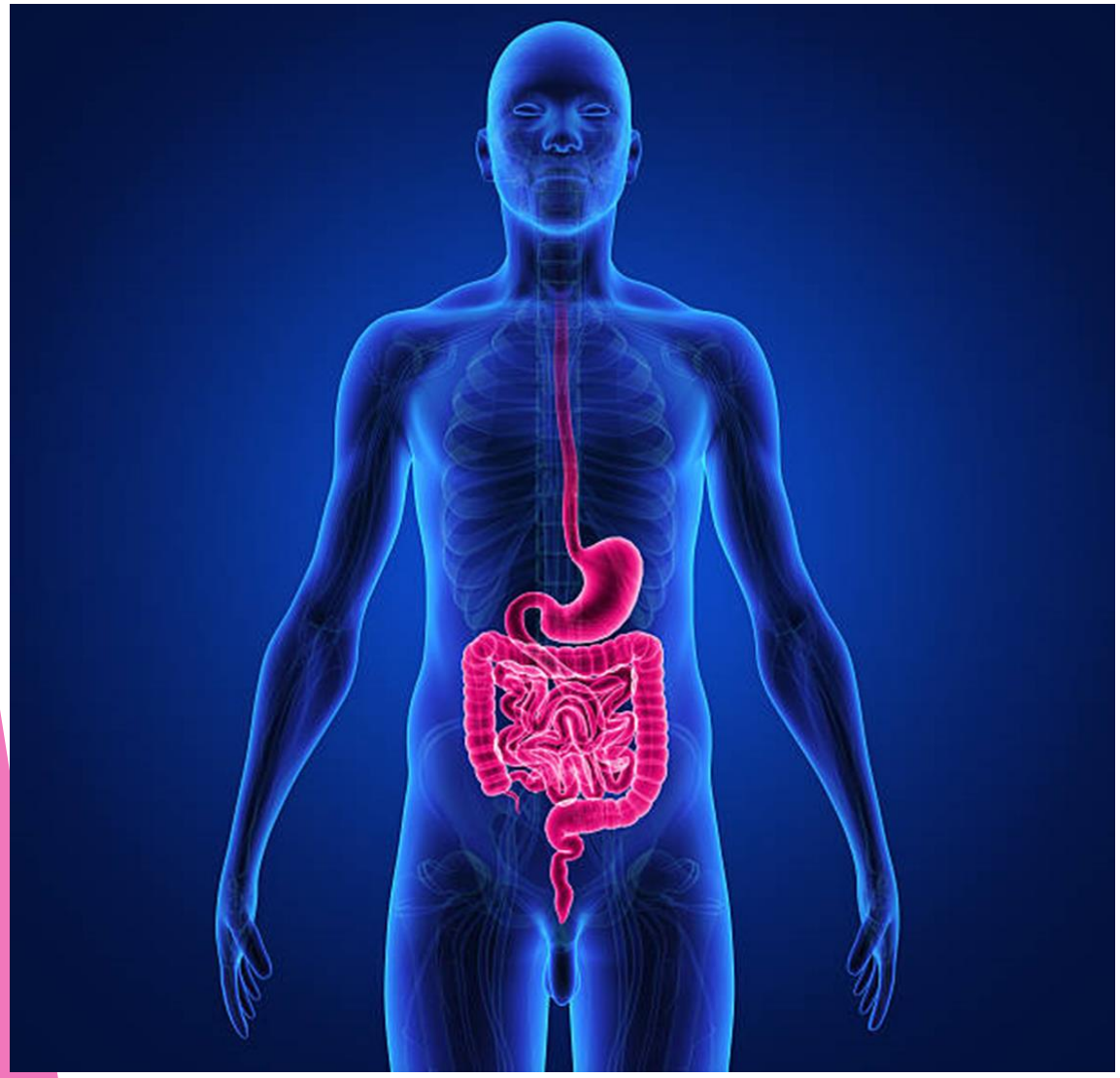
A) Detoxifying

B) Absorbing nutrients

C) Release of gastric juices containing enzymes to help break down food into small particles for absorption by the body

D) Releases insulin and glucagon to help maintain blood sugar levels

Digestive process

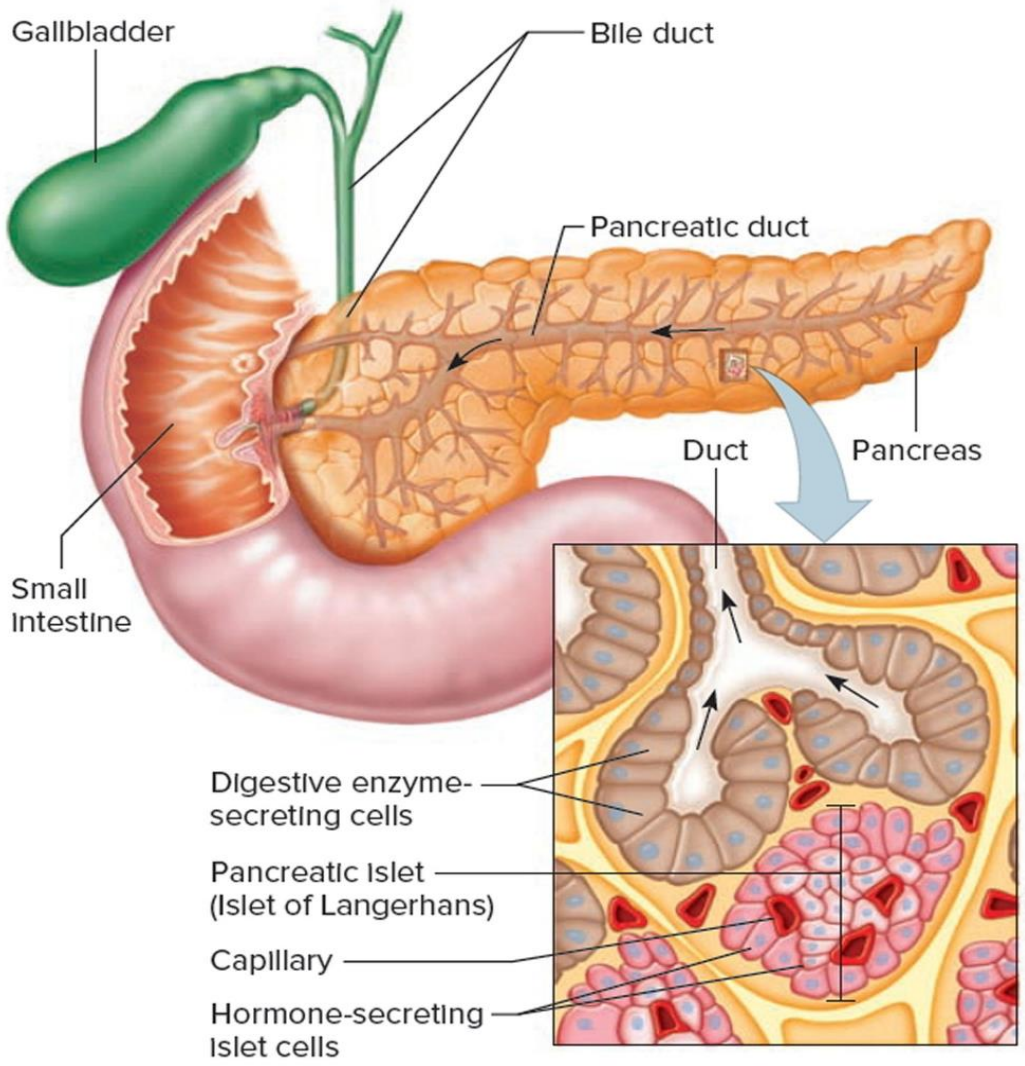


Digestive enzymes

Food group	Saliva	Gastric	Pancreatic	Jejunal /Ileal
Carbohydrate	Salivary amylase	Gastric amylase	Amylase	Sucrase, Maltase, Lactase, Isomaltase
Fat	Salivary lipase	Gastric lipase	Lipase , Steapsin	Intestinal lipase
Protein		Pepsin, Rennin, Gelatinase	Trypsin, Elastase, Chymotrypsin, Carboxypeptidase	Brush Border Peptidases

Keller and Layer (2005)
Imrie , C.W et al., (2010)

Digestion and the role of the pancreas



Endocrine function
(maintenance of blood glucose levels)
Throughout the pancreas
Secretes from the islets of langerhans

- Beta cells –insulin
- Alpha cells –glucagon
- Delta Cells –Somatostatin
- Pancreatic polypeptide

Exocrine function
(secretion of digestive enzymes)
Acinar cells –digestive enzymes
Ductal cells –bicarbonate

Optimal pH 6.5 for effective functioning

Digestive enzymes

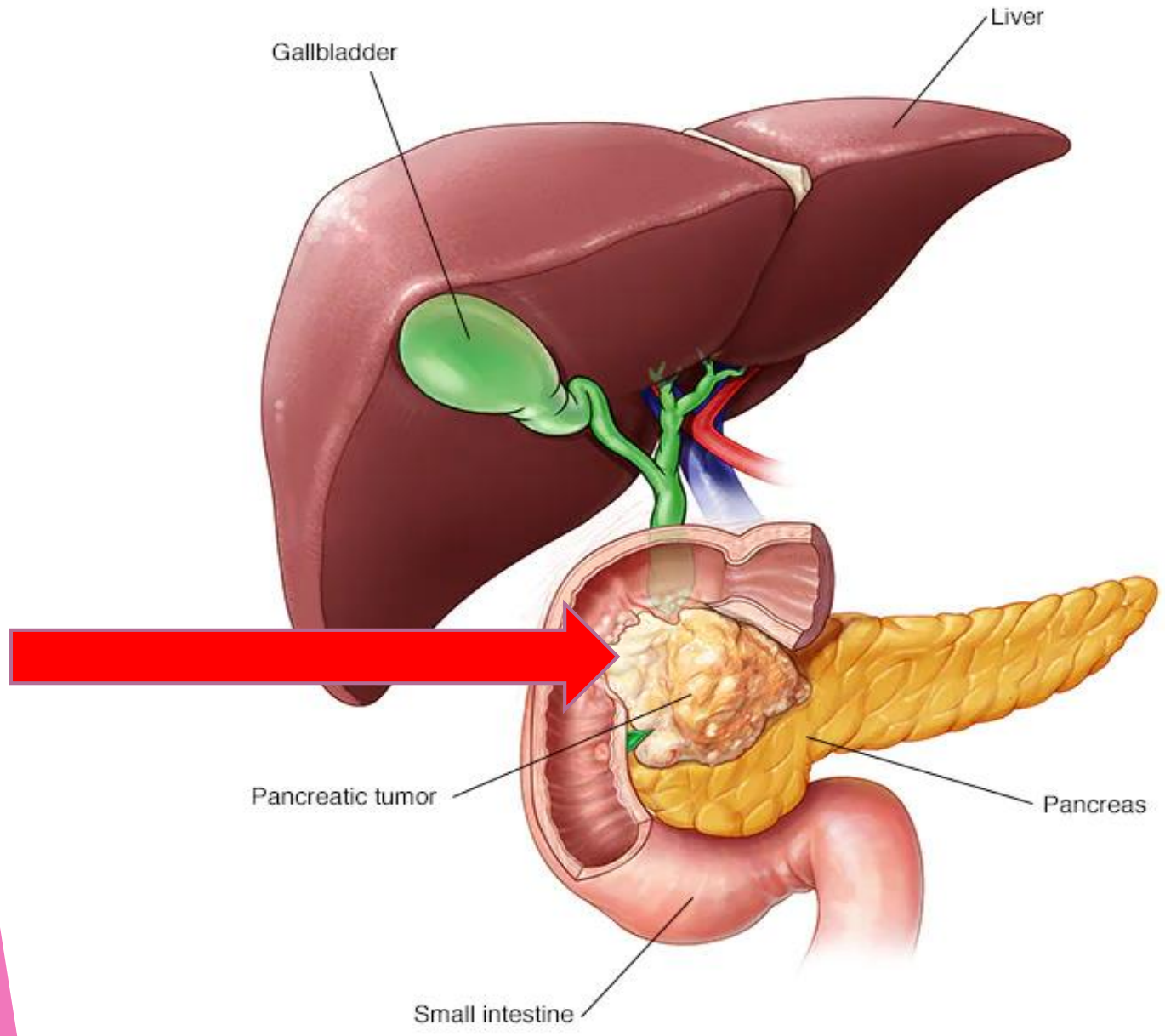
Carbohydrates	Fats	Protein
Amylase	Lipase	Protease
Disaccharides and glucose	Fatty acids	Peptides and amino acids

Pancreatic exocrine insuffiency/ PEI

Definition:

‘PEI is defined as a reduction of pancreatic exocrine activity in the intestine at a level that prevents normal digestion.’

Phillips et al., (2021)



Incidence of PEI

Inoperable pancreatic cancer –50-100%

Operable pancreatic cancer -

- 12% following central pancreatectomy
- 20% following distal pancreatectomy
- 20-45% pre-op for head of pancreas
- 70-98% following pancreatico-duodenectomy

Bartel et al.,(2015)
Philips et al., (2015)
Sabateret et al., (2016)

Causes of pancreatic exocrine insuffiency

Primary causes (lack of healthy tissue)	Secondary causes (lack of pancreatic stimulation)
Obstruction of pancreatic duct by tumour	Changes in intestinal pH following gastric/duodenal resection
Damage to the exocrine pancreas	Asynchrony in the delivery of pancreatic juice following a bypass of the bile duct, pancreas, stomach or duodenum
Loss of pancreatic tissue (surgery)	Abnormal CCK & secretin release
Pancreatitis	
Cystic fibrosis	

Keller and Layer,(2005)

Other conditions /causes of pancreatic exocrine insuffiency

Condition	Prevalence of abnormal FEL-1
Diabetes	Type 1: 26-44% Type 2: 12-20%
Elderly population	11.5 – 20% in patents 50-80 years 1.5% in patients >90 years
Renal disease	10-48%
Coeliac Disease	Around 30% with diarrhoea
Inflammatory bowels disease (IBD)	6.1-8.6%
Irritable bowel syndrome – D (IBS-D)	19-30%
HIV	23-54%
Alcohol related liver disease	7-20%
Somatostatin analogues e.g. Ocreotide	24% after a median of 2.9months of therapy

Phillips et al., (2021)

Poll two
Identify which of these is NOT a symptom / sign of PEI

- Hypoglycaemia / low blood sugars
- Unexplained weight loss
- Increased frequency / urgency of stools
- Hyperglycaemia / high blood sugars
- Stomach cramps and pain after eating

Symptoms and signs of PEI

Steatorrhea

Bloating

Reflux

Burping

Abdominal pain

Deficiency of vitamins and minerals

Increased wind / flatulence

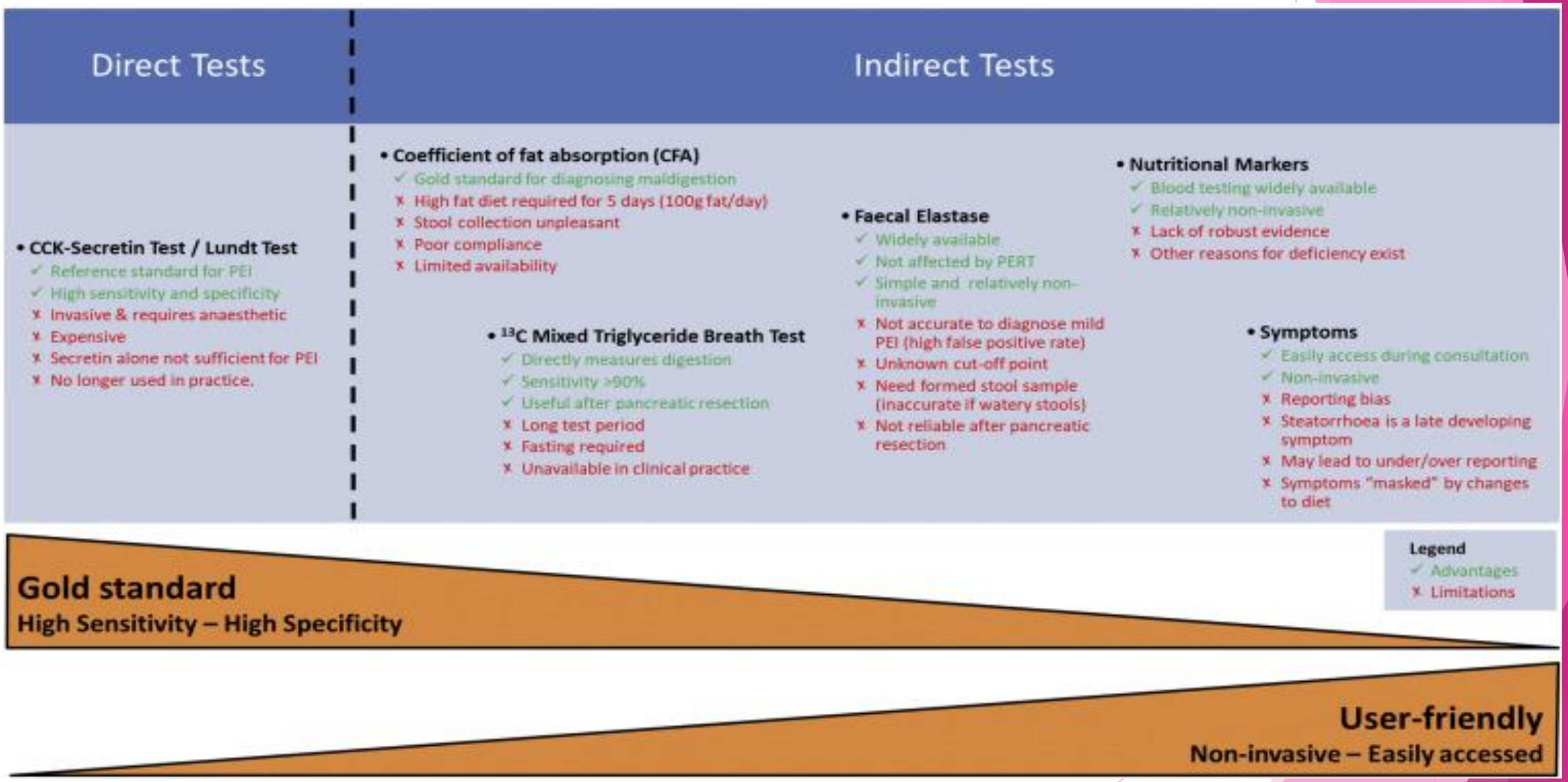
Nausea

Increased stool frequency / urgency

Unexplained weight loss

Hypoglycaemia

Pancreatic function tests



Carnie et al., (2020)

Diagnosing PEI

Statement 1.2: Although the coefficient of fat absorption is regarded as the gold-standard diagnostic test for PEI, we recommend that the faecal pancreatic elastase (FEL-1) test is a suitable first-line test for PEI (grade 1B) (note this was not submitted for consensus voting)

Phillips et al., (2021)

Interpreting Faecal elastase results

Faecal Elastase

- <200ug/g moderate PEI
- <100ug/g severe PEI
- 200 –500ug/g (low sensitivity/specificity)
- >500ug/g: Consider age; dilutional samples (watery / large volume stool); sample collection technique

Lohr et al., (2017)

Who benefits from testing?

Patients that require initial investigation with FEL-1

- GI symptoms of maldigestion in secondary care with or without known associated conditions
- Maldigestion symptoms: steatorrhoea, weight loss, diarrhoea, abdominal pain or bloating
- Associated conditions: patients with coeliac disease, IBS-D, HIV, type 1 diabetes and acute severe pancreatitis after initial phase

Who benefits from PERT?

Box 1 Diagnosis of PEI

PEI is highly likely with high benefit from PERT: no further test required as significant benefit from treatments and the negative predictive value of FEL-1 is not strong enough to prevent starting treatment

- Head of pancreas cancer
- Pre-surgery and post-surgery for head of pancreas cancer with or without pylorus preserving operation
- Total pancreatectomy
- Steatorrhea or malabsorption symptoms in patients with CP with dilated pancreatic duct or severe pancreatic calcification
- Severe necrotising pancreatitis

Why is PERT important?

Pancreatology 19 (2019) 114–121

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Enzyme replacement improves survival among patients wit
pancreatic cancer: Results of a population based study

K.J. Roberts [a, *], C.A. Bannister [b], H. Schrem [c]

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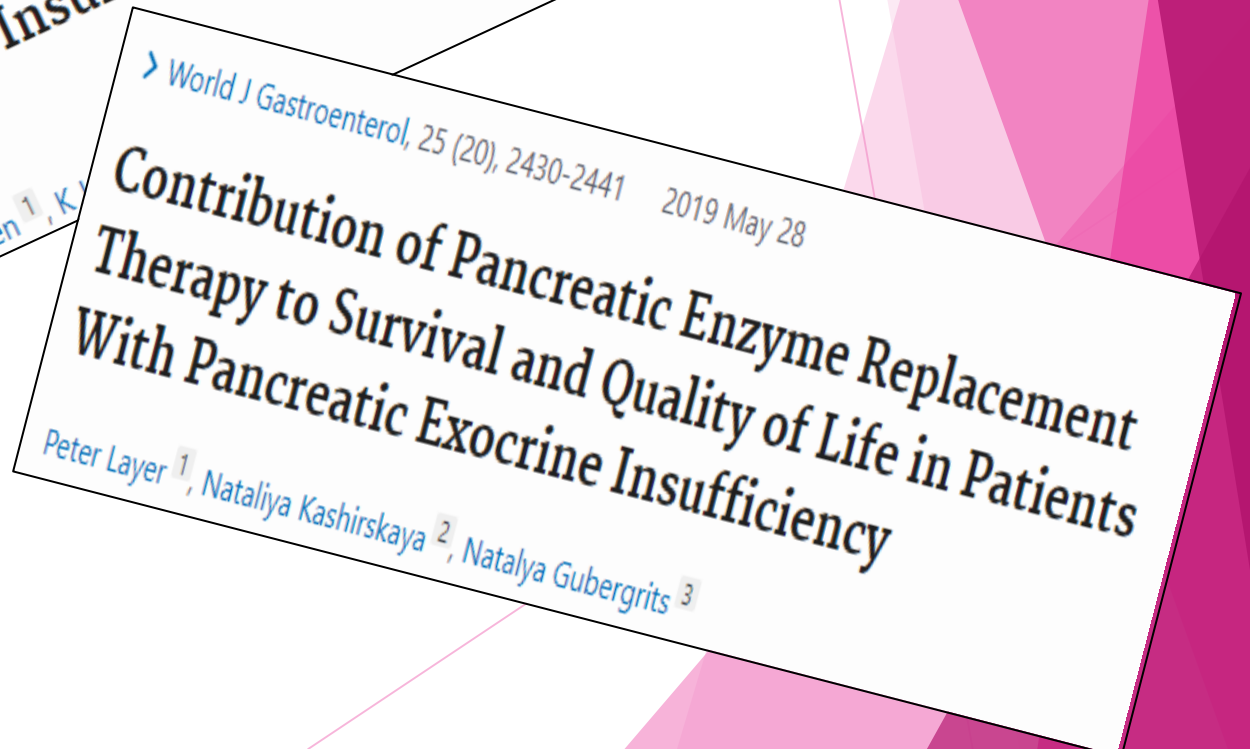
› Support Care Cancer, 21 (7), 1835-41 Jul 2013

Pancreatic Cancer and Supportive Care--Pancreatic Exocrine Insufficiency Negatively Impacts on Quality of Life

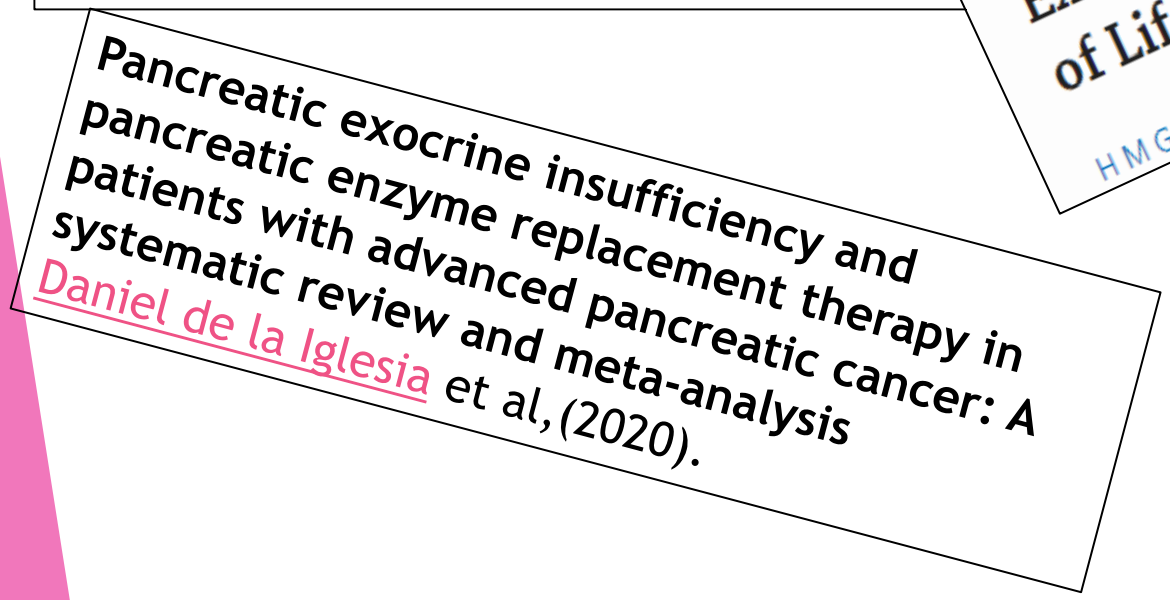
H M Gooden [1], K



› World J Gastroenterol, 25 (20), 2430-2441 2019 May 28

Contribution of Pancreatic Enzyme Replacement Therapy to Survival and Quality of Life in Patients With Pancreatic Exocrine Insufficiency

Peter Layer [1], Nataliya Kashirskaya [2], Natalya Gubergrits [3]



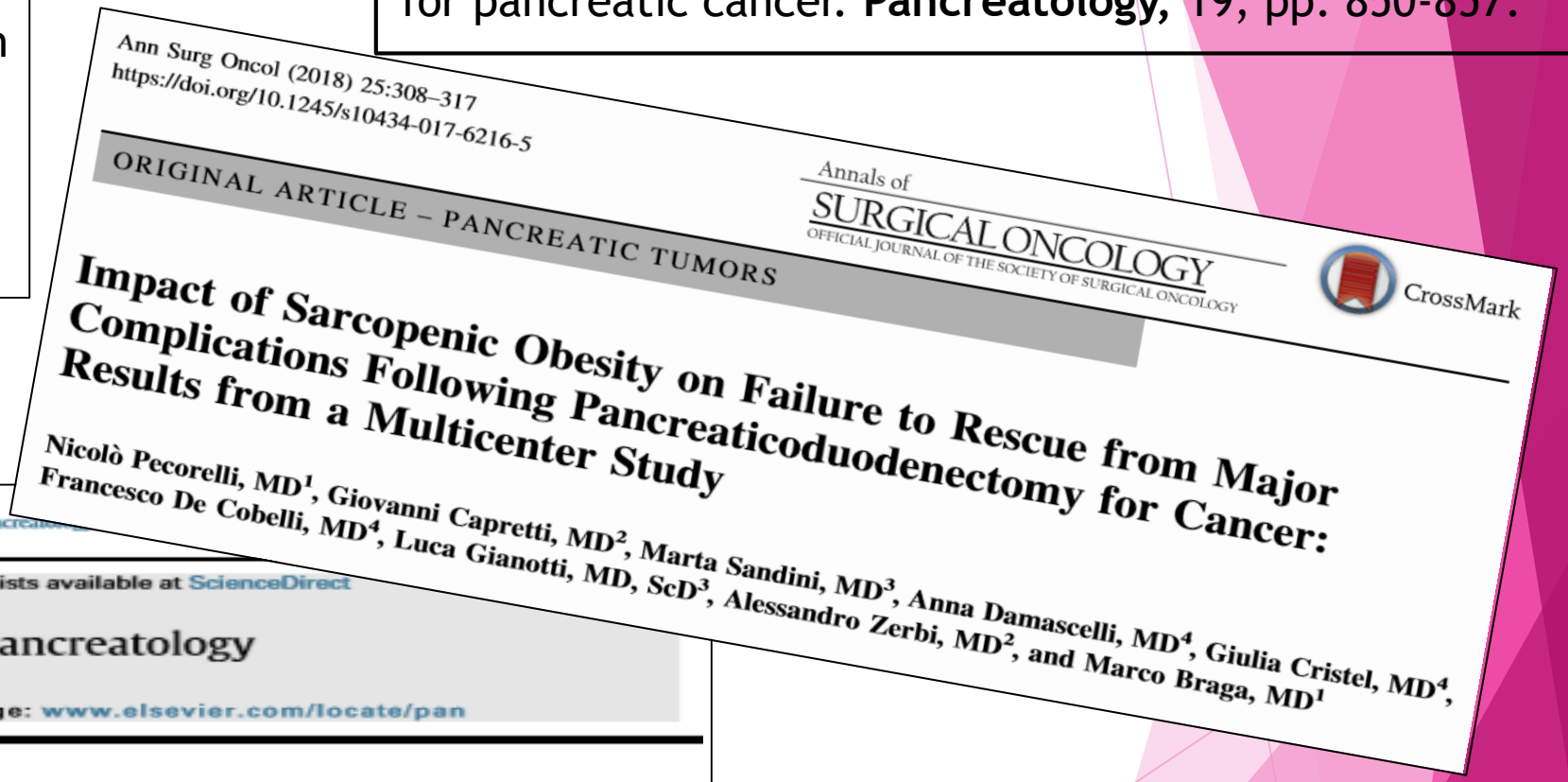
Pancreatic exocrine insufficiency and pancreatic enzyme replacement therapy in patients with advanced pancreatic cancer: A systematic review and meta-analysis

Daniel de la Iglesia et al, (2020).

Why is PERT important?

Shintakuya, R, et al., (2019). Sarcopenia is closely associated with pancreatic exocrine insufficiency in patients with pancreatic disease. **Pancreatology.** 17, 1, pp.7-75.

Griffin, O.M, et al., (2019). Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer. **Pancreatology,** 19, pp. 850-857.



Ann Surg Oncol (2018) 25:308–317
https://doi.org/10.1245/s10434-017-6216-5

ORIGINAL ARTICLE – PANCREATIC TUMORS

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

Impact of Sarcopenic Obesity on Failure to Rescue from Major Complications Following Pancreaticoduodenectomy for Cancer: Results from a Multicenter Study

Nicolò Pecorelli, MD[1], Giovanni Capretti, MD[2], Marta Sandini, MD[3], Anna Damascelli, MD[4], Giulia Cristel, MD[4], Francesco De Cobelli, MD[4], Luca Gianotti, MD, ScD[3], Alessandro Zerbi, MD[2], and Marco Braga, MD[1]

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

ELSEVIER

Review article

Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: A systematic review

I. Ozola Zalite [a], R. Zykus [b], M. Francisco Gonzalez [c], F. Saygili [d], A. Pukitis [a, e], S. Gaujoux [f, g], R.M. Charnley [h], V. Lyadov [i, *]

Impact of PEI

- Weight loss
- Malnutrition / Sarcopenia
- Nutritional deficiencies (fat-soluble vitamins A, D, E, K , zinc, selenium, magnesium , potassium, phosphate,)
- Symptoms of maldigestion
- Poor treatment tolerance
- Delays in treatment
- Reduced quality of life & well-being
- Increased risk of mortality

RICOCHET data

< 50% of patients prescribed PERT!!

- 45% of unresectable patients prescribed PERT
- 74.4% potentially resectable patients prescribed PERT
- 96.9% of pancreatic head resection patients prescribed PERT

- PERT prescription was more likely if:

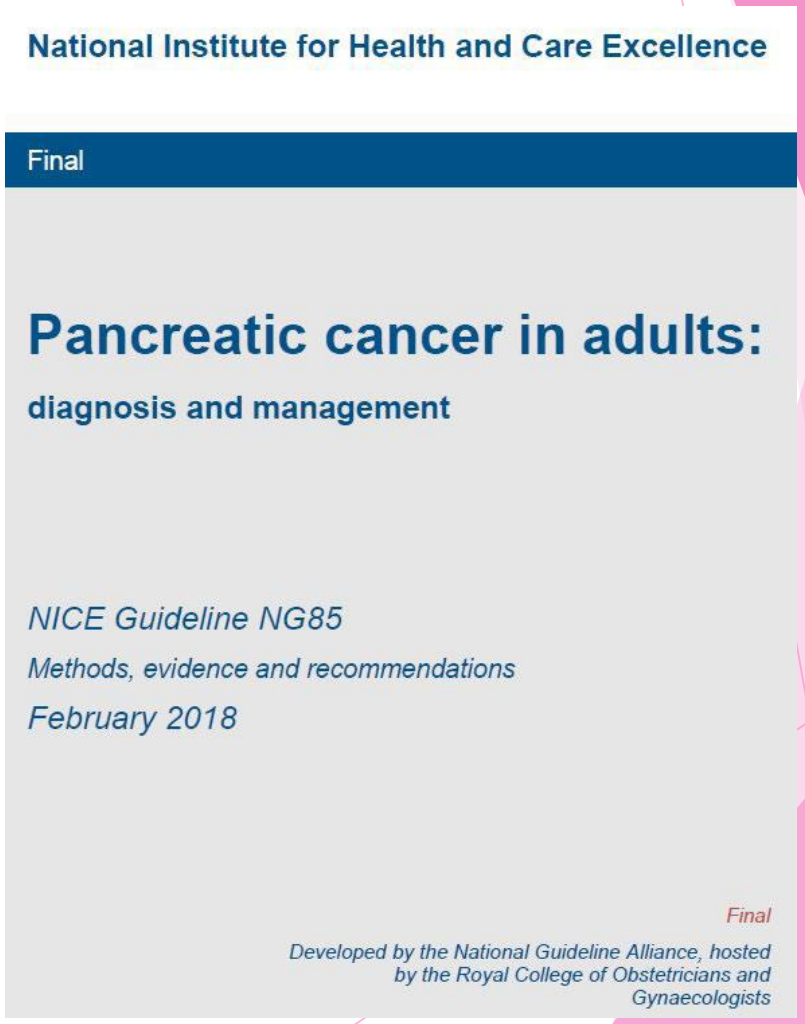
Seen by a dietitian (p = 0.001)

Seen in a specialist centre (p= 0.049 –HPB; p=0.009 –pancreas)

Seen by a clinical nurse specialist (p = 0.028)

Pancreatic enzyme replacement therapy

- Offer enteric-coated pancreatin with unresectable pancreatic cancer
- Consider enteric-coated pancreatin before and after pancreatic cancer resection



Pancreatic enzyme replacement therapy

Brand	Amylase	Protease	Lipase
Creon micro (100mg)	3600	200	5000
PancrexV capsule	9000	460	8000
Creon10,000	8000	600	10000
Nutrizym22	19800	1100	22000
Creon25,000	18000	1000	25000
Pancrease HL	22500	1250	25000
PancrexV powder (1g)	30000	1400	25000

Creon 40,000iu has been discontinued

Doses and timings

- Minimum of 44,000units - 50 000 units lipase per meal and 22,000iu -25 000 units lipase per snack
- Ensure taken with all food and milky drinks, spread throughout the meal rather than taking all at the start of the meal
- Ensure PERT is being taken with nutritional supplements, milky drinks, eating outside the home, takeaways and snacks
- Dose escalation is vital!

CCC audit on starting PERT doses in pancreatic cancer

- 6 months data
- 93 pancreas cancer patients
- 83% referred to CCC HPB dietitian
- 95% prescribed PERT at diagnosis/on initial oncology assessment/ dietetic assessment
- All on Creon25,000 to start

Starting doses with a meal:

50,000units or less – 16%

51,000units – ≤100,000units -51%

101,000units - ≤150,000units – 14%

151,000units - ≤200,000units – 7%

201,000units and over - 1%

Unknown – 11%

Starting doses with a snack:

25,000units – 50,000units – 71%

51,000units – ≤100,000units -10%

101,000units - ≤150,000units -7%

Unknown 12%

PERT- considerations and useful tips

PERT storage (<25°C)

Swallow capsules whole with a cold drink

If need to open; mix into yoghurt or acidic fruit puree

Consider gastric acid suppression / PPI e.g. Omeprazole

Consider gastric emptying

If a delay between meal courses/ slowly drinking supplements-extra enzymes needed

If having a fatty / larger meal –take more than normal. Titrate doses if ongoing symptoms

If tolerance issues try alternative brand

PERT- considerations

Contains Porcine!!

Statement 4.1:

Patients should consent for the porcine nature of PERT (GPP; 97% agreement). All currently available PERT preparations are porcine (a non-porcine PERT formulation was in development, but it failed to meet its primary endpoint in a phase III clinical trial).

Administration of PERT with enteral feeds

Powdered enzymes and feeding tubes

- Giving PERT as flushes: mix 1 g scoop pancreatin powder (Pancrex V Powder, Essential Pharmaceuticals, UK) with 50 mL sterile water.
- Shake well and immediately flush via a feeding tube. Do not give with other medication.
- Do not flush between the feed and the enzyme as this will reduce the mixing of the feed with the PERT.
- Administer every 2 hours throughout enteral feeding, increase dose of PERT if needed.

Mixing PERT with feed

- Add 1–2 g Pancrex V Powder directly to the feed in a feeding reservoir. Shake well. Hang straight away and for 4 hours only and increase dose of PERT if needed.

Flushing granules/mini-microspheres via large bore tubes (>CH20):

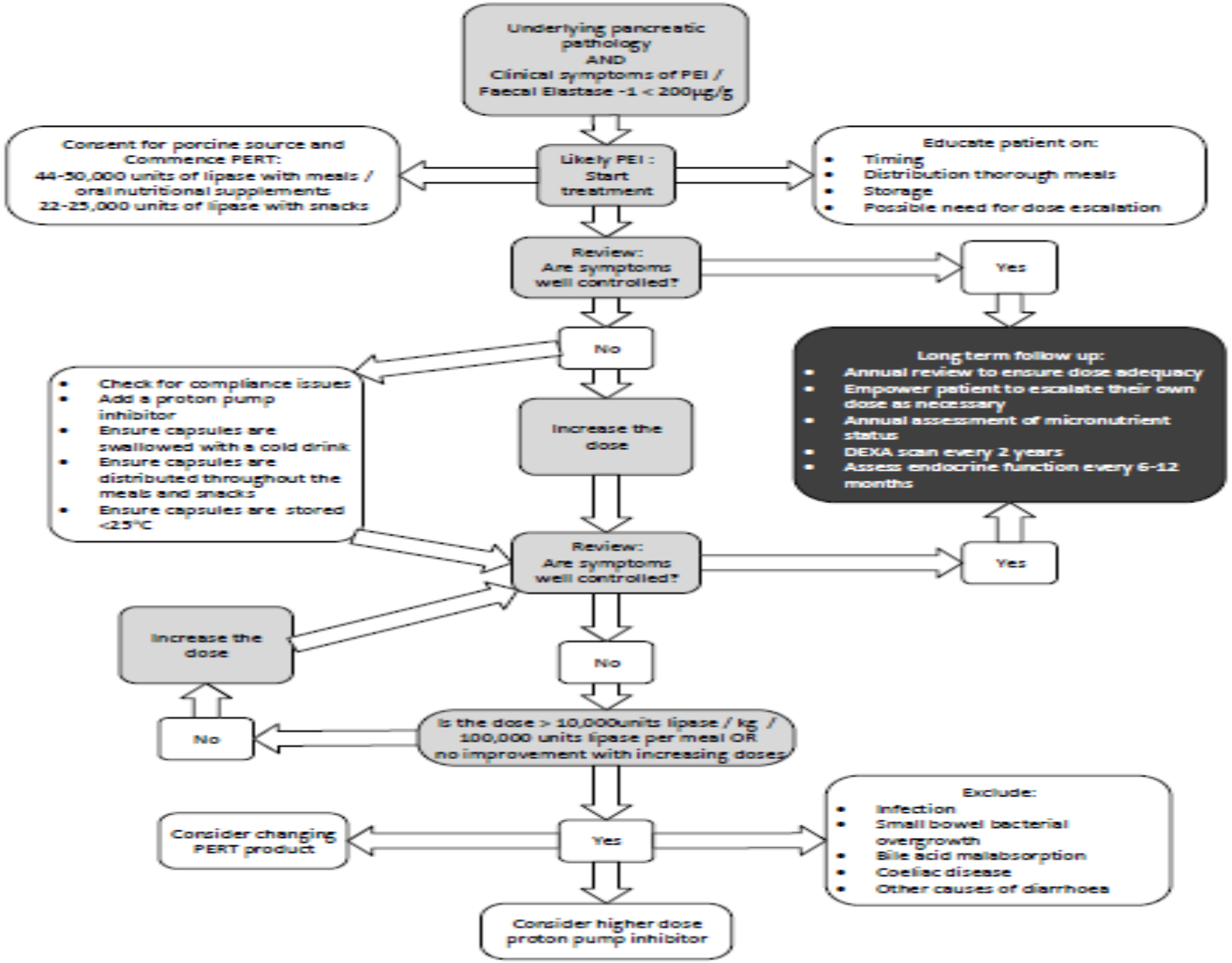
- Mix with an acidic juice and flush via the feeding tube every 2 hours throughout enteral feeding, increase dose of PERT if needed.

Differential diagnosis

- Coeliac disease
- Bile acid malabsorption (BAM)
- Small bowel bacterial overgrowth (SIBO),
- Food intolerance ,
- Lactase deficiency,
- Infective diarrhoea e.g. C.Diff
- Chemotherapy related diarrhoea

Keller and Layer (2005)
Phillips et al., (2021)

Considerations and troubleshooting



Phillips et al., (2021)

Case study

- 52 year old lady, Mrs R
- Pancreatic cancer with liver mets , due to start palliative chemotherapy
- Referred to HPB dietitian at initial oncology consultation due to significant weight loss 15% over 6 weeks and loose stools (after eating each meal), some abdominal cramps and increased indigestion.
- She takes Creon 25,000iu x1 capsule per meal, nil with a snack , nil with her juice based oral supplement drinks (ONS) of which she consumes twice a day
- Dietary assessment reveals she is eating well , three small meals a day and supplement drinks in between with occasional snack as able. No change in portion sizes of meals but still loosing weight.

Poll three
What changes would you consider to this patients PERT prescription?

1) Increase Creon to x2capsules with a meal and start x1 per nutritional supplement drink as well as with a snack
2) Continue with same doses as she is on
3) Increase Creon to x2capsules with a meal and x1 capsule per snack, nil with juice based supplements as little/no fat in them

Case study

- Mrs R returns to clinic a week later
- Weight has dropped a further 2kg in a week
- Reports still eating very well , no changes
- Has increased her Creon as advised to x2 capsules per meal , x1 per snack and per nutritional supplement drink and reports this has helped reduce stool frequency but she is still getting some abdominal cramping after eating and indigestion.

Poll four
What would you consider doing next?

1) Nothing as she is on recommended starting doses of PERT now. Would advise her to speak to her oncologist / GP re her symptoms
2) Increase Creon further to x3 capsules per meal, x2 per snacks and per nutritional supplement drinks and discuss starting a PPI (discuss with oncologist/GP)
3) Leave Creon doses alone but consider starting a PPI (discuss with oncologist/GP)

Summary

- Many patients will be on sub optimal doses of PERT
- PEI has multiple causes and consequences
- Pancreatic cancer is progressive and thus PEI is progressive
- Individualised dose escalation is vital and monitoring
- Effective PERT management can improve outcomes

References

Keller J, Layer P. (2005). Human pancreatic exocrine response to nutrients in health and disease. Gut, 54(6) pp. 1-28.

Imrie , C.W et al., (2010). Introduction; raising awareness of pancreatic exocrine insufficiency – does your patient need enzyme supplementation? Ailment Pharmacol Ther 2010; 32 (Suppl.1): 1-25.

Phillips et al., (2021). Consensus for the management of pancreatic exocrine insufficiency. UK practical guidelines. BMJ Open Gastroenterology 2021

Bartel et al., (2015). Pancreatic exocrine insufficiency in pancreatic cancer: A review of the literature. Dig Liver Dis. 2015 Dec;47(12):1013-20. doi: 10.1016/j.dld.2015.06.015. Epub 2015 Jul 6. PMID: 26211872.

Philips et al.,(2015). Pancreatic exocrine insuffiency following pancreatic resection. Pancreatology. 15 (5): 449-455. doi: 10.1016/j.pan.2015.06.003.

Sabateret et al., (2016). Evidence-based Guidelines for the Management of Exocrine Pancreatic Insufficiency After Pancreatic Surgery. Ann Surg;264(6):949-958.

Carnie et al., (2020). The assessment of pancreatic exocrine function in patients with inoperable pancreatic cancer: In need of a new gold-standard. Pancreatology. 20. 10.1016/j.pan.2020.03.020.

Lohr, J.M. (2017) United European Gastroenterology evidence based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU) United European Gastroenterology Journal, 5(2), pp. 153–199.

NICE guidelines (2018). Pancreatic cancer in adults: diagnosis and management.

RICOCHET study group (2021). Pancreatic enzyme replacement therapy in patients with pancreatic cancer. A national prospective study.