

SUPPLEMENTARY DATA

Database Search Strategies

Table S1. Search terms for MEDLINE (searched via Ovid SP on 12th September 2018)

Term	#	Searches	Results
Group			
GEP-NETs	1	exp neuroendocrine tumors/ or exp carcinoma, neuroendocrine/	157721
or			
carcinoid	2	((neuroendocrine adj2 (tumo?r\$ or cancer\$ or neoplas\$ or carcino\$)) or NET or NETs).tw.	119303
syndrome	3	1 or 2	266559
	4	(bowel\$ or gastrointestin\$ or intestin\$ or gut\$ or midgut\$ or ileum or ileal or jejunum or jejunal or pancrea\$).tw.	912527
	5	3 and 4	18517
	6	(gep-net\$ or gepnet\$ or gi-net\$ or ginet\$ or p-net\$ or pnet\$ or pan-net\$ or pannet\$).tw.	3481
	7	carcinoid\$.mp.	17392
	8	exp carcinoid tumor/	12330
	9	((functional or functioning or symptom\$) adj2 (neuroendocrine or NET or NETs)).tw.	652
	10	or/5-9	34315
Diarrhoea	11	exp diarrhea/ or steatorrhea/	50561
	12	(diarrh?ea\$ or steatorrh?ea\$ or loose stool\$ or (bowel\$ adj1 movement\$)).tw.	102487
	13	exocrine pancreatic insufficiency/	1900
	14	((pancrea\$ adj2 insufficien\$) or (pancreatic enzyme\$ adj2 replace\$) or PI or PEI).tw.	131370
	15	short bowel syndrome/	2729
	16	(short bowel or SBS).tw.	5744

Term Group	#	Searches	Results
	17	((bile acid or bile salt) adj2 (malabsor\$ or sequest\$)).tw.	1106
	18	((cholerheic or cholaretic) adj enteropath\$).tw.	7
	19	(bacteria\$ adj1 overgrow\$).tw.	2383
	20	or/11-19	256572
Combined	21	10 and 20	1627
Exclusion terms	22	exp animals/ not exp humans/	4496387
	23	21 not 22	1372
Date limit	24	limit 23 to yr="2008-2018"	482

Table S2. Search terms for Embase (searched via Ovid SP on 12th September 2018)

Term Group	#	Searches	Results
GEP-NETs or carcinoid syndrome	1	neuroendocrine tumor/ or exp neuroendocrine carcinoma/	21506
	2	((neuroendocrine adj2 (tumo?r\$ or cancer\$ or neoplas\$ or carcino\$)) or NET or NETs).tw.	146035
	3	1 or 2	150720
	4	(bowel\$ or gastrointestin\$ or intestin\$ or gut\$ or midgut\$ or ileum or ileal or jejunum or jejunal or pancrea\$).tw.	1160350
	5	3 and 4	20658
	6	gastroenteropancreatic neuroendocrine tumor/	1235
	7	(gep-net\$ or gepnet\$ or gi-net\$ or ginet\$ or p-net\$ or pnet\$ or pan-net\$ or pannet\$).tw.	6877
	8	carcinoid\$.mp.	23106
	9	exp carcinoid syndrome/ or exp carcinoid/	18552

Term Group	#	Searches	Results
	10	((functional or functioning or symptom\$) adj2 (neuroendocrine or NET or NETs)).tw.	1131
	11	or/5-10	45323
Diarrhoea	12	exp diarrhea/	225889
	13	(diarrh?ea\$ or steatorrh?ea\$ or loose stool\$ or (bowel\$ adj1 movement\$)).tw.	143828
	14	exp pancreatic insufficiency/	819
	15	((pancrea\$ adj2 insufficien\$) or (pancreatic enzyme\$ adj2 replace\$) or PI or PEI).tw.	137640
	16	short bowel syndrome/	5415
	17	(short bowel or SBS).tw.	6960
	18	((bile acid or bile salt) adj2 (malabsor\$ or sequest\$)).tw.	1497
	19	((cholerheic or choleric) adj enteropath\$).tw.	1
	20	bacterial overgrowth/	4159
	21	(bacteria\$ adj1 overgrow\$).tw.	3767
	22	or/12-21	417776
Combined	23	11 and 22	3525
Exclusion terms	24	(conference abstract or conference review).pt.	3148278
	25	limit 24 to yr="1946-2015"	2260023
	26	exp animals/ not exp humans/	4289668
	27	25 or 26	6343948
	28	23 not 27	2598
Date limit	29	limit 28 to yr="2008-2018"	1492

Table S3. Search terms for The Cochrane Library (searched via Wiley Online on 12th September 2018)

Term Group	#	Searches	Results
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Term Group	#	Searches	Results
GEP-NETs or carcinoid syndrome	1	[mh "neuroendocrine tumors"] or [mh "neuroendocrine carcinoma"]	1873
	2	((neuroendocrine near/2 (tumo?r* or cancer* or neoplas* or carcino*)) or NET or NETs):ti,ab,kw	7431
	3	#1 or #2	9204
	4	(bowel* or gastrointestin* or intestin* or gut* or midgut* or ileum or ileal or jejunum or jejunal or pancrea*):ti,ab,kw	64686
	5	#3 and #4	822
	6	(gep-net* or gepnet* or gi-net* or ginet* or p-net* or pnet* or pan-net* or pannet*):ti,ab,kw	258
	7	carcinoid*:ti,ab,kw	322
	8	[mh "carcinoid tumor"]	85
	9	((functional or functioning or symptom*) near/2 (neuroendocrine or NET or NETs)):ti,ab,kw	80
	10	{or #5-#9}	1190
Diarrhoea	11	[mh "diarrhea"] or [mh "steatorrhea"]	3128
	12	(diarrh?ea* or steatorrh?ea* or "loose stool*" or (bowel* near/1 movement*)):ti,ab,kw	5333
	13	[mh "exocrine pancreatic insufficiency"]	116
	14	((pancrea* near/2 insufficien*) or ("pancreatic enzyme" near/2 replace*) or PI or PEI):ti,ab,kw	5021
	15	[mh "short bowel syndrome"]	86
	16	("short bowel" or SBS):ti,ab,kw	405
	17	((("bile acid" or "bile salt") near/2 (malabsor* or sequest*)):ti,ab,kw	146
	18	((cholerheic or choleric) next enteropath*):ti,ab,kw	0

Term Group	#	Searches	Results
	19	(bacteria* near/1 overgrow*):ti,ab,kw	202
	20	{or #11-#19}	13175
Combined	21	#10 and #20	98
		("conference abstract" or "conference review"):pt	
Exclusion terms	22	<i>with Cochrane Library publication date from Jan 1900 to Dec 2015</i>	47677
	23	#21 not #22	97
Total	24	<i>#23 in Cochrane Reviews and Trials</i>	96

Table S4. Search terms for DARE (searched via the CRD platform on 12th September 2018)

Term Group	#	Searches	Results
	1	MeSH DESCRIPTOR Neuroendocrine Tumors EXPLODE ALL TREES	303
	2	MeSH DESCRIPTOR Carcinoma, Neuroendocrine EXPLODE ALL TREES	20
	3	(neuroendocrine adj2 (tumor* or tumour* or cancer* or neoplas* or carcino*)) or ((tumor* or tumour* or cancer* or neoplas* or carcino*) adj2 neuroendocrine)	2423
GEP-NETs or carcinoid syndrome	4	or NET or NETs #1 or #2 or #3	2682
	5	bowel* or gastrointestinal* or intestin* or gut* or midgut* or ileum or ileal or jejunum or jejunal or pancrea*	4512
	6	#4 and #5	167
	7	gep-net* or gepnet* or gi-net* or ginet* or p-net* or pnet* or pan-net* or pannet*	198
	8	carcinoid*	15

Term Group	#	Searches	Results
	9	MeSH DESCRIPTOR Carcinoid Tumor EXPLODE ALL TREES	8
	10	((functional or functioning or symptom*) adj2 (neuroendocrine or NET or NETs)) or ((neuroendocrine or NET or NETs) adj2 (functional or functioning or symptom*))	2
	11	#6 or #7 or #8 or #9 or #10	371
	12	MeSH DESCRIPTOR Diarrhea EXPLODE ALL TREES	228
	13	MeSH DESCRIPTOR Steatorrhea EXPLODE ALL TREES	0
	14	diarrhea* or diarrhoea* or steatorrhea* or steatorrhea* or "loose stool*" or (bowel* adj1 movement*) or (movement* adj1 bowel*)	861
	15	MeSH DESCRIPTOR Exocrine Pancreatic Insufficiency EXPLODE ALL TREES	3
Diarrhoea	16	(pancrea* adj2 insufficien*) or (insufficien* adj2 pancrea*) or ("pancreatic enzyme" adj2 replace*) or (replace* adj2 "pancreatic enzyme") or PI or PEI	230
	17	MeSH DESCRIPTOR Short Bowel Syndrome EXPLODE ALL TREES	14
	18	"short bowel" or SBS	25
	19	("bile acid" or "bile salt") adj2 (malabsor* or sequest*) or ((malabsor* or sequest*) adj2 ("bile acid" or "bile salt"))	11
	20	((cholerheic or cholaretic) adj1 enteropath*) or (enteropath* adj1 (cholerheic or cholaretic))	0
	21	(bacteria* adj1 overgrow*) or (overgrow* adj1	6

Term Group	#	Searches	Results
		bacteria*)	
	22	#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	1124
Combined	23	#11 and #22	14
Total	24	#23 <i>in DARE</i>	6

Table S5. Eligibility criteria for the SLR

Domain	Inclusion criteria	Exclusion criteria
Sample	Adults with GEP-NETs who are experiencing diarrhoea	<ul style="list-style-type: none"> • Adults without GEP-NETs • Adults with GEP-NETs who do not have diarrhoea • Non-human participants
	<p>Studies with mixed populations were initially considered for inclusion if results were reported separately for the population of interest or for a group where there were $\geq 15\%$ patients with GEP-NETs and diarrhoea, if the study was sufficiently relevant</p>	
Phenomenon of interest	Diagnosis of the cause of diarrhoea among adults with GEP-NETs	N/A
	<p>Note that this could be identified from explicit approaches to diagnosis (e.g. laboratory tests) or inferred from treatments that patients were receiving (e.g. if patients are receiving pancreatic enzyme replacement therapy, it may be inferred that they have been diagnosed with pancreatic enzyme insufficiency)</p>	
Design	Any, including: <ul style="list-style-type: none"> • Interventional studies • Observational studies • Case reports 	N/A

Domain	Inclusion criteria	Exclusion criteria
Evaluation	<ul style="list-style-type: none"> • Guidelines • Opinion pieces or narrative reviews <p>It was pre-specified that relevant outcomes would be likely to fall into the following categories:</p> <ul style="list-style-type: none"> • Approaches used to diagnose cause of diarrhoea • Effectiveness of approaches for diagnosing cause of diarrhoea • Clinical opinions on approaches to diagnosing cause of diarrhoea • Proportion of patients with each cause of diarrhoea • Consequences of misdiagnosis of cause of diarrhoea <p>However, reviewers took a pragmatic approach when considering the eligibility of studies for inclusion in the review, and consulted with Ipsen and clinical experts if evidence was identified that was potentially relevant to the broader research question but did not relate directly to any of these categories</p>	<p>Specific outcomes that are not of interest include:</p> <ul style="list-style-type: none"> • Treatment pathways for patients diagnosed with each cause of diarrhoea, <u>except</u> where this information is used to infer that they have been diagnosed with a specific cause of diarrhoea • Outcomes relating to the diagnosis of NETs in patients who initially present with diarrhoea
Research type	<p>Any, including:</p> <ul style="list-style-type: none"> • Qualitative research • Quantitative research 	N/A

Domain	Inclusion criteria	Exclusion criteria
Other considerations	<ul style="list-style-type: none"> • Mixed-methods research • Opinions or guidelines <p>Date limits:</p> <ul style="list-style-type: none"> • Journal articles from 2008 onwards • Guidelines from 2008 onwards • Conference abstracts from 2016 onwards 	Studies in resource-limited settings
<p>Articles had to have an abstract, poster, report or full-text article in English. If the full-text article was non-English, the abstract was considered for inclusion in the review in its own right.</p>		

Extracted Data for Each Theme

Table S6. Initial investigations into the cause of diarrhoea

Study	Study design	Initial approach used or recommended	Supporting data
Subtheme: Assess disease progression			
Boudreaux 2010 ^[24]	Clinical guideline (NANETs)	Assess disease progression (imaging, biomarkers, history taking and physical examination)	<p>“...there can be multiple reasons for the exacerbation of symptoms in these patients. Imaging, biomarkers such as 5-HIAA, and careful history taking and physical examination can help select optimal therapeutic approaches.”</p> <p>“Progressive elevation of urinary 5-HIAA or imaging studies showing disease progression would suggest increased hormonal production to be a significant component cause of the diarrhea.”</p>
Kulke 2014 ^[55]	Randomised trial of telotristat etiprate	Caveat to assessing u5-HIAA levels	<p>“Alternatively, while the protocol required a diagnosis of carcinoid syndrome and excluded patients with short bowel syndrome, it is possible that some of the patients with normal u5-HIAA at baseline had diarrhea on the basis of other serotonin-mediated conditions. Finally, SSAs decrease serotonin secretion, which results in decreased systemic 5-HIAA levels. u5-HIAA levels may, therefore, be an imperfect predictor of</p>

			serotonin-mediated diarrhea in patients who are already receiving treatment with SSAs.”
Lagler 2016 ^[51]	Case report	Assess radiological and biochemical disease progression	“As progression/tachyphylaxis in symptomatic patients with CS undergoing therapy with SST-analogues, reassessment of disease status and analysis of tumor markers was initiated, and the interval of OCT-LAR intramuscular injections was shortened to 21 days. However, radiological findings disclosed no evidence of NET progression. Also the regularly monitored tumor marker levels of chromogranin A and serotonin had been stable over the last months and were not indicative of progression.”
Saif 2010 ^[39]	Expert opinion and case series	Assess disease progression	<p>“Two patients who were stable in their symptoms and biochemical profile (serum chromogranin, 5-HT) at a constant dose of octreotide analogs led us to investigate other etiologies for worsening diarrhea, including pancreatic insufficiency”</p> <p>“The octreotide LAR dose was escalated, with no improvement in diarrhea.”</p> <p>“Change in the form of diarrhea and no improvement, in fact worsening of the diarrhea, on escalation of the octreotide analog dose and</p>

			confirmation with a gastrointestinal consultation led to the diagnosis made in these cases. Stool studies for fat quantification were done to confirm the diagnosis.”
Saif 2018 ^[38]	Retrospective	Assess disease progression	“Quantitative measurement of fecal fat was performed in 47 patients with worsening diarrhea despite stable or improved CgA/urine 5-HIAA.”
Shi 2017 ^[50]	Retrospective	Assess radiographic disease progression	“Patients were categorized as having a likely adverse interaction (category 3) if they had worsening carcinoid syndrome within 3 months of initiating serotonergic medication, without radiographic disease progression.”
Simion 2013 ^[54]	Case report	Assess disease progression	“To confirm even more the absence of carcinoid syndrome, at 1 month after surgery, 5-HIAA revealed to be normal, and the 1-year follow-up CT scan did not show liver metastasis. The only explanation we could find for the recurrent diarrhoea syndrome in this case is that mechanically the tumour had caused intermittent bowel obstruction (obstructive diarrhoea).”
Subtheme: Assess response to treatment			
Carmona-Bayonas	Narrative review	Consider other causes of diarrhoea before escalating	“When diarrhea is not controlled with SSAs, other causes must be taken into account and ruled out before proceeding to therapeutic maneuvers such as increasing SSA dosages, and this can impact patients more than

2017 ^[56]		dose	conducting trials with expensive, apparently sophisticated drugs.”
Kiesewetter 2018 ^[36]	Retrospective	Assess response to treatment	“One patient, however, was excluded from the analysis, as the underlying cause of worsening diarrhea (which was also refractory to application of ondansetron) was identified as infection with multidrug-resistant <i>Campylobacter coli</i> , and symptoms promptly resolved following management of the infection.”
Lee 2017 ^[47]	Case report	Assess response to dose reduction	“Given the possibility of diarrhea due to adverse effects of sunitinib, the patient was treated with a reduced dose of sunitinib (25 mg/day) and loperamide concomitantly. After a brief period of improved diarrhea, however, she returned to the hospital complaining of severe diarrhea for over 1 week.”
Saif 2010 ^[39]	Expert opinion and case series	Assess response to dose escalation	<p>“The octreotide LAR dose was escalated, with no improvement in diarrhea.”</p> <p>“Change in the form of diarrhea and no improvement, in fact worsening of the diarrhea, on escalation of the octreotide analog dose and confirmation with a gastrointestinal consultation led to the diagnosis made in these cases. Stool studies for fat quantification were done to confirm the diagnosis.”</p>

Subtheme: Assess patient history		
Anthony 2013 ^[45]	Guideline	“As NET patients have multiple etiologies contributing to their diarrheal symptoms, a careful history assists in developing a differential diagnosis.”
Boudreaux 2010 ^[24]	Clinical guideline (NANETs)	“There can be multiple reasons for the exacerbation of symptoms in these patients. Imaging, biomarkers such as 5-HIAA, and careful history taking and physical examination can help select optimal therapeutic approaches”
Gregersen 2015 ^[57]	Prospective observational	“One of the patients in the present study had previously had 26 cm of the small intestine resected. Diarrhea was present before surgery and we do not consider the minor resection a significant cause of symptoms. Other potential causes of diarrhea in patients with NET include small intestinal bacterial overgrowth, intestinal stenosis with or without mesenteric fibrosis, ischemia, pancreatic insufficiency, bile acid malabsorption, or intestinal failure. Although not systematically ruled out in the present study, none of the patients had known strictures, small intestinal bacterial overgrowth or bile acid diarrhea.”
Gregersen 2016 ^[58]	Prospective observational	“In 7 patients prior resection on the small intestine and/or colon had been performed, however, all had diarrhea prior to surgery.”

Subtheme: Assess other symptoms of CS			
Juniku-Shkololli 2009^[53]	Case report	Assess liver metastases and other symptoms of CS	“Diarrhea is a consequence of the bowel obstruction. All this explains our patient’s symptoms. However, she had no flushing of the skin and therefore couldn’t be suspected clinically for this diagnosis [referring to CS]. The intestinal carcinoid does not usually produce the carcinoid syndrome unless hepatic metastases have occurred”
Simion 2013^[54]	Case report	Assess liver metastases and other symptoms of CS	“First of all, the 2-year history of diarrhoea and abdominal pain could have determined further investigation (eg, 5-HIAA or CgA) in searching of a carcinoid syndrome, but liver metastases were not found on CT. The presence of a carcinoid syndrome without metastasis is extremely rare.”

Abbreviations: CgA: chromogranin A; CS: carcinoid syndrome; CT: computed tomography; LAR: long-acting release; [NANETS: North American Neuroendocrine Tumor Society](#); NET: neuroendocrine tumour; OCT: octreotide; SSA/SST: somatostatin analogue; 5-HIAA: 5-hydroxyindoleacetic acid.

Table S7. Approaches for inferring the cause of diarrhoea

Patient symptoms: characteristics of CS/NETs

A total of ten publications described 'typical' diarrhoea associated with CS/NETs. Across these, five common features of CSD were identified:

- Secretory in nature^[24, 43-46, 48, 49, 59, 60]
- Watery/large stool volume^[43, 44, 48, 51, 59, 60]
- Persistent with fasting^[24, 43-46, 48, 49, 59, 60]
- Possibly nocturnal^[45, 46, 48, 49]
- No osmotic gap^[43, 44, 59]

Of these, persistence with fasting was emphasised by several studies as a 'key' to ascertain the secretory nature. For example, Cakir 2018 claim that "diarrhoea in NETs is always secretory, while diarrhoea from other gastrointestinal causes [and SSAs] is usually malabsorptive. Thus, the key question to ask is whether the diarrhoea persists with fasting, thus clarifying its secretory nature."^[49]

Whilst possible useful features to consider, these were not stated in every article and may not be exclusive to CSD.

Patient symptoms: characteristics of non-CSD

SSA-mediated

Six studies attributed specific characteristics to steatorrhoea associated with SSA treatment.

- The most common descriptions included 'foul-smelling', 'floating', 'greasy' stools that are 'difficult to flush'.^[24, 32, 39, 40, 49]
-

61]

- In Fiebrich 2010, patients were specifically asked if they experienced steatorrhoea, based on several of these characteristics.^[40]
- Neophytou 2018 employed a standardised survey to define new onset and severity of a patient's steatorrhea.^[61] Clinical steatorrhoea was defined as "more than three stools per day, faecal output of >200 g/d for at least three consecutive days, nauseating smell, pale or yellow stools, and the appearance of stools as pasty or greasy"; severe steatorrhoea required at least three of these criteria. Whilst this approach does not appear to be validated (no references to specific criteria were provided), this suggests that the use of a survey and specific definition based on such characteristics may be considered sufficient to delineate steatorrhoea from CSD.
- Whyand 2018 recommend that in patients with NETs, characteristics of the stool including frequency, consistency and colour should be recorded at every appointment, aiding patients receiving SSAs to distinguish between diarrhoea and steatorrhoea. The authors also note that loose stools and constipation require further investigation.^[32]

Other

Distinguishing features of other cause-specific diarrhoeas have also been reported.

- Lagler 2016 noted that CSD sometimes differs from diarrhoea caused by bacterial pathogens such as *Campylobacter*, where blood and mucus may be present in the diarrhoea stool.^[51]
 - BAM-associated diarrhoea was described as choloretic (bile-containing).^[62]
 - Diarrhoea due to IBS reported as alternating with constipation and not persisting with fasting.^[43]
-

- Postprandial diarrhoea was suggested to indicate intestinal ischaemia or dumping syndrome.^[45]
- Initially intermittent CSD may become continuous if complicated by lymphangiectasia and bacterial overgrowth.^[46]

Other concomitant symptoms

Several other sources identified symptoms which may be considered in specific differential diagnoses:

- PEI was associated with steatorrhea^[6, 61, 62] and/or a bloated abdomen,^[6] weight loss,^[45, 61] or malabsorption signs.^[61]
- SBS may be associated with significant weight loss, electrolyte disturbance and hydration issues whilst SIBO may be associated with borborygmic, flatulence and abdominal bloating.^[62]
- Intestinal ischaemia may induce gradually worsening symptoms which eventually result in food phobia and cachexia.^[45]

Lagler 2016 described a number of 'warning signs' to warrant fluid replacement and empiric antimicrobial therapy before first taking stool cultures. These included elevated signs of systemic inflammation (C-reactive protein 20 mg/dL) and acute renal failure (serum creatinine 6.7 mg/dL).^[51]

Caution should be applied when interpreting these findings because the quality of the evidence for inferring other causes was poor; single characteristics or symptoms not exclusive to these causes were reported.

Abbreviations: BAM: bile acid malabsorption; CSD: carcinoid syndrome diarrhoea; IBS: irritable bowel syndrome; NET: neuroendocrine tumour; PEI: pancreatic enzyme insufficiency; SBS: short bowel syndrome; SSA: somatostatin analogue.

Table S8. Approaches for confirming the cause of diarrhoea

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
Clinical tests			
PEI: faecal elastase			
Chaudhry 2017 ^[41]	Prospective observational	“FE was prospectively evaluated to investigate steatorrhoea.”	<ul style="list-style-type: none"> • “32/39 NETs had complete data, 78% (25/32) of which were established on long-acting somatostatin analogue therapy and 81% (26/32) had steatorrhoea” • “Only 6/32 patients had a low FE, four complaining of steatorrhoea (12.5%). 22/32 patients had steatorrhoea with a normal FE, 77% (17/22) of whom were on SSAs”
			<p>“Sensitivity of FE in detecting steatorrhoea in NET patients was 15.4%. Less than one fifth of patients exhibiting signs of pancreatic insufficiency had an</p>

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
Donnelly 2017 ^[34]	Prospective observational	"Faecal elastase (Normal >200)"	<p>abnormal FE prior to commencing a trial of pancreatic enzyme replacement therapy."</p> <p>"There appears to be a lack of association between FE and steatorrhoea in patients with NETs. Many patients experienced steatorrhoea on SSA despite normal FE; thus FE should not be used to evaluate pancreatic function in this group."</p> <p>"Only 17% had abnormal faecal elastase despite steatorrhoea"</p>
Kasi 2018 ^[63]	Narrative review	"The stool elastase test, if available, can help identify pancreatic enzyme insufficiency."	NR
Lamarca 2018 ^[6]	Prospective observational	<p>"PEI was diagnosed based on results of stool fecal elastase-1 (FE1) quantification, which was performed at baseline and 3-monthly thereafter. PEI was defined as an FE1 below normal level (limit of normal according to local laboratory was 200 µg/g) or by a</p>	<p>"This study has demonstrated that FE1 testing is feasible in this patient population, and informative for symptom management and decision-making regarding PERT. As a result of</p>

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
		<p>reduction of =21% (defined as FE1 uncertainty of measurement (threshold above which changes are considered clinically meaningful and not derived from random variations) in local laboratory) compared with baseline.”</p>	<p>our findings, we recommend FE1 testing in patients who develop any symptoms in-keeping with PEI, such as abdominal bloating, flatulence, or diarrhea. This recommendation is based on the increased risk of identification of PEI in symptomatic patients. It is worth recognizing that diarrhea can result in a false positive for FE1; nevertheless, FE1 remains the most accessible test for diagnosis of PEI in the clinical setting and we do still recommend its use in patients with chronic diarrhea.”</p> <p>"FE1 levels were analysed in the majority of participants (32/50) and was the basis for PEI diagnosis in 67% of patients who had developed PEI."</p>

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
Masood 2016 ^[64]	Retrospective	"Fecal elastase test was not available at our institution in that time period."	NR
Pavel 2017 ^[65]	Guideline	"[During treatment with SSAs] if diarrhea/loose stools occur, determination of fecal elastase to establish the diagnosis of pancreatic enzyme insufficiency is recommended as well as substitution with pancreatic enzymes, if confirmed"	NR
Sagar 2017 ^[62]	Narrative review	"Faecal elastase (low)", only reported in Table 1	NR
PEI: faecal fat			
Masood 2016 ^[64]	Retrospective	"EPI testing (72 hour stool fat testing)"	NR
Saif 2010 ^[39]	Expert opinion and case series	"Fecal tests were done for fat quantification with a referral to the gastroenterologist. Stool testing revealed a high fat content consistent with a diagnosis of fat malabsorption. Pancreatic insufficiency was diagnosed based on no previous	"The cheapest and easiest test to confirm the diagnosis is fat fecal quantification. Steatorrhea from pancreatic maldigestion implies a loss of > 90% of normal enzyme secretory output. These tests are easy to

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
		<p>history of pancreatitis, hemochromatosis, cystic fibrosis or pancreatic surgeries.”</p> <p>“Change in the form of diarrhea and no improvement, in fact worsening of the diarrhea, on escalation of the octreotide analog dose and confirmation with a gastrointestinal consultation led to the diagnosis made in these cases. Stool studies for fat quantification were done to confirm the diagnosis.”</p>	perform and require clinical suspicion of the drug side effects.”
Saif 2018 ^[38]	Retrospective	<p>“Quantitative measurement of fecal fat was performed in 47 patients with worsening diarrhea despite stable or improved CgA/urine 5-HIAA.”</p>	NR
Infectious diarrhoea: stool analyses			
Lagler	Case report	<p>Bacterial</p> <p>“...the outpatients was hospitalized and supportive therapy with intravenous hydration and maintenance of electrolyte balance plus empiric antimicrobial therapy with ciprofloxacin and metronidazole was</p>	
2016 ^[51]			

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
		<p>started. At this time-point the first stool cultures were taken to identify microorganisms causing diarrhea like <i>Salmonella</i>, <i>Campylobacter</i>, <i>Shigella</i> and <i>Yersinia</i>.”</p> <p>“In addition to the four most frequent and harmful bacterial enteric pathogens <i>Salmonella</i>, <i>Campylobacter</i>, <i>Shigella</i> and <i>Yersinia</i> tested by a routine stool culture, also other bacteria like <i>Clostridium difficile</i> and enteropathogenic <i>Vibrio</i> species or <i>Escherichia coli</i> strains could cause similar clinical symptoms.”</p> <p>Viral or parasitical</p> <p>"If bacterial stool examinations are negative, additional virological analyses for example for detecting cytomegaly virus (CMV) and parasitological analysis for example for detecting <i>Entamoeba histolytica</i> or <i>Giardia lamblia</i> in the stool should be considered."</p>	
SIBO: Breath tests			
Donnelly	Prospective	“13 patients underwent hydrogen breath test (8	NR

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
2017 ^[34]	observational	positive results, 5 negative) ^a	
Sagar	Narrative	“Glucose hydrogen breath test; other breath tests including methane breath test”	NR
2017 ^[62]	review		
Whyand	Retrospective	“Hydrogen Breath testing (HBT) using glucose may be more sensitive to proximal SIBO as glucose rarely reaches the colon. Many NET patients are likely to have distal SIBO however, as factors such as ileocecal valve removal apparently increase distal SIBO. Thus glucose BT alone may limit sensitivity for detecting SIBO in some NET diagnoses. ”	"Twelve patients (12/55) who tested negative for glucose HBT but continued to have diarrhoea +/- wind had repeat BT using lactulose. These patients had both H2 and CH4 BT." ... " Twelve patients who tested negative for glucose HBT had repeat testing using lactulose and measured both H2 and CH4 production. This led to an additional 3 (25%) positive results." "Additional lactulose use with H2 and CH4 measurement increases the sensitivity in diagnosing SIBO."
2017 ^[33]			
Bile acid malabsorption: SeHCAT scan			
Donnelly	Prospective	“80% of patients had bile acid malabsorption	NR

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
2017 ^[34]	observational	(SEHCAT <20%)”	
Sagar	Narrative	75 SeHCAT scan (reported in a table only)	NR
2017 ^[62]	review		
Colitis: CT scan			
Gorbunova	Single-arm	“...in one patients colitis identified by CT”	NR
2016 ^[35]	trial		
Intestinal ischaemia: angiography			
Anthony	Guideline	“Intestinal ischemia is definitively diagnosed with	NR
2013 ^[45]		angiography.”	
Laxative abuse: potassium hydroxide stool preparation, measurement of intestinal secretion, quantifying electrolytes			
Vinik	Narrative	"Laxative abuse is difficult to detect and, in all	NR
2009 ^[44]	review	circumstances, a potassium hydroxide stool preparation to detect laxatives is mandatory. Measurement of intestinal secretion by passing a multilumen tube and quantifying electrolytes and water transport, in addition to the measurement of stool electrolytes, which should account for the total osmolarity, helps to exclude laxative abuse but is rarely performed."	

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
Vinik 2011 ^[43]	Narrative review	<p>"A disturbing cause that may be very difficult to differentiate is laxative abuse, and in all circumstances, a KOH stool preparation to detect laxatives is mandatory."</p> <p>"Measurement of intestinal secretion by passing a multilumen tube and quantifying electrolytes and water transport, in addition to the measurement of stool electrolytes, which should account for the total osmolarity, will help to exclude laxative abuse, but is rarely performed."</p>	NR
Faecal elastase test for other causes of malabsorption			
Neophytou 2018 ^[61]	Prospective observational	<p>"A clinical steatorrhea was defined by more than three stools per day, faecal output of >200 g/d for at least three consecutive days, nauseating smell, pale or yellow stools, and the appearance of stools as pasty or greasy. A severe steatorrhea was define by at least three of these criteria. Faecal elastase was estimated in every patient that presented other causes of</p>	NR

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
		malabsorption (gastrectomy, small bowel syndrome)."	
Approaches for confirming the cause of diarrhoea (not diagnostic tests)			
Subtheme: General approaches			
Anthony 2013 ^[45]	Guideline	"A gastrointestinal workup inclusive of upper and lower endoscopy may assist in identifying or excluding an etiology"	NR
Lee 2017 ^[47]	Case report	A simple chest X-ray taken on admission showed subdiaphragmatic air on the right side of the upper abdomen with severe distension.	NR
Lamarca 2018	Prospective observational	"Symptom-based diagnosis (defined as development of steatorrhoea and/or bloated abdomen) was also accepted, however not encouraged, if FE1 could not be performed."	NR
Subtheme: Trials of treatment targeted at suspected cause of diarrhoea			
Anthony 2013 ^[45]	Guideline	"For those few patients who experience significant weight loss, a trial of pancreatic enzyme(s) may be warranted."	NR
Kasi	Narrative	"The stool elastase test, if available, can help identify	NR

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
2018 ^[63]	review	pancreatic enzyme insufficiency. However, it is not unreasonable to do a therapeutic trial of pancreatic enzyme replacement with meals to see if that helps with the symptoms of diarrhea."	
Subtheme: Discontinuation of treatment			
Cuyle	Narrative	"Rule out other causes (disease related, pancreatic insufficiency, infection, drugs, etc.); sunitinib diarrhea typically resolves a few days after discontinuation"	NR
2018 ^[66]	review		
Shi 2017 ^[50]	Retrospective	<p>"Case 1: Initiated bupropion and citalopram (20 mg every d) at the same time. Took citalopram for 21 d and developed nausea, bloating, and vomiting, which also were associated with diarrhea during this time period. Discontinued citalopram and reported improved symptoms.</p> <p>Case 2: Initiated escitalopram (20mg every d). Took escitalopram for 16 d and developed increased diarrhea symptoms as well as insomnia.</p>	NR

Study	Study design	Supporting data on use of test	Supporting data on evaluation/opinion of test
		<p>Discontinued escitalopram and did not report further diarrhea within the 4 wk after discontinuation.</p> <p>Case 3: Initiated citalopram (unknown dose) and developed diarrhea and cramping over the course of 1 mo. Tapered off citalopram and during the subsequent 4 wk did not experience further symptoms of carcinoid syndrome.”</p>	

^a While not explicitly stated, these values correspond to the number of patients diagnosed with SIBO

Abbreviations: BT: breath test; CH₄: methane; CT: computed tomography; EPI: exocrine pancreatic insufficiency; FE1: faecal elastase; H: hydrogen; HBT: hydrogen breath test; KOH: potassium hydroxide; MBT: methane breath test; NET: neuroendocrine tumour; NR: not reported; PEI: pancreatic enzyme insufficiency; PERT: pancreatic enzyme replacement therapy; SeHCAT: tauroselcholic [75 selenium] acid; SIBO: small intestinal bacterial overgrowth; wk: week.

1 **Table S9. Consequences if the cause of diarrhoea is not properly ascertained**

Study	Study design	Population/Patient	Consequence	Supporting data
Theme: Consequences if the cause of diarrhoea is not properly ascertained				
Boudreaux 2010 ^[24]	Narrative review	NA	Inappropriate intervention	"Patients with short-gut syndrome frequently will report the start or worsening of diarrhea after surgical resection of the small bowel or right colon. In some patients, this occurs after complete resection of the local-regional disease and leads to an extensive search for occult metastases in a patient without disease."
Carmona-Bayonas 2017 ^[56]	Narrative review	NA	Inappropriate intervention	"When diarrhea is not controlled with SSAs, other causes must be taken into account and ruled out before proceeding to therapeutic maneuvers such as increasing SSA dosages, and this can impact patients more than conducting trials with expensive, apparently sophisticated drugs."

Study	Study design	Population/Patient	Consequence	Supporting data
Saif 2010 ^[39]	Expert opinion and case series	NA	Perceived inefficacy of treatment and inappropriate intervention	“Although octreotide analogs are used to treat diarrhea in an unlabeled manner, paradoxically, they cause another type of diarrhea secondary to pancreatic insufficiency. This may lead to escalating [sic] the dose of the octreotide under the impression that the primary disease (neuroendocrine tumor) is not controlled while, on the contrary, it causes pancreatic dysfunction by more inhibition to the pancreatic hormone secretion, mainly secretin and CCK. This results in more diarrheas related to fat malabsorption.”
Boudreaux 2016 ^[25]	Monograph/case study compendium	100 patients referred to the authors’ institution for abdominal pain,	Cause of diarrhoea may remain untreated	“More than one-third of these patients had an occult bowel obstruction that was complete or nearly complete because their primary tumor had never been resected. The health care providers were so focused on the big tumors in the liver that they ignored the tumor in the small

Study	Study design	Population/Patient	Consequence	Supporting data
		weight loss, bloating and diarrhoea	Impact on nutritional status, leading to missed management opportunity	<p data-bbox="1182 389 1301 421">bowel."</p> <p data-bbox="1182 504 2040 791">"Persistent diarrhea can lead to nutritional challenges, and is seen in patients who have had the ileocecal valve removed. Diarrhoea can also persist in patients who have had large sections of the bowel removed owing to the presence of multiple tumours."</p> <p data-bbox="1182 855 2040 1254">"These multifactorial nutritional issues must be evaluated and corrected by health care providers who have experience with these types of patients. The cause of their diarrhea is not always easy to detect, and can be due to multiple factors. We often see patients who are not suitable for surgery but could be with the appropriate interventions."</p>

Study	Study design	Population/Patient	Consequence	Supporting data
Kasi 2018 ^[63]	Narrative review	NA	Cause of diarrhoea may remain untreated	“Bile salt malabsorption has been observed to respond extremely well to a trial of cholestyramine (sequestrant) in patients who for years had been struggling with diarrhea that was labeled as carcinoid syndrome diarrhea and that was in fact not secondary to the condition.”
Lagler 2016 ^[51]	Case report	72-year old male with a metastatic ileal NET	Cause of diarrhoea may remain untreated	“Interestingly this patient developed mainly watery diarrhea with a little mucus but without blood. However, the clinical symptoms with abdominal cramps caused by C. coli were very similar to the symptoms caused by the NET and therefore the infection was remaining undiagnosed for weeks.”
Lamarca 2018 ^[6]	Prospective observational		Cause of diarrhoea may remain untreated	“The higher rate of SSA-related PEI identified in the current study is most likely due to active identification of symptoms of PEI, prior to a formal diagnosis. Patients in previous studies may have had undiagnosed PEI which

Study	Study design	Population/Patient	Consequence	Supporting data
				was classified incorrectly as 'worsening carcinoid syndrome,' as a result of lack of clinician and patient awareness."
			Inappropriate intervention	"Misclassification of a patient as having 'worsening carcinoid syndrome' due to missed PEI could impact negatively on both patient and trial outcomes. Patients could be initiated on unnecessary treatments or have effective treatment interrupted."
			Perceived inefficacy of treatment	"...the implications are more significant in patients with NETs, where GI symptoms such as diarrhea may be confused with carcinoid syndrome and be misinterpreted as lack of treatment benefit."
				"Identifying SSA-related PEI is of special importance for

Study	Study design	Population/Patient	Consequence	Supporting data
Shi 2017 ^[50]	Retrospective observational		Cause of diarrhoea may remain untreated	<p>adequate patient selection for treatment of refractory carcinoid-syndrome (such as telotristat ethyl)"</p> <p>Impact on nutritional status "Steatorrhoea usually becomes apparent only when pancreatic enzymes are significantly decreased (i.e. when 90% of pancreatic function is lost). Thus, waiting for development of symptoms such as steatorrhoea delays PEI diagnosis and has a significant impact on nutrition and quality of life (QoL)."</p> <p>"Even among patients who did experience worsening symptoms after initiation of the antidepressant, many continued to take the medication for months to years thereafter. This could be because their symptoms were not believed to be due to the antidepressant, or that their disease was beginning to progress and symptoms of carcinoid were manageable with other medications or</p>

Study	Study design	Population/Patient	Consequence	Supporting data
				interventions.”
Pavel 2015 ^[68]	Single-arm trial	15 patients with CS were enrolled, 14 completed treatment	Perceived inefficacy of treatment	“One patient had decreases in both stool frequency and u5-HIAA (reductions of 31 and 33%, respectively, at wk 3–4) but withdrew consent on day 50 due to “insufficient efficacy.” This patient was on pancreatic enzyme supplement after a pancreaticoduodenectomy (Whipple procedure) and had baseline u5-HIAA in the normal range, suggesting that serotonin may not have been the major cause of diarrhea.”
Saif 2010 ^[39]	Expert opinion/ editorial including a case series	NA	Impact on nutritional status	“Malabsorption of lipids can result in several micronutrient deficiencies. Unabsorbed fats trap fat soluble vitamins A, D, E and K and may also prevent mineral absorption. Absorption of cobalamin (vitamin B 12) requires pepsin, which is released through stimulation

Study	Study design	Population/Patient	Consequence	Supporting data
				of gastrin, and thus prolonged malabsorption can result in cobalamin deficiency, especially in individuals with other risk factors, such as those who have a history of antacid use.”
Fiebrich 2010 ^[40]	Prospective observational	35 carcinoid patients receiving treatment with SSAs	Impact on nutritional status	“Despite this supplementation, all five patients [with steatorrhoea] had abnormal vitamin levels.”
Weickert 2010 ^[67]	Commentary	NA	Impact on nutritional status	“Without routine screening for malnutrition, gastrointestinal symptoms in patients with GEP-NET might be missed or solely and sometimes incorrectly attributed to functioning symptoms, which may result in missed opportunities to optimise the nutritional status of the patient.”
Saif	Retrospective	110 patients with	Impact on	“Deficiency of vitamins and trace elements was found in

Study	Study design	Population/Patient	Consequence	Supporting data
2018 ^[38]	observational	NETs	nutritional status	11 of 19 patients [patients with evidence of steatorrhea who received PER], which led to supplementation"
Scenario arising from successful differential diagnosis of NET diarrhoea				
Donnelly 2017 ^[34]	Prospective observational	57 patients with NETs, 20 completed	Impact on quality of life	"75% (15) of patients experienced an improvement on 'impact of bowel symptoms on quality of life(QoL)' scale (0-10), 20% (4) experienced no change" "Only 10 patients completed repeated EORTC GI.NET21 questionnaires but there was a significant improvement of overall quality of life scores, median reduction 11 points (P=0.02)" "Systematic gastrointestinal investigation and management appears to improve impact of bowel symptoms on quality of life in patients with NETs."
Flaherty 2014 ^[52]	Case report	59-year-old woman diagnosed	Prioritisation of treatment	"Her chronic diarrhea worsened and she was diagnosed with Clostridium difficile and capecitabine chemotherapy

Study	Study design	Population/Patient	Consequence	Supporting data
		with metastatic carcinoid of the terminal ileum		was held until it resolved, taking about four months. During this time, C.P.'s diarrhea was difficult to control and she lost about 20 pounds, causing decline in her performance status, weakness, fatigue, and dyspnea on exertion. Her disease as well as her symptoms, which were driven by carcinoid syndrome, progressed while off treatment."

1 **Abbreviations:** CCK: cholecystokinin; GI: gastrointestinal; NA: not applicable; NET: neuroendocrine tumour; PEI: pancreatic
2 enzyme insufficiency; SSA: somatostatin analogue; wk; week.

3

4 **Table S10. Advice and suggestions for the differential diagnosis of diarrhoea¹ in patients with NETs**

Study	Study design	Supporting data
Subtheme: Improve awareness and education		
Lamarca	Prospective observational (discussion)	"Improvements to patient information are also needed to

Study	Study design	Supporting data
2018 ^[6]		<p>educate and empower patients to consider the possibility of PEI."</p> <p>"Identification and management of long-term SSA-toxicities and side effects do also required increased awareness within health care professional and patients."</p>
Saif 2010 ^[39]	Expert opinion with case series	<p>"Our experience alerts doctors treating neuroendocrine tumors to be aware of this common and forgotten side effect of the octreotide analogs, resulting in better patient management and cost reduction."</p>
Subtheme: Multidisciplinary team of specialists, particularly gastroenterologists		
Donnelly 2017 ^[34]	Prospective observational	<p>"The addition of a gastroenterology service or gastroenterologist to a NET service may help improve symptoms and quality of life in patients with NETs"</p>
Saif 2010 ^[39]	Expert opinion with case series	<p>"Early referral to a gastroenterologist might help aid and lead with the diagnosis and treatment."</p>

Study	Study design	Supporting data
Boudreaux 2010 ^[24]	Narrative review	<p>“Persistent diarrhea can lead to nutritional challenges, and is seen in patients who have had the ileocecal valve removed. Diarrhea can also persist in patients who have had large sections of the bowel removed owing to the presence of multiple tumors. In addition, long-acting somatostatin analogs can cause pancreatic insufficiency and steatorrhea. Diarrhea, a hallmark of carcinoid syndrome that results from high concentrations of serotonin and other vasoactive and bioactive amines, can be exacerbated by the wrong diet. Diarrhea can result from an unrecognized partial bowel obstruction caused by an unresected primary tumor. These multifactorial nutritional issues must be evaluated and corrected by health care providers who have experience with these types of patients. The cause of their diarrhea is not always easy to detect, and can be due to multiple factors.”</p>

Subtheme: Direct questioning about diarrhoea

Study	Study design	Supporting data
Whyand 2018 ^[32]	Cross-sectional study	“It is clear that consultants should include more direct questions because patients may not report adverse events without direct prompts.”
Subtheme: Screen regularly for malnutrition		
Weickert 2016 ^[67]	Commentary	“Without routine screening for malnutrition, gastrointestinal symptoms in patients with GEP-NET might be missed or solely and sometimes incorrectly attributed to functioning symptoms.”
Whyand 2018 ^[32]	Cross-sectional study	“Malnutrition screening should be in place to enable referrals to specialist NET dietitians, although there is as yet no validated screening tool specific to NETs.”

1 **Abbreviations:** GEP-NET: gastroenteropancreatic neuroendocrine tumour; PEI: pancreatic enzyme insufficiency; SSA:
2 somatostatin analogue.

3