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Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (Upper GI)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected Upper GI cancer. Key themes have been determined from the literature. For each key theme e.g. individual symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NICE NG12 and SRG guidelines can be found for reference.

This document includes evidence on the following topics:

- Individual Symptoms
- Symptom Combinations
- Investigations completed in, or accessed by, primary care
- Safety Netting
- Risk Stratification
- Emerging topics of interest

Background

Upper gastrointestinal (GI) cancer is an umbrella term for multiple different cancer types, including oesophageal, stomach, pancreatic, gallbladder and liver. These cancers present with different symptoms, have different stage distributions and outcomes.

Upper GI cancers (excluding gallbladder due to data availability) account for around 1 in 10 new cancer cases in Scotland (data from 2018, 2019 and 21). Scotland stage at diagnosis data is not publicly available for upper GI cancers. In Wales (2019), among upper GI cancer cases with a recorded stage, the proportion diagnosed at stage 1 was generally low (5% for oesophageal, 10% for stomach, 8% for pancreatic, 5% for gallbladder, and 14% for liver cancers) [1].

Scotland survival by stage data is not publicly available for upper GI cancers. In England (2016-20), net survival for upper GI cancers varies with stage at diagnosis, most markedly in oesophageal cancer where 89% of those diagnosed at stage 1 survived their disease for one year or more, compared to 26% diagnosed at stage 4[1].

[1] Cancer Research UK (2022a). Early Diagnosis. [online] crukcancerintelligence.shinyapps.io. Available at: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/.

Being diagnosed via emergency presentation is associated with later stage at diagnosis, worse survival and limited treatment options. Scotland routes to diagnosis data is not publicly available for upper GI cancers. In England (2018), among cases with a known route to diagnosis, 19-44% of upper GI cancer cases (excluding gallbladder due to data availability) were diagnosed via emergency presentation[1].

Early diagnosis is challenging in upper GI cancers such as pancreatic cancer, as they typically present with non-specific symptoms that have low positive predictive values (PPVs) for cancer, such as abdominal pain, back pain, and weight loss[2]. Evidence suggests that documentation of vague abdominal symptoms (a common presentation of upper GI cancer) in medical notes often does not match patient description, which may have implications in the decision to investigate possible upper GI cancers[3].

Due to the challenges in recognising upper GI cancers for both the public and health professionals, delays can often occur. For example, an English study reported that gallbladder cancer had the longest median primary care interval (period from the first relevant symptomatic presentation to their first specialist referral for further investigation), and oesophageal cancer had a relatively long patient interval (length of time from symptom onset to first consultation) in comparison to 28 other cancers[4]. Research also found those who experienced either one or two consultations prior to referral, who were subsequently diagnosed with oesophago-gastric cancers, had a significantly improved prognosis compared to those that experience three or more consultations[5].

[2] Johnston AJ, Sivakumar S, Zhou Y, Funston G, Bradley SH. Improving early diagnosis of pancreatic cancer in symptomatic patients. British Journal of General Practice [Internet]. 2023 Dec 1 [cited 2024 Feb 16];73(737):534–5. Available from: https://bjgp.org/content/73/737/534

[3] Hardy V, Usher-Smith J, Archer S, Barnes R, Lancaster J, Johnson M, et al. Agreement between patient's description of abdominal symptoms of possible upper gastrointestinal cancer and general practitioner consultation notes: a qualitative analysis of video-recorded UK primary care consultation data. BMJ open [Internet]. 2023 Jan 5;13(1):e058766. Available from: https://pubmed.ncbi.nlm.nih.gov/36604136/

[4] Lyratzopoulos G, Saunders CL, Abel GA, McPhail S, Neal RD, Wardle J, et al. The relative length of the patient and the primary care interval in patients with 28 common and rarer cancers. British Journal of Cancer [Internet]. 2015 Mar 31 [cited 2022 Feb 3];112(Suppl 1):S35–40. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4385974/

[5] Arhi CS, Markar S, Burns EM, Bouras G, Bottle A, Hanna G, et al. Delays in referral from primary care are associated with a worse survival in patients with esophagogastric cancer. Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus [Internet]. 2019 Dec 13;32(10):1–11. Available from: https://pubmed.ncbi.nlm.nih.gov/30820525/

Qualitative evidence suggests that the public's understanding of heartburn, reflux and indigestion, and associated symptoms of oesophago-gastric cancers differ from clinical definitions, which in turn could lead to delayed help-seeking, investigation, or referral. Symptoms are commonly attributed to personal and/or lifestyle factors and are then subsequently self-managed, delaying help-seeking[6].

Inequalities exist within upper GI cancer diagnosis. All upper GI cancers have a higher incidence in those who are more deprived[7]. England data suggests that odds of presenting as an emergency increase with increasing deprivation quintile and age for liver cancer[8]. In Scotland, evidence demonstrates that rurality is independently associated with improved survival for oesophago-gastric cancers, the reasons for which are uncertain[9]. Continued review of the evidence underpinning referral guideline recommendations and their use, will help ensure people are referred along the most appropriate route at the right time.

Search Strategy

Search terms: PubMed search for combinations of the following terms: Upper GI, oesophageal, stomach, oesophago-gastric, pancreatic, liver, gall bladder, hepatobiliary cancer, PPV, risk, prevalence, symptomatic, presentation, primary care, dysphagia, odynophagia, unexplained weight loss, upper abdominal pain, unexplained iron deficiency anaemia, reflux, dyspepsia, vomiting, haematemesis, jaundice, weight loss, upper abdominal mass, epigastric mass, diabetes, back pain, diarrhoea, abdominal pain, nausea, vomiting, constipation, investigation, endoscopy, blood tests, low haemoglobin levels, raised platelet count/thrombocytosis, CT, ultrasound, recognition, referral, stage, routine, routes to diagnosis, comorbidity, safety netting, direct access

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences in Scottish Referral Guidelines (SRG) and NICE NG12 guidelines. These have been gathered from NICE NG12 Evidence Review document.

[6] Humphrys, E., Walter, F.M., Rubin, G., Emery, J.D., Johnson, M., Richards, A., Fitzgerald, R.C., Viswanath, Y.K. and Burt, J. (2020). Patient symptom experience prior to a diagnosis of oesophageal or gastric cancer: a multi-methods study. BJGP Open, 4(1), p.bjgpopen20X101001. doi:https://doi.org/10.3399/bjgpopen20x101001.
[7] Cancer Research UK. Statistics by cancer type [Internet]. Cancer Research UK. 2015. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type
[8] Burton A, Balachandrakumar VK, Driver RJ, Tataru D, Paley L, Marshall A, et al. Regional variations in hepatocellular carcinoma incidence, routes to diagnosis, treatment and survival in England. British Journal of Cancer. 2021 Nov 26;
[9] Griffin F, Hunter R, McCouaig P, Murchie P, Nanthakumaran S, Ramsay G. Assessing the impact of rurality on oesophagogastric cancer survival in the North-East of Scotland- a prospective population cohort study. The Surgeon. 2022 May;

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Peer-reviewed literature

Note: grey rows in the table represent studies that have already been summarised earlier in the document.

Topic: Individual Symptoms				
Summary: PPV data published since 2015 are only available for certain (abdominal) symptoms for both pancreatic and oesophageal cancers. Prevalence of symptoms by cancer site are summarised by Zakkak et al (see paper 2). Please see summaries below split by oesophago-gastric, and hepatobiliary cancers.				
Paper number	**Study**	**Cancer**	**Summary**	**Notes**
			All Upper GI	
1	Koo MM, Swann R, McPhail S, Abel GA, Elliss-Brookes L, Rubin GP, et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. The Lancet Oncology. 2019 Nov;21(1).	All	There has been some debate around whether cancers present symptomatically at an early enough stage for meaningful clinical intervention. This study aimed to examine associations between common presenting symptoms of cancer and stage at diagnosis. After adjusting for demographic factors, back pain was the only upper GI cancer symptom associated with increased odds of stage 4 disease as a single symptom (for all cancers, not upper GI alone). This suggests that upper GI cancers could potentially be diagnosed symptomatically at an earlier stage, where the likelihood of successful treatment is greater. Proportion diagnosed at stage 4, and odds of stage 4 diagnosis associated with symptoms when recorded alone: • Back pain: 58% (3·19 (95% CI: 1·82–5·59))	Cross-sectional, population-based study England data using National Cancer Diagnosis Audit (NCDA) data (2014) N=7997 (for all cancers) **Limitation:** this study uses primary care records, which may be incomplete and prone to bias

			• Abdominal pain: 33% (1·45 (95% CI: 0·81–2·59)) • Weight loss: 38% (1·23 (95% CI: 0·66–2·28))	
2	Zakkak N, Barclay ME, Swann R, McPhail S, Rubin G, Abel GA, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. British Journal of Cancer [Internet]. 2024 Feb 1 [cited 2024 Feb 1];130(2):297–307.	All	This study aimed to (1) examine the relative frequency of presenting symptoms by cancer site (the 'symptom signature' of each cancer site), and (2) to examine the relative frequency of cancer sites by presenting symptom (the 'cancer site case-mix' of each symptom), among incident cancer cases. The proportion of patients with Upper GI cancer presenting with the following symptom groups was: • **Upper abdominal: 66%** • Non-specific: 29% • Lower abdominal: 15% • Respiratory: 9% • Musculoskeletal: 2% • Lump/mass/lymph node: 1% • Urological: 1% • CNS: 1% • None recorded: 12% Mean number of symptoms for each cancer: oesophageal (1.8), stomach (1.9), liver (1.8), pancreatic (2.1), other HPB (gallbladder) (1.8)	Data from 2018 National Cancer Diagnosis Audit (England) N=55,122 (total cohort) **Limitations:** this is a case-only analysis (only patients with diagnosis of cancer were included), so cannot make inferences about PPV

			Of all patients diagnosed with **oesophageal cancer**, the proportion that experienced *x* symptom are as follows: • Dysphagia: 46% • Weight loss: 21% • Dyspepsia: 18% • Nausea/vomiting: 12% • Upper abdominal pain: 9% • Reflux: 8% • Loss of appetite: 5% • Chest pain, other: 4% • Cough, abdominal pain (NOS), fatigue: 3% • Sore throat, dyspnoea, distention, constipation, CIBH, early satiety: 2% • Back pain, hoarseness, rectal bleeding, lower abdominal pain, diarrhoea, haematemesis : 1% Of all patients diagnosed with **stomach cancer**, the proportion that experienced *x* symptom are as follows: • Weight loss: 21% • Dyspepsia: 17% • Dysphagia, upper abdominal pain: 15% • Nausea/vomiting: 12% • Abdo pain (NOS): 10% • Loss of appetite: 9% • Fatigue: 7% • Other, reflux: 6% • CIBH: 4%	

			• Early satiety, haematemesis, constipation, diarrhoea, distension, rectal bleeding, dyspnoea: 3% • Pallor, lower abdominal pain, chest pain, cough, back pain: 2% • Chest infection, headache: 1% Of all patients diagnosed with **liver cancer**, the proportion that experienced *x* symptom are as follows: • Weight loss: 13% • Abdo pain (NOS): 12% • Jaundice: 11% • Upper abdominal pain: 10% • Fatigue, loss of appetite: 8% • Other, nausea/vomiting: 7% • Distention: 6% • Diarrhoea: 4% • Dyspepsia, CIBH. dyspnoea: 3% • Pruritus, constipation, rectal bleeding, chest pain: 2% • Fever, pallor, dysphagia, early satiety, reflux, haematemesis, lower abdominal pain, cough, haemoptysis, haematuria, LUTS, UTI, back pain: 1% Of all patients diagnosed with **pancreatic** cancer, the proportion that experienced *x* symptom are as follows:	

			• Weight loss: 22% • Abdo pain (NOS): 20% • Upper abdominal pain: 19% • Jaundice: 14% • Loss of appetite: 12% • Nausea/vomiting: 11% • Fatigue: 8% • Other, CIBH: 7% • Dyspepsia, diarrhoea, distention: 6% • Constipation, back pain: 5% • Lower abdominal pain: 4% • Pruritus, dysphagia, reflux, chest pain: 2% • DVT, night sweats, early satiety, haematemesis, new onset diabetes, rectal bleeding, cough, dyspnoea, haematuria, LUTS, UTI: 1% Of all patients diagnosed with **'Other HPB: Gallbladder'** cancer, the proportion that experienced *x* symptom are as follows: • Jaundice: 23% • Upper abdominal pain: 17% • Abdo pain (NOS): 16% • Weight loss, nausea/vomiting: 12% • Loss of appetite: 8% • Other, Pruritus, dyspepsia, diarrhoea: 6% • Fatigue: 5% • Distention, lower abdominal pain: 4% • CIBH, constipation: 3% • Chest pain: 2%	

			• DVT, fever, dysphagia, haematemesis, rectal bleeding, cough, dyspnoea, haematuria, headache, back pain: 1%	
Oesophago-gastric Cancers				
Summary: For oesophageal cancer in those aged >30 years, PPVs of the following abdominal symptoms (abdominal bloating/distension, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding) are reported to be <1%, except for dysphagia which was 1% in women and 2.7% in men. For dysphagia, PPVs are highest in the age 60-69 years category for men (4.3%) and women (1.7%). Dysphagia was found to be the symptom present in the greatest proportion of those diagnosed with oesophageal cancer (46%) in both paper 2 and 4, supporting its inclusion in referral guidelines. Weight loss has been reported to be the symptom present in the greatest proportion of those diagnosed with stomach cancer (21%). Another study found weight loss was a presenting feature in around 1 in 10 gastro-oesophageal cancers. Unexplained weight loss is included in SRG, particularly for those aged >55 years in combination with other symptoms (same as NG12). Loss of appetite is found in 9% of those diagnosed with stomach cancer, and 5% of those diagnosed with oesophageal cancer, which is currently not included in SRG or NG12. No recent PPV estimates are available for weight loss or appetite loss for oesophago-gastric cancers. Pre-2015, PPV estimates of weight loss for oesophageal and stomach cancers ranged from 0.8-1.2% for all patients (Collins, 2012; Hippisley-Cox, 2011; Stapley, 2013) and 0.6-1.1% for appetite loss (Collins, 2012; Hippisley-Cox, 2011). Collins (2012) and Hippisley-Cox (2011) included all patients in the study sample, whereas Stapley (2013) investigated PPVs in those aged >55 years only, which may explain the age thresholds set by both NG12 and SRG. In paper 6, 26% of patients that presented with a >3% risk symptom for oesophago-gastric cancers presented with anaemia in the year preceding the 3% risk symptom presentation, which may suggest an opportunity for earlier recognition of OG cancers. Currently, unexplained iron deficiency anaemia is included in the SRG, in combination with weight loss in those aged over 55 years. NG12 recommends non-urgent, direct access endoscopy for those aged >55 years with upper abdominal pain with low haemoglobin levels.				
3	Herbert A, Rafiq M, Pham TM, Renzi C, Abel GA, Price S, Hamilton W, Petersen I, Lyratzopoulos G. Predictive values for different cancers	Oesophageal (and pancreatic, see next section)	This study aimed to estimate the positive predictive values of common abdominal symptom presentations to primary care for (i) cancer; (ii) IBD; and (iii) the composite outcome of cancer or IBD in the year post-consultation in those aged >30 years.	Retrospective population-based cohort study, using data from The Health Improvement Network (THIN) in the UK (2000–2017)

	and inflammatory bowel disease of 6 common abdominal symptoms among more than 1.9 million primary care patients in the UK: A cohort study. PLoS Med. 2021 Aug 2;18(8):e1003708. doi: 10.1371/journal.pmed.1003708.		Six symptoms were included: abdominal bloating/distension, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding. PPVs (95% CI) for oesophageal cancer in men: • Abdominal bloating/distention: 0.05 (0.03-0.08) • Abdominal pain: 0.10% (0.09-0.11) • CIBH: 0.05% (0.03-0.07) • Dyspepsia: 0.26% (0.23-0.28) • **Dysphagia: 2.74% (2.57-2.90)** • Rectal bleeding: 0.05% (0.04-0.07) PPVs (95% CI) for oesophageal cancer in women: • Abdominal bloating/distention: 0.01% (0.01-0.02) • Abdominal pain: 0.03% (0.02-0.03) • CIBH: 0.02% (0.01-0.03) • Dyspepsia: 0.08% (0.07-0.09) • **Dysphagia: 1.06% (0.97-1.15)** • Rectal bleeding: 0.02% (0.01-0.03) PPVs generally increase as age increases in both men and women for all symptoms. For dysphagia, PPVs are highest in the age 60-69 years category for men (4.3%) and women (1.7%).	N= 102,785 for abdominal bloating/distension, 909,451 for abdominal pain, 108,698 for change in bowel habit, 528,428 for dyspepsia, 87,971 for dysphagia, and 240,253 for rectal bleeding Age threshold: 30-99 years **Limitations:** analysed data only included coded symptoms, which may underestimate the true prevalence of symptoms.

4	Quiroga M, Shephard EA, Mounce LTA, Carney M, Hamilton WT, Price SJ. Quantifying the impact of pre-existing conditions on the stage of oesophagogastric cancer at diagnosis: a primary care cohort study using electronic medical records. Family Practice. 2020 Dec 21;	OG	This study aimed to investigate associations between oesophago-gastric cancer stage and pre-existing conditions. Most included participants (1387/1749, 79.3%) had recorded features of possible oesophago-gastric cancer before diagnosis. Symptoms in order of prevalence: • Dysphagia in men (324/1236, 26.2%) and women (159/513, 31.0%). • Dyspepsia and/or reflux (men: 231/1236, 18.7%; women: 83/513, 16.8%) • Anaemia (men: 194/1236, 15.7%; women: 69/513, 13.5%) • Upper abdominal pain (men: 143/1236, 11.6%; women: 63/513, 12.3%). Weight loss, vomiting, nausea and haematemesis were **relatively infrequent** (reported in <4% of participants)	Retrospective cohort study using Clinical Practice Research Datalink (CPRD) data, with English cancer registry linkage from 2010-2015. Those aged >40 years were included N=1749 **Limitations:** the sample contained large amounts of missing data (695 (28.4%) of the sample with no recorded stage), which may impact the results
5	Astin MP, Martins T, Welton N, Neal RD, Rose PW, Hamilton W. Diagnostic value of symptoms of oesophagogastric cancers in primary care: a systematic review and	Oesophago-gastric	This study aimed to systematically review the presenting features of oesophago-gastric cancers in primary care, including those assessed in open-access endoscopy clinics. The strongest summary **sensitivity** and **specificity** estimates were found for the following symptoms:	Systematic review and meta-analysis Papers included from 1998-2014 N=14 studies included

	meta-analysis. British Journal of General Practice. 2015 Sep 27;65(639):e677–91.		• Dyspepsia: 0.42 (95% CI: 0.29-0.56) and 0.48 (95% CI:0.31-0.65) • Pain*: 0.41 (95% CI: 0.24-0.62) and 0.75 (95% CI:0.51-0.89) • Dysphagia: 0.32 (95% CI: 0.17-0.52) and 0.92 (95% CI: 0.81-0.97). Summary positive likelihood ratios (LR+) and diagnostic odds ratios were: • Dyspepsia: 0.79 (95% CI: 0.55-1.15) and 0.65 (95% CI:0.32-1.33) • Pain: 1.64 (95% CI: 1.20-2.24) and 2.09(95% CI: 1.57-2.77) • Dysphagia: 4.32 (95% CI: 2.46-7.58) and 5.91 (95% CI: 3.56-9.82). Other LR+ (without ORs) were: • Anaemia: 4.32 (95% CI: 2.64-7.08) • Nausea/vomiting/bloating: 1.07 (95% CI: 0.52-2.19) • Reflux: 0.78 (95% CI: 0.47-1.78) • Weight loss: 5.46 (95% CI: 3.47-8.60). *Pain grouped as: upper abdominal, epigastric, retrosternal, cardiac-like, and ulcer-like pain	Most originated in the UK (n=6) or Europe (n=7), and one from Canada. **Limitations:** most symptoms were not uniformly defined across studies, which may have impacted the results
6	Moore SF, Price SJ, Bostock J, Neal RD, Hamilton W. Incidence of "Low-Risk but Not No-Risk" Features of	OG	This study aimed to investigate the number and percentage of patients with a PPV ≥ 3% feature who also presented with a 2–2.99% or 1–1.99% feature in the preceding year.	Cross-sectional study English primary care data from 2015-2016

	Cancer Prior to High-Risk Feature Occurrence: An Observational Cohort Study in Primary Care. Cancers [Internet]. 2023 Aug 2;15(15):3936.		Of 212 patients with >3% risk symptom for **upper GI cancers,** 2 presented with a 2-2.99% symptom, and 65 with a 1-1.99% PPV symptom in the previous year. **Haematemesis** was the only 2-2.99% feature present in the year preceding a 3% symptom. (*Note*: small sample size). **Anaemia** was the most common 1-1.99% feature present in the year preceding a 3% symptom (n=56). (anaemia defined by CPRD code) Median time between presenting with 2-2.99% symptom and >3% symptom was 115 days (IRQ: 3-227 days), and between 1-1.99% symptom and >3% symptom was 216 days (73-290 days).	N= 150,921 for all cancers combined N=7,108 patients with >3% risk symptom **Note:** PPVs derived from a list of features of cancer from the systematic reviews published in NG12 2015 update for each of the cancer sites. **Limitation:** only coded data was used for this analysis, so there may be underestimation of threshold for symptoms, due to missing data in free text.

HPB Cancers – Pancreatic, Liver, Gallbladder

Summary:

Paper 1 found back pain was the only upper GI cancer symptom associated with an increased odds of stage 4 disease as a single symptom (for all cancers, not upper GI alone). This evidence highlights that other HPB symptoms could be detected at earlier stages, suggesting there are opportunities to diagnose hepatobiliary cancers earlier. Back pain is currently included in both NG12 and SRG for HPB cancer, in combination with weight loss in either those aged >55 (SRG) or >60 (NG12) years.

Estimates of PPV for pancreatic cancer using more recent data (since 2015) were only available for abdominal symptoms (abdominal bloating/distension, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding) and were all reported to be <1%. None of these symptoms are included in SRG, but abdominal pain, constipation and diarrhoea are included in NG12 where direct access CT or ultrasound is recommended in those aged >60, combined with weight loss. Paper 2 reported that abdominal pain (location not specified) was present in 20% of those diagnosed with pancreatic cancer,

16% of those diagnosed with gallbladder cancer and 12% of those diagnosed with liver cancer. Upper abdominal pain was also present in 19% of those diagnosed with pancreatic cancer and 17% with gallbladder cancer in the same study. This may support inclusion of these symptoms in guidance, either as part of SRG guidelines or linked to RCDS pathways.

Weight loss is the symptom present in the highest proportion of both liver (13%) and pancreatic (22%) cancers, demonstrating the broad symptom signature of liver cancer. Another study reported that weight loss was a presenting feature in approximately 1 in 10 pancreatic cancer diagnoses. Unexplained weight loss is included in SRG, particularly for those >55 years, in combination with other symptoms, but it is not included in NG12 for HPB cancers. Pre-2015 PPV estimates of weight loss for pancreatic cancer range from 0.3-0.8% (Collins, 2012; Hippisley-Cox, 2011; Stapley, 2013).

Paper 7 reported that jaundice is strongly associated with both PDAC and PNEN*. Jaundice and GI bleeding were statistically significantly associated with a diagnosis of PNEN within 3 months of presentation, and a further 7 symptoms were associated with a diagnosis within 1 year (diarrhoea, bowel change, vomiting, indigestion, abdominal mass, abdominal pain, and weight loss).

Additional symptoms reported to be significantly associated with PDAC include:

- constipation, steatorrhea, abdominal distension, nausea, flatulence, heartburn, fever, tiredness, appetite loss, itching, back pain, thirst, and dark urine.
- **Thirst and dark urine** were the two newly identified symptoms associated with PDAC, not previously reported in other studies. No studies have estimated the PPV of thirst or dark urine for pancreatic cancer.

Paper 9 found in men with new onset fatigue, the observed risk of pancreatic cancer diagnosis was 3-4x greater than the expected cancer risk in the general population. For women with new onset fatigue, the observed risk of diagnosis of pancreatic cancer was 2-4x greater than expected. New onset fatigue would not fully defined in this paper. According to NICE Guidelines, there is no universal definition of fatigue. The authors developed medical code lists used to identify fatigue to attempt to ensure fatigue records were appropriate for the study.

* Pancreatic tumours can be classified as exocrine (make up approximately 95% of pancreatic tumours) or neuroendocrine (≤5%) neoplasms, known as pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine neoplasms (PNEN), respectively. This study's descriptive statistics demonstrated that those with PNEN are typically diagnosed at an earlier age than those diagnosed with PDAC (62 years vs 73 years).

-	Moore SF, Price SJ, Bostock J, Neal RD, Hamilton W.	Pancreatic	This study aimed to investigate the number and percentage of patients with a PPV >3% feature who	See above.

	Incidence of "Low-Risk but Not No-Risk" Features of Cancer Prior to High-Risk Feature Occurrence: An Observational Cohort Study in Primary Care. Cancers [Internet]. 2023 Aug 2;15(15):3936 This paper is also summarised above, please see paper 6.		also presented with a 2-2.99% or 1-199% feature I the preceding year. Of 78 patients with >3% risk symptom for pancreatic cancer, 0 presented with a 2-2.99% PPV symptom in the previous year. 2 (2.6%) presented with a 1-1.99% symptom in the previous year. Abdominal pain (2x attendances) was the only 1-1.99% feature present in the year preceding a 3% symptom. (*Note*: small sample size). Median time between presenting with 1-1.99% symptom and >3% symptom was 97.5 days (IQR: 18-177 days).	
-	Herbert A, Rafiq M, Pham TM, Renzi C, Abel GA, Price S, Hamilton W, Petersen I, Lyratzopoulos G. Predictive values for different cancers and inflammatory bowel disease of 6 common abdominal symptoms among more than 1.9 million primary care patients in the UK: A cohort study. PLoS Med. 2021 Aug 2;18(8):e1003708.	Pancreatic	This study aimed to estimate the predictive values of common abdominal symptom presentations to primary care for (i) cancer; (ii) IBD; and (iii) the composite outcome of cancer or IBD in the year post-consultation in those aged >30 years. Six symptoms were included: abdominal bloating/distension, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding. PPVs (95% CI for pancreatic cancer in men):	See above.

	doi: 10.1371/journal.pmed.1003708. This paper is summarised above, please see paper 3.		• Abdominal bloating/distention: 0.05% (0.03-0.08) • Abdominal pain: 0.09% (0.08-0.10) • CIBH: 0.07% (0.04-0.09) • Dyspepsia: 0.06% (0.05-0.07) • Dysphagia: 0.03% (0.01-0.04) • Rectal bleeding: 0.01% (0.01-0.02) PPVs (95% CI for pancreatic cancer in women): • Abdominal bloating/distention: 0.02% (0.01-0.03) • Abdominal pain: 0.04% (0.04-0.05) • CIBH: 0.06% (0.04-0.07) • Dyspepsia: 0.03% (0.03-0.04) • Dysphagia: 0.01% (0.00-0.02) • Rectal bleeding: 0.02% (0.01-0.03)	
7	Liao, W., Clift, A.K., Patone, M., Coupland, C., González-Izquierdo, A., Pereira, S.P. and Hippisley-Cox, J. (2021). Identifying symptoms associated with diagnosis of pancreatic exocrine and neuroendocrine neoplasms: a nested case-control study of the UK primary care population. British Journal of General Practice, 71(712), pp.e836–e845. doi:10.3399/	Pancreatic	This study aimed to investigate the symptoms associated with different types pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine neoplasms (PNEN). Descriptive statistics demonstrated those with PNEN were typically diagnosed at a younger age (mean: 62 years) compared to those diagnosed with PNEN (mean: 73 years). No differences were seen in deprivation quintile or sex. Slight differences were seen for ethnicity, but large amounts of ethnicity data was coded as 'not recorded' which may have impacted this.	Nested case-control study using the QResearch database (primary care database comprising records of >35 million patients registered in ~1500 GP surgeries, throughout the UK) Sample included those aged >25 years, registered to the database between 2000-2019 N= 15,194,279 patients aged ≥25 years,

	bjgp.2021.0153.		Jaundice had the strongest association of all investigated symptoms for both PDAC and PNEN. There was some overlap in the symptoms associated with PNEN and PDAC, but the strength of association differed between the two sub-types. Nine symptoms were significantly associated with the diagnosis of PNEN in the timeframe of either 3 months or 1 year prior to diagnosis: **Within 3 months:** • Jaundice (OR 125.35 (95% CI: 28.25-556.26) • GI bleeding (OR 33.89 (95% CI 6.56 to 174.97)) **Within 1 year:** • diarrhoea, bowel change, vomiting, indigestion, abdominal mass, abdominal pain, and weight loss. The additional symptoms significantly associated with PDAC included: • constipation, steatorrhea, abdominal distension, nausea, flatulence, heartburn, fever, tiredness, appetite loss, itching, back pain, thirst, and dark urine	N= 23,640 PDAC cases N=596 PNEN cases **Limitations:** large amount of missing data in cancer staging meant they were unable to identify any differences in symptomology by stage

			Thirst and dark urine were the two newly identified symptoms associated with PDAC, not previously reported in other studies.	
8	Nicholson BD, Hamilton W, O'Sullivan J, Aveyard P, Hobbs FR. Weight loss as a predictor of cancer in primary care: a systematic review and meta-analysis. British Journal of General Practice. 2018 Apr 9;68(670):e311–22.	Pancreatic	This study aimed to summarise the available evidence on weight loss as a clinical feature of cancer in patients presenting to primary care. Weight loss was a presenting feature in 1 in 10 **gastro-oesophageal** or **pancreatic** diagnoses. The pooled sensitivity of weight loss for pancreatic cancer was 13% (95% CI = 8 to 20%) and pooled specificity was 99% (95% CI = 98 to 99%).	Diagnostic test accuracy review and meta-analysis. N=25 studies included (23 using primary care data) published between 1994-2015. One study was conducted in the US and all others in the UK. **Limitations:** no studies reported the code lists used by the authors to define weight loss, so the authors are unable to report with confidence whether weight loss was unexpected or expected
9	White B, Rafiq M, Gonzalez-Izquierdo A, Hamilton W, Price S, Lyratzopoulos G. Risk of cancer following primary care presentation with fatigue: a population-based cohort study of a quarter of a million patients. British Journal of Cancer [Internet].	Pancreatic	This study aimed to establish the risk of cancer among patients who presented with 'new onset' fatigue to their GP. New onset fatigue would not fully defined in this paper. According to NICE Guidelines, there is no universal definition of fatigue. The authors developed medical code lists used to identify	Cohort study of patients with a record of fatigue presentation in primary care in England between 2007 and 2013, using electronic health records (EHRs) from the Clinical Practice Research Datalink (CPRD) GOLD

	2022 Feb 18 [cited 2023 Feb 2];126(11):1627–36.		fatigue to attempt to ensure fatigue records were appropriate for the study. For men with new onset fatigue, the observed risk of pancreatic cancer diagnosis was 3-4x greater than the expected cancer risk in the general population. For women with new onset fatigue, the observed risk of pancreatic cancer diagnosis was 2-4x greater than the expected cancer risk in the general population.	N=250,606 **Limitations:** some instances of a patient's presentation with fatigue may not be recorded by the GP, due to its non-specific nature, which could underestimate prevalence of fatigue

Topic: Symptom Combinations

Summary:

PPV estimates published since 2015 for symptom combinations are available from one study, and for those aged >60 years only. This study found there are some symptom combinations where the PPV for pancreatic and oesophago-gastric cancers equals or exceeds 3% risk in those aged 60+ years.

For pancreatic cancer, these combinations are:

- **abdominal pain and constipation** for men aged 60-69 years
- **abdominal pain and nausea/vomiting** for men aged 60-69 years
- **abdominal pain and weight loss for women** aged 60-69 years and men aged 60+ years

Abdominal pain, constipation, nausea/vomiting do not warrant urgent suspicion of cancer referral in SRG, but are noted in good practice points (excluding constipation). These symptoms are included in NG12.

For oesophago-gastric cancers, these combinations are:

- **abdominal pain and abdominal mass** in men aged over 60+ years
- **abdominal pain and weight loss** in men aged over 70+ years

Abdominal mass is not included in SRG or NG12. PPV data demonstrates that abdominal mass plus abdominal pain as a symptom combination exceeds 3% for men aged >60 years only. It may be worth considering whether symptom combinations for certain patient groups are warranted in the guidelines.				
Paper number	**Study**	**Cancer**	**Summary**	**Notes**
10	Price, S., Gibson, N., Hamilton, W., King, A. and Shephard, E. (2022). Intra-abdominal cancer risk with abdominal pain: a prospective cohort primary-care study. British Journal of General Practice, p.BJGP.2021.0552. doi:https://doi.org/10.3399/bjgp.2021.0552.	Pancreatic and oesophago-gastric	This study aimed to quantify cancer risk in primary care patients with abdominal pain. Pancreatic Cancer **Abdominal pain and constipation** 1% (95% CI: 0.4-2.2%) of **women** aged 60-69 years were diagnosed with pancreatic cancer in the year following symptom presentation. This was lower in those aged 70+ (0.6% (0.3 -1.1)). **2.8%** (95% CI: 1.6-4.5) of **men** aged 60-69 years were diagnosed with pancreatic cancer in the year following symptom presentation. This was lower in those aged 70+ (1.2% (0.6-2.0)). **Abdominal pain and diarrhoea** 0.5% (95% CI: 0.1-1.3) of **women** aged 60-69 years were diagnosed with pancreatic cancer in the year following symptom presentation. This was lower in those aged 70+ (0.3% (0.1-0.8)). 0.9% (95% CI: 0.3-2.0) of **men** aged 60-69 years were diagnosed with pancreatic cancer in the year following	Prospective cohort study using English primary care data and Clinical Practice Research Datalink (CPRD) dataset between 2009–2013. N=125,793 Age threshold: >40 years **Limitations:** some data may be missing, due to only using coded data in the analysis

			symptom presentation. This was lower in those aged 70+ (0.3% (0.0-1.1)). **Abdominal pain and nausea/vomiting** 1.2% (95% CI: 0.5-2.5) of **women** aged 60-69 years were diagnosed with pancreatic cancer in the year following symptom presentation. This was lower in those aged 70+ (0.5% (0.2-1.1)). **3.1%** (95% CI: 1.5-5.6) of **men** aged 60-69 were diagnosed with pancreatic cancer in the year following symptom presentation. This was lower in those aged 70+ (2.2% (95% CI: 1.2-3.8%)). **Abdominal pain and weight loss** **3%** (95% CI: 1-9%) of **women** aged 60-69 years were diagnosed with pancreatic cancer in the year following symptom presentation. This was lower in those aged 70+ (1.3% (0.3-3.2)). **6%** (2-12%) of **men** aged 60-69 years were diagnosed with pancreatic cancer in the year following symptom presentation. This was lower in those aged 70+ (3% (1-6)). <u>Oesophago-gastric cancer:</u> **Abdominal pain and nausea/vomiting**	

			0.9% (95% CI: 0.2-2.7) of **men** aged 60-69 years were diagnosed with oesophago-gastric cancer in the year following symptom presentation. This was higher in those aged 70+ (1.4% (0.6-2.7). 0.2% (95% CI: 0.1-1.0) of **women** aged 60-69 years were diagnosed with oesophago-gastric cancer in the year following symptom presentation. This was higher in those aged 70+ (0.6% (0.3-1.1)). **Abdominal pain and abdominal mass** **3%** (95% CI: 0-16) of **men** aged 60-69 years were diagnosed with oesophago-gastric cancer in the year following symptom presentation. This was higher in those aged 70+ (4% (0-12)). **Abdominal pain and weight loss** 0.9% (95% CI: 0.2-2.7%) **women** aged 70+ years were diagnosed with oesophago-gastric cancer in the year following symptom presentation. 2% (95% CI: 0-6%) of **men** aged 60-69 years were diagnosed with oesophago-gastric cancer in the year following symptom presentation. This was higher in those aged 70+ (**3%** (1-6)).	

Topic: Investigation findings

Summary:

Rates of blood testing have been increasing in the UK primary care setting over the last two decades, with considerable variation by geographic location. PACT (Primary care Academic CollaboraTive) investigated the reasons for blood testing in primary care, in a UK wide study. The most common reasons for testing in primary care were symptoms (43.2%), monitoring of existing disease (30.1%), and monitoring of existing medications (10.1%). On average 4.5 tests were requested simultaneously per patient, and abnormal and borderline results were common, with only 26.6% of patients having completely normal test results. Around a quarter of tests were thought to be partially or fully unnecessary when reviewed retrospectively by another clinician. Overall, 6.2% of tests in primary care led to a new diagnosis or confirmation of diagnosis. Around half of tests (48.8%) did not lead to any change in management or reassurance[10]. This highlights the need to optimise the use of blood tests in primary care. Additionally, some of the evidence outlined below will need to be considered in light of the blood test 'bundle' used in RCDS in Scotland e.g. FBC, LFTs.

Oesophago-gastric

In paper 12, oesophago-gastric cancer was found to be associated with raised platelet count (>400 × 109/l). In paper 11, out of all cancers diagnosed in men presenting with thrombocytosis, 8% were diagnosed with OG cancers (OG data not available for women in this study). Thrombocytosis is currently noted in SRG as an area of 'emerging evidence'. NG12 recommends non-urgent, direct access to endoscopy for those with raised platelets in combination with other symptoms. There is ongoing research in this space, particularly around repeat testing and how levels vary by demographics.

Hepato-biliary

HPB cancers are particularly challenging to recognise, and further research is needed to understand the clinical features that may present opportunities for earlier recognition. Paper 13 reported that several blood markers are associated with an increased risk of PDAC: **raised HbA1c, liver markers, white cell count and platelets**. A U-shaped relationship was observed for haemoglobin levels, with higher risk in patients with both low and high values.

Thrombocytosis in combination with a **raised ALP** (alkaline phosphatase, typically raised in liver disorders) was found to have a PPV of **20%** for cancer detection (all cancers) in paper 14. Out of those diagnosed with cancer presenting with thrombocytosis, pancreatic cancer accounted for 7% of the

[10] Watson J, Burrell A, Duncan P, Bennett-Britton I, Hodgson S, Merriel SW, et al. Exploration of reasons for primary care testing (the Why Test study): a UK-wide audit using the Primary care Academic CollaboraTive. British Journal of General Practice [Internet]. 2023 Jul 14 [cited 2023 Nov 24]; Available from: https://bjgp.org/content/early/2023/10/02/BJGP.2023.0191

localised cancers and 6% of the advanced cancers. Gall bladder cancer accounted for 4% of advanced cancers, and liver was the most common metastases site.				
Paper number	**Study**	**Cancer**	**Summary**	**Notes**
			Oesophago-gastric cancers	
11	Bailey SE, Ukoumunne OC, Shephard EA, Hamilton W. Clinical relevance of thrombocytosis in primary care: a prospective cohort study of cancer incidence using English electronic medical records and cancer registry data. British Journal of General Practice. 2017 May 22;67(659):e405–13.	OG	The aim of this study was to examine the incidence of cancer in a cohort of patients with thrombocytosis, to determine how clinically useful this risk marker could be in predicting an underlying malignancy. Out of all men with raised platelets who were subsequently diagnosed with cancer, 8% of those were diagnosed with oesophago-gastric cancer (4th most common diagnosis, after lung, CRC and prostate).	Prospective cohort study using Clinical Practice Research Datalink data from 2000 to 2013, linked to English National Cancer Registry. N=31,261 patients with thrombocytosis N=1098 cancers diagnosed **Limitation:** the study does not provide data for all cancer sites, just those that were most commonly diagnosed with thrombocytosis. This means we cannot ascertain the incidence of upper GI cancers for women with thrombocytosis
12	Mounce LT, Hamilton W, Bailey SE. Cancer incidence following a high-normal platelet count: cohort study using electronic healthcare records from English primary care. British	OG	This study aimed to investigate cancer incidence following a normal, high-normal or high platelet count in primary care. Diagnosis with oesophago-gastric cancer was associated with the highest bracket of platelet counts	Prospective cohort study using English data from the Clinical Practice Research Datalink (CPRD) and National Cancer Registration and Analysis Service (NCRAS), from 2005-2014.

	Journal of General Practice. 2020 Jul 27;70(698):e622–8.		used in this study (>400 × 109/l), which is commonly used as the definition of thrombocytosis.	N=226,262 patients with high-normal counts, and 69,050 patients with a lower-normal count N=5178 cancers diagnosed **Limitations:** the data collection period is relatively dated, which may impact applicability to current health system context
Hepato-biliary cancers: pancreatic, liver and gallbladder				
13	Tan PS, Garriga C, Clift A, Liao W, Patone M, Coupland C, et al. Temporality of body mass index, blood tests, comorbidities and medication use as early markers for pancreatic ductal adenocarcinoma (PDAC): a nested case–control study. Gut. 2022 Jun 27;72(3):512–21.	Pancreatic	This study aimed to assess the relationship between BMI, blood-based markers, comorbidities, medication use and PDAC risk. Risk of PDAC was increased with **raised HbA1c, liver markers, white cell count and platelets**. A U-shaped relationship was observed with Hb, with higher risk in patients with both low and high values. Generally, the risk associated with increases in blood markers increased closer to diagnosis.	Population-based, nested case–control study, using QResearch primary care database, linked to national cancer registry, Hospital Episode Statistics (HES) and Office for National Statistics death registry in England. n=28,137 PDAC cases and n=261,219 matched-controls **Limitations:** this study is potentially susceptible to residual confounding variables not included in analysis

14	Gold LC, Macpherson I, Nobes JH, Dow E, Furrie E, Jamieson S, et al. Thrombocytosis and abnormal liver enzymes: A trigger for investigation of underlying malignancy. Yen HH, editor. PLOS ONE. 2022 Apr 28;17(4):e0267124.	Liver, pancreatic, gall bladder	This study aimed to investigate the use of thrombocytosis combined with liver function tests (LFTs) in predicting risk of cancer. **Raised LFT**: one or more of alanine aminotransferase, bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase. This study found 7.7% (95% CI: 4.7–11.8%) of the cohort with thrombocytosis were subsequently diagnosed with cancer (all cancers), compared to 2% of those with platelets in the normal reference range. This study also reported that 1 in 9 patients with an abnormal LFT result and unexplained thrombocytosis were subsequently diagnosed with cancer, compared to 1 in 40 of those with normal platelet count. **ALP** was the only liver marker found to be associated with cancer. ALP in combination with raised platelets had a positive predictive value (PPV) of **20%** for cancer detection (all cancers). Pancreatic cancer made up 7% of the localised cancers and 6% of advanced cancers. Gall bladder made up 4% of advanced cancers, and liver was the most common site of metastasis.	Case-control study (ratio 1:2), from a single centre retrospective evaluation in English health service in 2018-2020. N=6792 patients underwent iLFT, with 246 found to have both thrombocytosis and at least one abnormal LFT. **Limitations:** the sample sizes for specific cancer sites are small, which means the PPV for individual sites cannot be calculated

Topic: Safety Netting

Summary:
People who have been investigated along an urgent pathway for suspected upper GI cancer are at greater risk of being diagnosed with an upper GI cancer in the 1-5 years following referral, which could provide opportunities for earlier recognition of this higher risk group.

Paper 16 found that increased travel time to primary care services was associated with unmanaged routes to diagnosis for stomach cancer. Among stomach cancer patients, an increase in travel time from <10 minutes to >over 30 minutes led to a 10x increase in likelihood of having a DCO (death certificate only) diagnosis. This is particularly relevant to areas of Scotland that are more rural.

Upper GI cancers have been found to have greater odds of having >3 consultations prior to referral, compared to other cancers. Evidence also shows that some groups are more likely to be diagnosed via emergency presentation. For example, paper 17 found people who are older, female, had alcohol-related liver disease, or are from a more deprived area have greater odds of being diagnosed with liver cancer via emergency presentation. Paper 16 reported those who are older or are from areas of greater deprivation also have increased incidence of liver cancer. Incidence of all upper GI cancers is greater in those from more deprived background (see introduction). This information could be incorporated into safety netting guidelines, to reduce missed opportunities in higher risk cohorts.

Paper number	Study	Cancer	Summary	Notes
			All upper GI cancers	
15	Scott SE, Gildea C, Nicholson BD, Evans RE, Waller J, Smith D, et al. Future cancer risk after urgent suspected cancer referral in England when cancer is not found: a national cohort study. The Lancet Oncology [Internet]. 2023 Nov 1 [cited 2024 Jan 26];24(11):1242–51.	All	This study aimed to investigate the risk of cancer occurrence within 1-5 years of finding no cancer following an urgent suspected cancer referral. In years 1-5 post urgent referral for suspected upper GI cancer, people who were not diagnosed with upper GI cancer had a higher incidence rate of upper GI cancer than the rate expected in the general population (incidence ratio 1·35 (95% CI: 1·26–1·44))	National cohort study (England) Data from Cancer Waiting Times dataset and National Cancer Registration Dataset from April 2013 – March 2014 N= 63,112 subsequent cancers **Limitations:** Clinical context has changed since the data collection e.g. guideline changes which may limit the applicability of the results to current setting.

			Upper GI cancers diagnosed subsequently were mostly commonly diagnosed along both upper or lower GI pathways (12% each).	
Oesophago-gastric cancers				
16	Murage P, Bachmann MO, Crawford SM, McPhail S, Jones A. Geographical access to GPs and modes of cancer diagnosis in England: a cross-sectional study. Family Practice. 2018 Nov 19;36(3):284–90.	Stomach	This study aimed to investigate if and how travelling time to a GP is associated with route to diagnosis. Longer travel to the patients GP significantly increased the likelihood of having a cancer diagnosis through unmanaged routes such as emergency or post-mortem diagnosis. For example, among stomach cancer patients, longer travel time (over 30 minutes) was associated with increased likelihood of having a DCO (death certificate only) diagnosis compared to a shorter travel time (less than 10 minutes).	Retrospective analysis of English linked dataset of cancer registry and hospital records, between 2006- 2010 across eight different cancer sites. N= 737,495 **Limitations:** this study did not consider forms of public transport other than driving which may have influenced the results
Hepato-biliary cancers: Pancreas, Liver, Gallbladder				
17	Burton A, Wilburn J, Driver RJ, Wallace D, McPhail S, Cross TJS, et al. Routes to diagnosis for hepatocellular carcinoma patients: predictors and associations with treatment and mortality. British Journal of Cancer [Internet]. 2024 Mar 18 [cited 2024 Mar 29];1–12.	Liver	This study aimed to explore predictors of routes to diagnosis, differences in route to diagnosis presentations over time and associations with mortality for hepatocellular carcinoma. Some groups were found to be more likely to be diagnosed via an EP including people who were older,	Retrospective analysis of English data extracted from the National Cancer Registration Dataset, linked to Hospital Episode Statistics Those diagnosed with HCC 2006-2017 were included

			female, had alcohol-related liver disease, or were from a more deprived area. Those with known >3 or more comorbidities were less likely to be diagnosed via urgent referral compared to those with no recorded comorbidities.	n= 23,555 **Limitations:** some important liver cancer risk factors such as BMI, smoking and alcohol consumption, or indicators of liver function, were not considered which may have impacted the results
18	Mendonca SC, Abel GA, Lyratzopoulos G. Pre-referral GP consultations in patients subsequently diagnosed with rarer cancers: a study of patient-reported data. British Journal of General Practice. 2016 Feb 25;66(644):e171–81.	Liver/ Gallbladder	This study aimed to examine the frequency and predictors of repeat GP consultations in people diagnosed with rarer cancers. A higher proportion of people diagnosed with liver or gallbladder had ≥3 consultations, compared to the average (>30.0%, mean for all cancers: 23%) Adjusted ORs for experiencing greater than >3 consultations, compared to reference cancer (rectal): • Pancreatic cancer: 2.52 (2.21 to 2.89) • Liver cancer: 1.96 (1.60 to 2.40) • Stomach: 1.86 (1.65 to 2.09) • Gallbladder: 1.70 (1.03 to 2.80) • Oesophageal: 1.23 (1.11 to 1.37)	Analysis of patient-reported data on pre-referral consultations from the National Cancer Patient Experience Survey (2010, 2013, and 2014) England data N=95,582 responders N=7838 cancer diagnosis **Limitations:** patient-reported data was used for analysis, which may have reduced the reliability of the results

19	Tataru D, Khan SA, Hill R, Morement H, Wong K, Paley L, et al. Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation. JHEP reports : innovation in hepatology [Internet]. 2023 [cited 2024 Mar 23];6(3):100983.	HPB	This study aimed to analyse data on the incidence, mortality, survival and routes to diagnosis of Cholangiocarcinoma (CCA) and other biliary tract cancers (including gall bladder and ampulla of Vater (AoV) cancers). AoV cancers develop where the bile duct and pancreatic duct join. The most common route to diagnosis was the emergency route for all sub-types (ranging from 43-50%), followed by the GP referral route (ranging from 21-25%) and urgent referrals (ranging from 12-14%). There was a greater proportion of those from the most deprived group diagnosed through an emergency route compared to all non-emergency routes for all three cancer sites. Age-standardised incidence rates were consistently higher in patients who were in the most socioeconomically deprived group at the time of diagnosis compared to the least deprived group for CCA and GBC.	Analysis of all biliary tract cancers diagnosed in England between 2001-2018 Data from NHS Digital's National Cancer Registration Dataset N= 50,871 **Limitations:** main ICD coding system has historically lacked a specific code for certain types of CCA (pCCA), which will have led to miscoding and may have impacted the results

Topic: Risk Stratification
Summary: **Oesophago-gastric:**

- Paper 20 demonstrates there are several long-term conditions associated with increased risk of being diagnosed with oesophageal or stomach cancer, which may be important for health professionals to have an awareness of. Paper 25 found low dose aspirin appears to reduce the risk of developing oesophageal and stomach cancer.

- There are also factors that impact a patient's risk of worse outcomes in a variety of ways e.g. altering help-seeking behaviours. Paper 4 found that in those diagnosed with oesophago-gastric cancer, the proportion with multimorbidity was higher in those with early-stage (71.1%) than with advanced-stage (62.6%) disease. For men, the association was greater than for women.

SRG includes some risk factors for developing oesophago-gastric cancer, including: East Asian origin, pernicious anaemia, previous gastric surgery, achalasia (dysfunction of oesphageal muscle), dysplasia, atrophic gastritis or intestinal metaplasia. Other risk factors for upper GI cancers (including hepatobiliary and pancreatic) noted in SRG are smoking, alcohol, obesity and family history. Risk factors are currently not included in NG12.

Hepato-biliary:

- Development of early onset PDAC is associated with risk factors such as smoking exposure, alcohol consumption, history of pancreatitis and hepatitis B infection.
- The risk of developing HPB cancers varies by age, sex, deprivation and ethnicity.
    - Paper 7 found that risk of developing PDAC varies by ethnicity. Compared with people of white ethnicity, people of Indian, Bangladeshi, and other Asian (not including Chinese) ethnicity were less likely to develop PDAC. There were also observed differences between ethnic groups in the likelihood of being diagnosed with a particular liver cancer sub-types in paper 23.

- When considering comorbidities, type 2 diabetes mellitus (T2DM), venous thromboembolism, Cushing's syndrome, and presence of pancreatic cysts significantly increased the risks of PDAC and PNEN. Acute pancreatitis, cholangitis, a family history of GI cancer, and type 1 diabetes were significant risk factors for PDAC, but not for PNEN.

New onset diabetes is a recognised risk factor for pancreatic cancer and is included in both SRG and NG12. NHS England recently announced a 'Type 2 Diabetes Path to Remission Programme'. Services such as these could help reduce the risk of developing pancreatic cancer, but also offer earlier opportunities for recognition.

Paper number	Study	Cancer	Summary	Notes

Oesophago-gastric cancers				
-	Quiroga M, Shephard EA, Mounce LTA, Carney M, Hamilton WT, Price SJ. Quantifying the impact of pre-existing conditions on the stage of oesophagogastric cancer at diagnosis: a primary care cohort study using electronic medical records. Family Practice. 2020 Dec 21; **This paper is also summarised above, see paper 4.**	OG	This study aimed to investigate associations between oesophago-gastric cancer stage at diagnosis and pre-existing conditions. The probability of advanced-stage diagnosis in men was lower for those with multimorbidity (OR 0.70, 0.67–0.74, P<0.0001, n = 783) than in those without (OR 0.79, 0.75–0.83, P<0.0001, n = 453).	See above.
20	Marley J, Nicholl BI, Macdonald S, Mair FS, Jani BD. Associations between long-term conditions and upper gastrointestinal cancer incidence: A prospective population-based cohort of UK Biobank participants. Journal of Multimorbidity and Comorbidity. 2021 Jan;11:263355652110561.	OG	This study aimed to determine if there is an association between a range of long-term conditions (LTCs) and incidence of UGI cancers. LTCs with a statistically significant association with **oesophageal** cancer after adjusting for age, sex, socioeconomic status, BMI, level of physical activity, alcohol consumption and smoking status: • Alcohol addiction (HR 4.11, 95% CI 2.01–8.43) • Barrett's oesophagus (HR 5.68, 95% CI 3.36–9.58), • Bronchiectasis (HR 2.72, 95% CI 1.01–7.31)	Prospective-based cohort study of UK Biobank participants (age 37-73 years) N=487,798 **Limitations:** this study may be prone to selection bias, as the UK Biobank population is less ethnically diverse and less socioeconomically deprived than the general UK population

			• Diabetes (HR 1.38, 95% CI 1.06–1.81) • Hiatus hernia (HR 1.69, 95% CI 1.16–2.45) • Parkinson's disease (HR 3.86, 95% CI 1.60–9.37) • Psoriasis/eczema (HR 1.53, 95% CI 1.08–2.17). LTCs with a statistically significant association with **stomach** cancer after adjusting for age, sex, socioeconomic status, BMI, level of physical activity, alcohol consumption and smoking status: • anorexia/bulimia (HR 8.86, 95% CI 1.20–65.14) • Barrett's oesophagus (HR 3.37, 95% CI 1.39–8.14) • Chronic fatigue syndrome (HR 3.36, 95% CI 1.25–9.03) • Glaucoma (HR 2.06, 95% CI 1.16–3.67) • Multiple sclerosis (HR 4.60, 95% CI 1.71–12.34) • Oesophageal stricture (HR 1.04, 95% CI 1.46–74.46) • Pernicious anaemia (HR 6.93, 95%CI 3.42–14.03).	
21	García Rodríguez LA, Soriano-Gabarró M, Vora P, Cea Soriano L. Low-dose aspirin and risk of gastric and oesophageal	OG	This study aimed to quantify the association between use of low-dose aspirin and risk of	Population matched case-control study

	cancer: A population-based study in the United Kingdom using The Health Improvement Network. International Journal of Cancer. 2020 May 7.		being diagnosed with gastric/oesophageal cancer. Compared to non-use of low-dose aspirin, current use of low-dose aspirin was associated with a 54% reduced risk of gastric cancer (OR 0.46, 95% CI: 0.38-0.57) Compared to non-use of low-dose aspirin, current use of low-dose aspirin was associated with a 41% reduced risk of oesophageal cancer (OR 0.59, 95% CI: 0.51-0.69).	UK data collected between 2005-2015 using The Health Improvement Network N=223,640 new users of low-dose aspirin (75-300mg/day) N=727 incident cases of gastric cancer and n=1394 incident cases of oesophageal cancer **Limitations:** the study was unable to evaluate associations according to stage because this information is not recorded in THIN.
Hepato-biliary cancers: Pancreas, Liver, Gallbladder				
22	Chandana SR, Woods L, Maxwell F, Gandolfo R, Tanios Bekaii-Saab. Risk factors for early-onset pancreatic ductal adenocarcinoma: a systematic literature review. European Journal of Cancer. 2024 Feb 1;198:113471–1.	Pancreatic	This study aimed to identify non-heritable, potentially modifiable risk factors for the development of early-onset PDAC*. There was evidence for a potential association between younger (vs older) age of disease onset and smoking exposure, alcohol consumption, history of pancreatitis and hepatitis B infection.	Systematic review N=24 studies included (only 2 included based in UK) **Limitations:** only a minority of the studies (33%) adjusted for potential confounders; most were unadjusted descriptive statistics which may influence the reliability of the findings.

			*early-onset PDAC is defined as PDAC diagnosed at younger ages (~50 years)	
-	Liao, W., Clift, A.K., Patone, M., Coupland, C., González-Izquierdo, A., Pereira, S.P. and Hippisley-Cox, J. (2021). Identifying symptoms associated with diagnosis of pancreatic exocrine and neuroendocrine neoplasms: a nested case-control study of the UK primary care population. British Journal of General Practice, 71(712), pp.e836–e845. doi:10.3399/bjgp.2021.0153 This paper was also summarised above, see paper 7.	Pancreatic	This study aimed to investigate and compare the symptoms, demographics and comorbidities associated with diagnosis of pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine neoplasms (PNEN). Compared with people of white ethnicity, people of Indian, Bangladeshi, and other Asian (not including Chinese) ethnicity were found to be less likely to develop PDAC. When considering comorbidities, type 2 diabetes mellitus (T2DM), venous thromboembolism, Cushing's syndrome, and presence of pancreatic cysts significantly increased the risk of PDAC and PNEN. Acute pancreatitis, cholangitis, a family history of GI cancer, and type 1 diabetes were significant risk factors for PDAC, but not for PNEN.	See above.
23	Liao W, Coupland C, Innes H, Jepsen P, Matthews PC, Campbell C, et al. Disparities in care and outcomes for primary liver cancer in England during 2008–2018: a cohort study of 8.52 million	Liver	This study aimed to understand the disparities in diagnosis of primary liver cancer in England.	Analysis of English primary care cohort of 8.52 million individuals aged ≥25 years in the QResearch database during 2008-2018, followed up to June 2021.

	primary care population using the QResearch database. EClinicalMedicine. 2023 May 1;59:101969–9.		The hazard ratio (HR) for an incident diagnosis increased with increasing age and socioeconomic deprivation quintile in all three liver cancer subtypes (hepatocellular carcinoma (HCC, the most common type), intrahepatic cholangiocarcinoma (CCA, also known as bile duct cancer), and other specified/unspecified primary liver cancer). Compared with women, **men** were more likely to be diagnosed with liver cancer, but the hazard ratios differed among subtypes: HCC: 3.9 (95% CI 3.6–4.2) CCA: 1.2 (95% CI 1.1–1.3) Other: 1.7 (95% CI 1.5–2.0) There were observed differences between ethnic groups in the likelihood of being diagnosed with a particular sub-type. **Age** (>80 years compared to >60 years) **and increasing socioeconomic deprivation** were significantly associated with emergency presentations in all subtypes.	N=7331 **Limitations:** there may be some coding errors in the "other specified/unspecified liver cancer" group, and 21% of participants did not have ethnicity documented, which could result in misclassification bias
-	Tan PS, Garriga C, Clift A, Liao W, Patone M, Coupland C, et al. Temporality of body mass index, blood tests, comorbidities and medication use as early markers for pancreatic ductal adenocarcinoma	Pancreatic	This study aimed to assess the relationship between BMI, blood-based markers, comorbidities, medication use and risk of developing PDAC.	See above.

	(PDAC): a nested case–control study. Gut. 2022 Jun 27;72(3):512–21. This paper was also summarised above, see paper 13.		T2DM was approximately twice as common in cases than controls (24.6% vs 12.6%, respectively), and recent-onset T2DM was approximately four times as common (9.7% vs 2.5%, respectively).	

Emerging Topics

Alternative pathways to diagnosis

There is limited evidence based on small scale, single centre evaluations investigating how one stop clinics or straight to test pathways can impact the OG pathway[11,12]. Further research is needed to understand how these pathways, including direct access, can have a positive impact on pathways and outcomes.

Capsule sponge testing

Capsule sponge tests, also known as 'pill on a string' was developed by Cancer Research UK-funded researchers. It is used to sample cells from the lining of the oesophagus to detect cell changes associated with potential oesophageal cancer or Barrett's Oesophagus. Pilot studies are underway across the UK for 3 main use cases: triaging patients in secondary care to prioritise use of endoscopy capacity, surveillance of those diagnosed with Barrett's and proactive case finding of those with Barrett's or oesophageal cancer. Capsule sponge tests have the potential to improve patient experience and to free-up endoscopy capacity in the UK health system. However, evidence is still emerging and there are various challenges associated with the technology and its implementation.

[11] Yiasemidou M, Lathan R, Lambertz M, Oommen C, Chetter I. "One stop" clinic for upper gastrointestinal cancer—an alternative to "straight to test" referrals?. Irish Journal of Medical Science. 2021 Jul 20.
[12] Jones JA, Catton J, Howard G, Leeder P, Brewer L, Hatton J, et al. Impact of straight to test pathways on time to diagnosis in oesophageal and gastric cancer. BMJ Open Quality [Internet]. 2018 Jul 1 [cited 2021 Sep 27];7(3):e000328.

Risk stratification or prediction tools

There are some risk scores[13] developed to aid oesophageal cancer triage in secondary care, such as the Edinburgh Dysphagia Score which was recommended to risk-stratify dysphagia referrals during the endoscopy COVID recovery phase by the BSG[14]. However, it is not clear how these would be used in a primary care setting, to help identify those appropriate for urgent referral.

There is emerging evidence investigating how risk scores can incorporate other factors with new onset diabetes, to identify pancreatic cancer at an earlier stage. Research conducted in Australia aimed to develop and validate a model to predict pancreatic cancer among women with new-onset diabetes, which included prescription medications, severity of diabetes (i.e., change/addition of medication within 2 months after first medication), and age at diabetes diagnosis as potential predictors of pancreatic cancer. Using a risk threshold of 50%, sensitivity and specificity were 69% and the positive predictive value (PPV) was 1.3%[15]. An American study used change in weight, change in blood glucose, and age at onset of diabetes to develop and validate a model (named END-PAC)[16]. These models are not based on a symptomatic cohort, but is a cohort that primary care would interact with. Further independent prospective studies are needed to further validate these models, which could contribute to early detection of pancreatic cancer. A feasibility study is underway to apply the ENDPAC model to a UK primary care context (the project is called DEFEND-PRIME).

SBRI NHS Cancer Programme awarded a grant to accelerate new innovations to detect and diagnose HCC earlier. This 18-month project will explore the use of an innovative solution, called Elecsys®GAAD, to improve early Hepatocellular Carcinoma (HCC) detection. Elecsys®GAAD is a fully regulated, accurate test that combines blood tests with gender and age. If raised, it can suggest the presence of HCC. It will be

[13]Ho KMA, Rosenfeld A, Hogan Á, McBain H, Duku M, Wolfson PB, et al. Development and validation of a multivariable risk factor questionnaire to detect oesophageal cancer in 2-week wait patients. Clinics and Research in Hepatology and Gastroenterology [Internet]. 2023 Mar 1 [cited 2023 Feb 6];47(3):102087. Available from: https://www.sciencedirect.com/science/article/pii/S2210740123000128?via%3Dihub#sec0023

[14] Kamran U, King D, Banks M, Nylander D, Shetty S, Hebbar S, et al. Assessment of the role of the Edinburgh dysphagia score in referral triage in a national service evaluation of the urgent suspected upper gastrointestinal cancer pathway. Alimentary Pharmacology & Therapeutics [Internet]. 2022 May 1;55(9):1160–8. Available from: https://pubmed.ncbi.nlm.nih.gov/35247000/

[15]Ali S, Coory M, Donovan P, Na R, Pandeya N, Pearson SA, et al. Predicting the risk of pancreatic cancer in women with new-onset diabetes mellitus. Journal of Gastroenterology and Hepatology [Internet]. 2024 Feb 19 [cited 2024 Apr 18]; Available from: https://pubmed.ncbi.nlm.nih.gov/38373821/

[16] Sharma A, Kandlakunta H, Nagpal SJS, Feng Z, Hoos W, Petersen GM, et al. Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes. Gastroenterology. 2018 Sep;155(3):730-739.e3.

used alongside routine surveillance tests to see if it can help in finding HCC earlier so patients have the best chance of surviving this cancer.

Prescription patterns

Prescription data are included as one of the variables in the Australian risk prediction tool noted above, and there is some evidence emerging investigating how prescription patterns can determine oesophago-gastric cancer risk. A case-control study using the Primary Care Clinical Information Unit Research (PCCIUR) database from Scotland investigated 3 medications known to increase GI inflammation (bisphosphonate, tetracycline and spironolactone) which is a known risk factor for upper GI cancers. The study found little evidence that their use is associated with increased risk of gastro-oesophageal cancer[17]. Further research is needed to determine whether prescription patterns can determine risk of OG cancer.

Suspected Upper GI Cancer Referral Guidelines: NICE NG12 and SRG

NICE NG12	SRG

Oesophageal cancer
Offer urgent, direct access upper gastrointestinal endoscopy (to be done within 2 weeks) to assess for oesophageal cancer in people:
 	
• with dysphagia or
• aged 55 and over with weight loss and any of the following:
• upper abdominal pain
• reflux
• dyspepsia.
 	
Consider non-urgent, direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people with haematemesis.
	Oesophago-gastric cancer:
	• Dysphagia (interference of the swallowing mechanism that occurs within five seconds of the swallowing process) or unexplained odynophagia (pain on swallowing) at any age
	• Unexplained weight loss, particularly >55 years, combined with one or more of the following features:
	  ○ new or worsening upper abdominal pain or discomfort
	  ○ unexplained iron deficiency anaemia
	  ○ reflux symptoms
	  ○ dyspepsia resistant to treatment
	  ○ vomiting
	• New vomiting persisting for more than two weeks

[17] Busby J, Murchie P, Murray LJ, Iversen L, Lee AJ, Spence AJ, et al. The effect of medications which cause inflammation of the gastro-oesophageal tract on cancer risk: a nested case–control study of routine Scottish data. International Journal of Cancer. 2017 Apr 15;140(8):1828–35.

Consider non-urgent, direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people aged 55 or over with:

- treatment-resistant dyspepsia or
- upper abdominal pain with low haemoglobin levels or

- raised platelet count with any of the following:
- nausea
- vomiting
- weight loss
- reflux
- dyspepsia
- upper abdominal pain or

- nausea or vomiting with any of the following:
- weight loss
- reflux
- dyspepsia
- upper abdominal pain.

Pancreatic cancer

Refer people using a suspected cancer pathway referral for pancreatic cancer if they are aged 40 and over and have jaundice.

Consider an urgent, direct access CT scan (to be done within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 and over with weight loss and any of the following:

- diarrhoea

Hepatobiliary and pancreatic cancer:

- Painless obstructive jaundice
- Unexplained weight loss, particularly >55 years, combined with one or more of the following features:
    - upper abdominal or epigastric mass
    - new onset diabetes
    - any suspicious abnormality, in the hepatobiliary tract, found on imaging (such as biliary dilatation or pancreatic/liver lesion)
    - new onset, unexplained back pain (consider other cancer causes including myeloma or malignant spinal cord compression)
    - ongoing GI symptoms despite negative endoscopic investigations

There is emerging evidence that thrombocytosis is a risk marker for underlying cancer, including gastric and oesophageal. Remember "LEGO-C".

• back pain • abdominal pain • nausea • vomiting • constipation • new-onset diabetes. **Stomach cancer** Consider a suspected cancer pathway referral for people with an upper abdominal mass consistent with stomach cancer. Offer urgent, direct access upper gastrointestinal endoscopy (to be done within 2 weeks) to assess for stomach cancer in people: • with dysphagia or • aged 55 and over with weight loss and any of the following: • upper abdominal pain • reflux • dyspepsia. Consider non-urgent, direct access upper gastrointestinal endoscopy to assess for stomach cancer in people with haematemesis. Consider non-urgent, direct access upper gastrointestinal endoscopy to assess for stomach cancer in people aged 55 or over with: • treatment-resistant dyspepsia or • upper abdominal pain with low haemoglobin levels or	

• raised platelet count with any of the following: • nausea • vomiting • weight loss • reflux • dyspepsia • upper abdominal pain or nausea or vomiting with any of the following: • weight loss • reflux • dyspepsia • upper abdominal pain. **Gall bladder cancer** Consider an urgent, direct access ultrasound scan (to be done within 2 weeks) to assess for gall bladder cancer in people with an upper abdominal mass consistent with an enlarged gall bladder. **Liver cancer** Consider an urgent, direct access ultrasound scan (to be done within 2 weeks) to assess for liver cancer in people with an upper abdominal mass consistent with an enlarged liver.	