Mr Soonawalla - Surgery and pNETs : Q&A session February 2023

1. What is PERT?

PERT stands for Pancreatic Enzyme Replacement Therapy. It is the term given to medicines that provide enzymes in a capsule form to help treat Pancreatic Enzyme Insufficiency (PEI).
Capsule preparations include Creon® , Nutrizym 22® , Pancrease HL® and Pancrex®V
PEI is the inability of the pancreas to secrete the enzymes needed for digestion. These enzymes help break down fats, proteins and carbohydrates, from the food we eat, therefore, PEI, can result in malnutrition, due to malabsorption of nutrients. Symptoms may include steatorrhoea (pale, fatty/greasy, loose stools) weight loss, diarrhoea, abdominal pain and bloating.
PERT is the cornerstone of treatment and is associated with improved survival and quality of life (QoL) in patients with PEI.

Watch expert dietitian Mary Philips video on PERT & PEI here

2. Does the effectiveness of Creon reduce over time?

For those with Neuroendocrine Cancer, it is important to ensure that PERT is prescribed for the right reason. There are a number of potential causes for bloating and/or diarrhoea – PERT is a treatment for Pancreatic Enzyme Insufficiency (PEI) – and may not benefit those with other cause e.g., Bile Salt Malabsorption, SIBO (small intestinal bacterial overgrowth) …

For those with PEI: It is not that PERT (e.g., Creon®) necessarily becomes less effective, but more that changes in the pancreas occur over time – from changes in disease and / or treatments to simply ageing. It may also be that an alternative form of PERT (e.g., Pancrease HL®, Nutrizym 22® and Pancrex V®) may suit you better.

The pancreas changes its shape, structure and function with age.
According to published research, ~5% of people older than 70 years and 10% of those over 80 will develop pancreatic exocrine insufficiency (PEI). Whether intervention, with PERT and/or vitamin supplementation, is required in older individuals (with proven exocrine pancreas insufficiency) is debatable. Some researchers suggest it could contribute to healthy ageing.

Pancreatic Exocrine Insufficiency (PEI) & Pancreatic Enzyme Replacement Therapy (PERT)

3. How many 25000 Creon capsules would be considered too many?

According to prescribing guidance, studies support the use of at least 50 000 units lipase (2 Creon capsules) as a suitable starting dose with meals and 25 000 units lipase (1 Creon capsule) with snacks. This dose can be increased if the initial (starting) dose is not effective.
There is no maximum dose of PERT in adults however, where symptoms appear to persist despite increasing doses, it is important to check whether PERT is being stored correctly, taken correctly, and that there isn't something else going on before further increasing dose:

Timing and dosing

- Ensure that the correct dose of enzymes is prescribed; minimum of 50 000 units lipase per meal and 25 000 units lipase per snack. Many patients require more than this for adequate digestion. Escalate the dose and monitor for effect
- Check PERT is taken appropriately, that is, with all food and milky drinks, spread throughout the meal rather than taking at the start or end of the meal

- Ensure PERT is being taken with all intake, for example, nutritional supplements, milky drinks, eating outside the home, snacks

Storage

- Check how the PERT is stored (avoid storage in direct sunlight, cars, near heat sources such as kettles)

Factors affecting interpretation of symptoms

- Exclude constipation and overflow diarrhoea
- Check if any other medication that may be causing abdominal symptoms is being taken, for example, laxatives, chemotherapy, metformin, antiemetics

If symptoms are not controlled

- If symptoms remain despite high dose, then other causes of the symptoms should be considered before increasing the dose of PERT further
- Other causes of loose stools should be investigated, for example, SBBO, IBD, BAM, infection, coeliac disease, lactase deficiency, other food intolerances

Pancreatic Enzymes: A video guide for patients
Phillips et al (2021) Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. Available here

4. What tests – apart from bloods – should a patient have to check there is no decline in the function of the pancreas over time?

Many people leading up to and following a diagnosis of Neuroendocrine Cancer will have regular scans and blood tests. In terms of the blood tests, there will be some that will check your general overall health and others that may be more specific to either your type of Neuroendocrine Cancer and/or treatment.

For example; *FBC (Full Blood Count) This is a test to check the types and numbers of cells in your blood, including red blood cells, white blood cells and platelets. This can help give an indication of your general health, as well as provide important clues about certain health problems you may have, e.g., anaemia (NHS UK website)*

Most 'regular' blood tests will give a picture of your overall health – and can help monitor the effect your diagnosis and/or treatment(s) may be having on your physical well-being.

In terms of function of the pancreas – If there is a suspicion of pancreatitis (inflammation of the pancreas) - your doctor may check your blood amylase level. But in terms of Neuroendocrine Cancer, it is more likely that if you need any additional tests, these will be related to checking for diabetes, nutritional status and/ or gut hormone levels (if you have a 'functioning' pNET).

5. What about diabetes and other checks?

Your doctor may check for diabetes, as part of an overall health check and/or as part of surveillance if your diagnosis, treatment and/or medical history shows you may be at risk. HbA1c is a test that can show what your average blood glucose (sugar) levels has been for the last two to three months, rather than just at a specific moment in time. It is helpful in diagnosing and monitoring diabetes.

The World Health Organisation (WHO) suggests the following diagnostic guidelines for diabetes:

- HbA1c below 42 mmol/mol (6.0%): non-diabetic
- HbA1c between 42 and 47 mmol/mol (6.0–6.4%): Impaired glucose regulation (IGR) or Prediabetes
- HbA1c of 48 mmol/mol (6.5%) or over: Type 2 diabetes

Prediabetes is characterised by the presence of blood glucose levels that are higher than normal but not yet high enough to be classed as diabetes.
For people with cancer, HbA1c may fall into the pre-diabetic or diabetic range – this could be due to altered pancreatic function due to disease (cancer, pancreatitis, or trauma injury) or treatment, e.g., steroids, somatostatin analogues and other types of medication used in cancer care, regardless of primary site of disease.
For others, who have a pancreatic primary, the risk of developing diabetes may also be due to surgery – and how much pancreas has been removed alongside age and life-time risk.

If you have a 'functioning' pancreatic Neuroendocrine Tumour (pNET) - your doctor may request a Fasting Gut Hormone Profile and /or Insulin and C-peptide level – depending on the type of functioning pNET you have. The profile includes the following gut hormones:

- Gastrin
- Glucagon
- Pancreatic polypeptide
- Vasoactive intestinal polypeptide
- Somatostatin

And can show whether your pNET is over-producing a specific hormone, for example, an insulinoma can produce abnormally high levels of insulin. A VIPoma – abnormally high Vasoactive Intestinal Polypeptide. Identifying this this can help tailor and monitor treatment more effectively.

- Chromogranin A and B

Can be taken as part of a Gut Hormone Profile or separately – and is a more general test for Neuroendocrine Cancer – though not everyone diagnosed will have raised levels.

6. Re: Alcohol Consumption with Pancreatic Neuroendocrine Cancer. What is the professional view? Everyone is aware that alcohol with Pancreatic Cancer / Liver Cancer is not recommended but does the same apply for <u>Neuroendocrine Cancer?</u>

Broadly speaking, it is usually ok for you to have a **small** amount of alcohol if you feel like it.

The UK Chief Medical Officers (CMOs) advise that to keep the risk from alcohol low, adults should not regularly drink more than 14 units of alcohol per week.
Alcohol adversely affects health in a range of ways and there is NO definitively 'safe' lower limit – NO level of regular alcohol consumption improves health.

The risk of developing a range of health problems (including primary cancers of the mouth, throat, oesophagus, pancreas, liver, and breast) increases the more you drink on a regular basis.
A risk factor is anything that increases your chance of getting a disease such as cancer. Different cancers have different risk factors. Some risk factors, like smoking or alcohol, can be changed. Others, like a person's age or family history, can't.

In terms of Neuroendocrine Cancer – alcohol intake depends on your overall health, primary site, current cancer status and treatment plan.

For example:

- If you have a history or high risk of pancreatitis – it is best to avoid alcohol. Some studies have shown a link between heavy alcohol use and pancreatic NETs. Heavy alcohol use (more than 14 units/wk) can also lead to conditions such as chronic pancreatitis and liver damage.
- If you have abnormal liver function, liver fibrosis or cirrhosis – it is best to avoid alcohol (note: a healthy liver that has tumour deposits in it is still a healthy liver, unless tumour affects overall liver function)

- If you are to undergo surgery – particularly liver surgery – then abstaining from alcohol in the weeks before and after surgery is recommended.
- If you are having chemotherapy - It will usually be all right for you to have a small amount of alcohol if you feel like it – a small amount may even help with appetite. However, alcohol can worsen some chemotherapy side effects, such as dehydration, diarrhoea, and mouth sores.
- For some, especially those with Carcinoid Syndrome, alcohol may increase symptoms such as flushing and / or diarrhoea.

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7. My GP wants to put me on Statins. Then he checks my cholesterol and realises not required.

a. **Is good cholesterol levels a side effect of not having a Pancreas (I make no dietary adjustments for fat etc.)?**
b. **As statins seem to be available for everyone (of a certain age) should we agree to them irrespective of cholesterol levels?**

Some cholesterol comes from the food we eat, but most (about 80%) is made in the **liver**.

Cholesterol and another type of blood fat called triglycerides can't circulate loosely in the blood, so the liver packages them into "parcels" called lipoproteins, including LDL and HDL cholesterol.

- 'good cholesterol' (called high-density lipoproteins or HDL) which take cholesterol you don't need back to the liver
- 'bad cholesterol' (called non-high-density lipoproteins or non-HDL) which can lead to fatty layers building up in your arteries that block the flow of blood to and from the heart. This can increase your risk of getting heart problems.

They are released into the blood to carry the fats around the body to wherever they're needed.

Once in the blood stream, some cholesterol will be carried back to the liver and broken down. The liver uses cholesterol to make bile acids which are released into the intestines to help with digestion. They break down the fats in food.
A small amount of bile acids will leave the body as a waste product in your poo. But most will be absorbed back into the blood (at the ileo-caecal junction - where the large and small bowel meets), returned to the liver and used again. If this junction has been removed as part of a small or large bowel resection, you may be at risk of bile salt malabsorption - which can be treated with medication.

Mr Soonawalla: so - there is no need for statins if your cholesterol is ok and you have no other health concerns which may indicate their use.

According to the British Heart Foundation, apart from treating high cholesterol levels, you may be given a statin if you:

- have angina or peripheral arterial disease
- have a high risk of developing angina or of having a heart attack or stroke
- have diabetes
- have had a heart attack or stroke
- have had an angioplasty or bypass surgery
- have the inherited condition familial hypercholesterolaemia (FH).

Even if you're in good health, you may be prescribed a statin **IF** you're considered to be at high risk of developing cardiovascular disease.

8. What's the average post total Pancreatectomy survival term?

In the last few years, postoperative outcomes following total pancreatectomy (TP) have improved with the advances in surgical techniques, glycemic monitoring, insulin delivery systems, insulin formulations, and

pancreatic enzyme preparations. A recent series also demonstrated that TP was not inferior to pancreaticoduodenectomy / Whipple's procedure regarding mortality, major morbidity, overall quality of life, and long-term survival. However, data beyond single centre experience is difficult to find and reports vary - and while they may distinguish between those who have surgery for benign disease and those who have surgery for cancer - they do not often distinguish between types of malignancy. Though where this is information is available, Grade 1-2 pNETs seem to have similar outcomes to those with benign disease. Zhao et al (2023) report a 5-year survival rates for patients with malignant and benign tumors were 42.6% and 86.1%, respectively. However closer analysis of the types of tumours showed early stage pNET had a 5-year survival rate of 100%, compared to pancreatic ductal adenocarcinoma (PDAC) of 23%. Others have quoted figures than range from 60-87% for pNET.
To be born in mind is overall survival rate and natural history of the disease being treated - pNET has a more favourable prognosis than PDAC with or without surgery.
Overall 5 yr survival of pNET (regardless of Grade/Stage/Functionality) is >60% compared to PDAC <20%.

9**. Following Total Pancreatectomy, I have a lifetime of:**

a. **Insulin**
b. **PERT (Creon)**
c. **Vitamin B12 (quarterly)**
d. **Iron tablets**

Are there other drugs / vitamins / hormones to be prescribed to replace lost "functionality"?

Medications, vitamins, and mineral requirements need to be assessed on an individual basis.
This clinician or dietitian-led assessment of need can be complex, depending on diagnosis – the site and type of Neuroendocrine Cancer – what treatment has already been undertaken – and whether there are any other health considerations that may need to be taken into account. Assessment that identifies a need, may require intervention and / or ongoing support for monitoring care.

For example: treatments such as somatostatin analogues (Octreotide and Lanreotide) can affect how the pancreas works – both its endocrine, or hormonal, function – in terms of producing insulin and glucagon to control blood sugar levels, and its exocrine function – in terms of producing the digestive enzymes we need to help our bodies breakdown and absorb the food we eat.
Nutrition and Neuroendocrine Cancer
Vitamins and Minerals – is supplementation necessary?

10a Re Total Pancreatectomy. Should a patient receive a personalised care plan that recognises that blood glucose management / insulin dependency is a 24/7 life time commitment?
10b And prior to authorising a Total Pancreatectomy (TP), does the MDT take the following into account to develop a patient specific pathway:

a. Provide the patient with a CGM for at least a month prior to the operation and for life afterwards
b. Refer the patient to a Diabetic Consultant to provide an overview of life post operation
c. Schedule DAFNE or similar Carb Counting training course to be attended before operation or ASAP post operation
d. Refer patient to there local hospital diabetes centre for ongoing support
e. Discuss transition on to a closed loop pump once patient has built up sufficient experience to set required pump ratios.

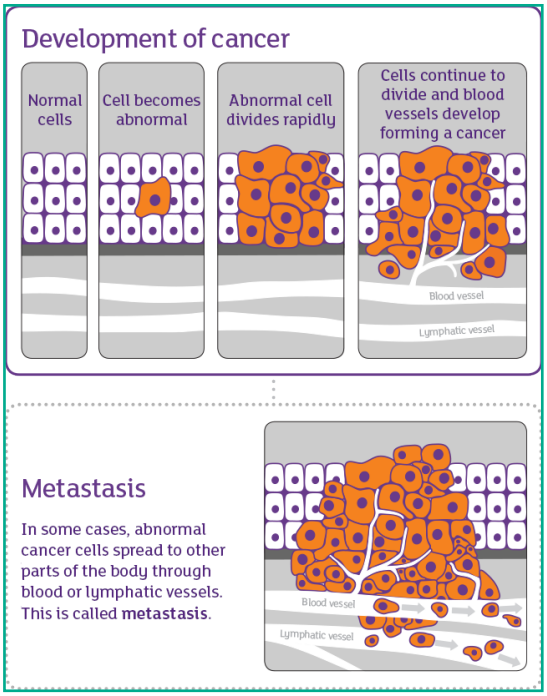
Yes - Mr Soonawalla would advocate for pre-surgery education and support including diabetic team referral.
Multidisciplinary management, including primary disease treatment, intensive diabetes care, adequate pancreatic enzyme supplementation, and nutritional support, have an essential role in improving the short- and long-term outcomes of TP.

Preoperative identification of blood sugar level status and diabetes classification in patients planned to undergo TP are important to guide postoperative insulin treatment. Diabetic control following TP can be more challenging as blood sugars can be more erratic and insulin requirements generally lower (note:may be higher in first days/weeks post-op), except in those with preoperative long-duration diabetes and/or those older or with high BMI (body mass index).
Zhao et al (2023) found that *"glycemic control after TP can be similar to T1DM under regular follow-up but indeed is influenced by more factors, such as diet recovery, pancreatic enzyme supplementation, and primary disease treatment."* For example, chemotherapy, tyrosine kinase inhibitors, or somatostatin analogues after surgery, may have an adverse effect on glycemic (blood glucose) control - which may also affect insulin requirements.
CGMs (Continuous Glucose Monitoring systems) can be useful, particularly in the first 3-6months after surgery. There are a number of CGM and blood sugar checking kits available in the UK - see information about these at Diabetes UK .
The DAFNE course is for adults (over 17 years old) with type 1 diabetes - and therefore can be helpful for those post TP. Similar courses include DESMOND (Type II Diabetes) and X-PERT diabetes (Type II): information on other Type I courses is available on the NHS website here
Diabetes UK provides further information on closed loop systems here - however, this information relates to insulin only pumps. There is ongoing research into the use of bihormone pumps eg insulin and glucagon, to assess safety and effectiveness in further improving blood sugar control post TP e.g., van Veldhuisen et al (2022)

11. During Total Pancreatectomy, a number of Lymph Nodes are removed. If these contain disease, is there an alternate treatment to close down the activity of the remaining Lymph Nodes?
My understanding is that Liver Metastasis can occur as a result of lymphatic system spread and that this involvement of lymph nodes (outside of the liver) would mean that in the future a liver transplant would not be an option for me.

In terms of spread of disease - this can happen in 3 ways:

- Local infiltration of nearby tissues and/or organs - where tumour may grow into surrounding tissue.
- Tumour cells entering the lymphatic system - lodging in lumps nodes or travelling further around the body
- Tumour cells entering the blood circulation system - may travel to other sites of the body.



Treatments such as somatostatin analogues (Octreotide or Lanreotide) may be used in Grade 1-2 pNETs to help stop or slow down NET cells from growing or spreading further.
For High-Grade 3 pNETs or pNECs, chemotherapy may be used. Other treatments include drugs such as Everolimus or Sunitinib may be considered.

In terms of liver transplantation - current criteria includes those who have Grade 1 and some Grade 2 NET (G2 with a Ki67 less than 10%), have had their primary tumour completely removed and have no evidence of extra-hepatic disease (no disease outside of the liver). If your tests show no active disease outside of the liver and you fulfil all criteria, as assessed by your "NET" team, you may be considered for liver transplant assessment.

Neuroendocrine Cancer UK's CEO, Catherine Bouvier, talks to Dr Tahir Shah about his work in developing a new service for Neuroendocrine Cancer patients to improve outcomes and their quality of life through using surgery and liver transplantation: you can listen to the podcast here

12 Is there a role for islet cell transplantation in pNETs?

Pancreatic islet cell transplantation, for non-cancerous conditions, has been undertaken at Oxford for the last 8-10years. Due to limitations in practical application and current criteria - it is not currently used in the treatment of pNETs.

Autologous pancreatic islet cell transplantation involves the removal of parts of the patient's own pancreas (the islet cells, which are responsible for insulin production), after the pancreas has been removed. These cells are then inserted into the patient's liver to restart insulin production within the body. However, this procedure can only be undertaken at the same time as pancreatectomy and there is the potential risk of re-implanting tumour cells when the cells are inserted into the liver.

Allogeneic pancreatic islet cell transplantation involves the removal of cells called islet cells, which are responsible for the production of insulin, from human donors. These cells are inserted into the patient's liver to restart insulin production within the body. However, patients who have this procedure will need to take medications to help their bodies' immune system to accept the cells.
Allogenic pancreatic islet cell transplantation is only considered for certain people with type 1 diabetes who have blood glucose levels that are difficult to manage, experience severe hypoglycemia, and have hypoglycemia unawareness.
It may also be considered for those who have type 1 diabetes and have had, or are planning to have, a kidney transplant to treat kidney failure. Islet transplantation may be performed at the same time as or after a kidney transplant.
NICE guidance is available here

13 Are there any family / genetic risks with pancreatic NET? Is it possible to have family members tested?

The majority of neuroendocrine tumors are thought to be sporadic (that is, **not** inherited).
However, there are some neuroendocrine tumors that are **associated** with inherited genetic syndromes: such syndromes, including Multiple Endocrine Neoplasia 1 (MEN1), Von-Hippel Lindau (VHL), Neurofibromatosis 1 (NF1) and Tuberous-Sclerosis (TS), are rare.
If there is a family history of any of these genetic syndromes - or there is a suspicion that you may have one of these syndromes - testing can be undertaken to confirm or rule it out.

There may also be certain tests that may be undertaken to see if a treatment carries any risk or better targeting for your cancer - for example, DPD deficiency and Capecitabine. Having a deficiency in the DPD enzyme could make the side effects of certain chemotherapy drugs worse. For some people, these side effects can be life threatening. This group of drugs are called fluoropyrimidines: and include 5-fluorouracil (5FU), capecitabine and tegafur.

Genomic testing in the NHS is being provided through a national testing network : the full range of genomic tests that are commissioned for the NHS in England is available through the National Genomic Test Directory.
(In Scotland: Scottish Germline Test Directory / In Wales: All Wales Medical Genomics Service / In Northern Ireland: information is provided here).

But you may have heard about genetic testing online or in the media - a current 'hot topic' is WGS (whole genome sequencing) - and there are a number of companies offering such a service.

The individual cost for WGS is quoted as anywhere between £1,500 to £5,000 (or more).

Cancer can occur due to changes in DNA and/or RNA called mutations, that affect the way your cells work and grow. However, each person's cancer is unique because mutations differ in type and number and between cancer types. Even if you have the same type of cancer as someone else, your mutations may differ to theirs, and you may need different treatment.

WGS can provide evidence of certain mutations - it may also provide information on what treatments may be more effective for your particular type of cancer. However, not all mutations have been identified, or even if they have, there may not be a treatment that specifically targets that mutation.

IF certain mutations are found in your cancer cells, your doctor may be able to give you a more precise treatment based on this finding - by matching the mutations to known mutations/treatment targets. HOWEVER, there are cases where either no relevant mutation is found or no targeted treatment option is available for the mutation that has been identified. This can also be valuable information for further / future treatment planning.