Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (Non-specific symptoms & malignant spinal cord compression)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for non-specific symptoms of cancer and malignant spinal cord compression (Appendix B). 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 signs, symptoms, and clinical features
- Combinations of signs, symptoms, and clinical features
- GP 'gut feeling'
- Investigation findings
- Evidence and evaluations from non-specific symptom pathways
- Emerging topics
- Other insights
- Appendix A: Background on non-specific symptom pathways across the UK and how they compare to each other
- Appendix B: Malignant spinal cord compression

Background

Earlier diagnosis can improve treatment options and survival outcomes for those with cancer. 'Red flag' or 'alarm symptoms' of cancer are usually associated with a higher predictive value for specific cancer sites. These symptoms are normally included in national guidelines for urgent suspected cancer referral, such as in the Scottish Referral Guidelines (SRG) in Scotland and NICE NG12 in England and Wales. However, there is evidence suggesting that over 50% of patients subsequently diagnosed with cancer do not initially present with alarm

symptoms to primary care.[1,2] Instead, patients might present with non-specific symptoms of cancer including unexplained weight loss, fatigue, abdominal symptoms (pain, bloating), nausea/vomiting, loss of appetite, or non-specific pain such as bone pain. Additionally, other clinical signs and features may be important to understanding cancer risk such as anaemia, thrombocytosis, or other blood test results. These signs and symptoms usually have a much lower positive predictive value (PPV) for cancer than site-specific alarm symptoms. General practitioners (GPs) may sometimes also experience uncertainty on how to proceed due to concern of serious disease in some patients presenting with more ambiguous symptoms or signs or there may be an intuition about possible adverse outcome despite a lack of clinical signs or symptoms. This is commonly known as GP 'gut feeling' of cancer.[3]

While some GPs might still investigate or refer based on their clinical judgement or gut feeling, non-specific symptoms often don't meet a threshold for referral, posing a challenge for primary care and potentially resulting in prolonged primary care and diagnostic intervals. Due to this, patients may experience prolonged diagnostic intervals and poorer outcomes. Pearson et al. (2020) found that patients presenting with non-specific symptoms are more likely to be diagnosed later stage or via emergency presentation compared to those presenting with alarm symptoms. Patients were also more likely to have multiple pre-referral consultations with a GP and more primary care diagnostic tests.[4]

In response to this, referral pathways have been created across the UK for patients with non-specific but concerning symptoms of cancer. These pathways allow GPs to refer patients who meet symptom criteria directly to a special secondary care pathway after they complete pre-requisite filter function tests. These pathways are primarily to rule out cancer. It should be acknowledged that other serious diseases are also often diagnosed. This helps to provide a more managed route for patients who do not experience alarm symptoms, but still are at an increased risk for cancer.

Search Strategy

[1] Ingeman ML, Christensen MB, Bro F, Knudsen ST, Vedsted P. The Danish cancer pathway for patients with serious non-specific symptoms and signs of cancer-a cross-sectional study of patient characteristics and cancer probability. BMC Cancer. 2015;15:421. Published 2015 May 20. doi:10.1186/s12885-015-1424-5
[2] Neal RD, Din NU, Hamilton W, et al. Comparison of cancer diagnostic intervals before and after implementation of NICE guidelines: analysis of data from the UK General Practice Research Database. Br J Cancer. 2014;110(3):584-592. doi:10.1038/bjc.2013.791
[3] Smith CF, Drew S, Ziebland S, Nicholson BD. Understanding the role of GPs' gut feelings in diagnosing cancer in primary care: a systematic review and meta-analysis of existing evidence. Br J Gen Pract. 2020;70(698):e612-e621. Published 2020 Aug 27. doi:10.3399/bjgp20X712301
[4] Pearson C, Poirier V, Fitzgerald K, Rubin G, Hamilton W. Cross-sectional study using primary care and cancer registration data to investigate patients with cancer presenting with non-specific symptoms. BMJ Open. 2020;10(1):e033008. Published 2020 Jan 10. doi:10.1136/bmjopen-2019-033008

Search terms: PubMed search for combinations of the following terms: cancer, risk, "predictive value", PPV, "non-specific symptoms", "vague symptoms", "weight loss", unexplained, unintended, fatigue, tiredness, "abdominal pain", "abdominal symptoms", bloating, nausea, "loss of appetite", anaemia, "low haemoglobin", thrombocytosis, "raised platelet", "bone pain", "GP gut feeling", "gut feeling", accuracy, diagnostic, "blood test", "full blood count", "primary care", "general practice", "investigation", "liver function test", "bone chemistry", ferritin, "serum electrophoresis", "prostate-specific antigen", PSA, test, CA-125, FIT, "faecal immunochemical test", "chest X-ray", "X-Ray", "CXR", "urinalysis", "urine test", "non-specific symptoms pathway", "vague symptoms pathway", "rapid diagnosis centre", "rapid cancer diagnostic service".

Date: 2015 – present.

Peer-reviewed literature

Notes:

- Grey rows in the table represent studies that have already been summarised earlier in the document.
- Some American studies identified but excluded due to question of relevance to context and/or not adding new insight to evidence base. Danish or other international studies have been included only where these provide additional insight.
- The following study was identified in the search: *Nicholson BD, Aveyard P, Price SJ, Hobbs FR, Koshiaris C, Hamilton W. Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study. BMJ. 2020;370:m2651. Published 2020 Aug 13. doi:10.1136/bmj.m2651.* However, the authors submitted an expression of concern to the journal due to a selection bias that they identified in their approach to the research during external validation. This is why the original paper has not been included in the evidence review tables. The authors have been working with the BMJ so that an updated manuscript will be published. We've contacted the author to get updated results from the corrected analysis that is currently being completed and have summarised this in the 'Other insights' section near the end of this document.

Topic: Individual signs, symptoms, and clinical features
Summary: Several studies explored the prevalence of individual non-specific signs and symptoms among those subsequently diagnosed with cancer. Note that some symptoms that may be considered 'red flag' symptoms for certain rarer or less common cancer sites have been included (such as bone pain for sarcoma). Evidence overall supports the inclusion of referral guidance related to individual non-specific symptoms with consideration to age, sex, and

smoking status. All symptoms highlighted in the referral criteria for Scotland's Rapid Cancer Diagnosis Services (RCDSs) (noted in Appendix A) have evidence supporting the increased risk of cancer compared to those without these symptoms- however risk only surpassed 3% in older age groups and when looking at cancer risk generally as opposed to for specific cancer sites.

- **Fatigue:** Paper 4 reported PPV for any cancer was between 3-6% for men aged 65-79 with fatigue and >6% in men 80+ with fatigue, however for women with fatigue, PPV only reached >3% at age 80+.
- **Weight loss:** Paper 6 found that PPV for any cancer was above 3% in men and women 60+ who experienced weight loss. It should be noted that studies had varying definitions of weight loss and there is not one agreed upon definition used in primary care. In some of England's non-specific symptoms pathway, the definition of weight loss is >5% in three months.
- **Abdominal pain:** Paper 12 showed that the PPV for any cancer across all age cohorts was 2.8% for men and 1.9% for women who experienced abdominal pain alone. PPV exceeded 3% in both men and women aged 60+ but was higher in men (range 4.2-8.6, increasing with age) than women (range 3.1-5.1, increasing with age). Paper 10 also showed that abdominal symptoms overlapped with benign conditions such as inflammatory bowel disease (IBD).
- **Abdominal bloating:** Paper 12 showed that the PPV for any cancer across all age cohorts was 2.6% for men and 2.1% for women. PPV exceeded 3% in both men and women aged 60+ but was higher in men (range 3.0-6.7, increasing with age) than women (range 3.5-4.6, increasing with age).
- **Loss of appetite:** There was a lack of evidence on loss of appetite, however paper 2 showed that loss of appetite was experienced most by those subsequently diagnosed with pancreatic, stomach, hepato-pancreatic-biliary (HPB) cancer, and cancer of the small intestine.
- **Back / bone pain:** There was a lack of evidence on back and bone pain, however paper 2 showed that both symptoms were most common in those diagnosed with multiple myeloma and bone sarcoma.
- **Thrombocytosis:** Paper 13 showed that 1 year incidence of cancer in those with thrombocytosis was almost three times higher than in those with normal platelet count (incidence = 11.6% in men and 6.2% in females).
- **Microcytosis:** Paper 16 showed that those with microcytosis only had a 1-year cancer incidence of 3.3% in men and 2.0% in women. Incidence increased with age.

Fatigue, back pain, and bone pain are more common in those diagnosed with haematological cancers, whereas abdominal symptoms and weight loss were associated with more diverse cancer sites (most commonly pancreatic, stomach, oesophageal, colorectal or HPB cancer). Thrombocytosis and microcytosis were more common in lung and colorectal cancer.

Paper number	Study	Summary	Notes
ANY NON-SPECIFIC SYMPTOM			

1	Koo MM, Swann R, McPhail S, et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. Lancet Oncol. 2020;21(1):73-79. doi:10.1016/S1470-2045(19)30595-9	There has been debate around whether symptoms are present at an early enough stage for meaningful clinical intervention. This paper examined associations between common presenting symptoms of cancer and stage at diagnosis.
		
		The following non-specific symptoms were experienced by those subsequently diagnosed with cancer:
		• 3.5% experienced lower abdominal pain, of which 29% were diagnosed stage 4.
		  ○ Lower abdominal pain alone was associated with bladder (4%), breast (1%), colon (40%), endometrial (4%), lung (4%), ovarian (21%), prostate (11%), rectal (9%), and renal (7%) cancers.
		• 5.3% experienced general abdominal pain, of which 37% were diagnosed stage 4.
		  ○ General abdominal pain alone was associated with bladder (1%), colon (48%), endometrial (1%), lung (8%), ovarian (13%), prostate (6%), rectal (11%) and renal (10%) cancers.
		• 4.5% experienced fatigue, of which 47% were diagnosed stage 4.
		  ○ Fatigue alone was associated with bladder (2%), breast (2%), colon (26%), endometrial (1%), lung (41%), melanoma (1%), oral/oropharyngeal (2%), ovarian (3%), prostate (12%), rectal (4%) and renal (6%) cancers.
		• 7.3% experienced weight loss, of which 49% were diagnosed stage 4.
			• Cross-sectional population-based study
			• N=7,997, aged 25 or older.
			• National Cancer Diagnosis Audit (NCDA) and National Cancer Registration and Analysis Service (NCRAS) data (2014)
			• England only
			Limitation: recording of symptoms and extraction of information from primary care records might be incomplete; surveys on presenting symptoms were filled out retrospectively and therefore, could be prone to bias.
			• Did not report positive predictive values (PPV).

		○ Weight loss alone was associated with bladder (2%), breast (3%), colon (20%), laryngeal (1%), lung (44%), oral/oropharyngeal (2%), ovarian (3%), prostate (10%), rectal (10%), and renal (6%) cancers. • 3.3% experienced back pain, of which 61% were diagnosed stage 4. ○ Back pain alone was associated with breast (3%), colon (4%), lung (86%), ovarian (1%), prostate (3%), and renal (2%) cancers. Non-specific symptoms had more diverse cancer signatures (associated with many cancer sites) compared to more specific alarm symptoms.	
2	Zakkak N, Barclay ME, Swann R, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. Br J Cancer. 2024;130(2):297-307. doi:10.1038/s41416-023-02507-4	This paper examined (1) the frequency of presenting symptoms by cancer site and (2) the frequency of cancer site by presenting symptom. In general, those with non-specific symptoms were diagnosed with a variety of different cancers, most commonly haematological, HPB, upper gastrointestinal (GI), lower GI, or cancer of unknown primary. • Weight loss was most common in pancreatic cancer (22%), stomach cancer (21%), and oesophageal cancer (21%). • Fatigue was most common in acute leukaemia (25%), Hodgkin's lymphoma (12%), multiple myeloma (10%) and other haematological cancers (13%). • Fever was most common in acute leukaemia (5%).	• Sample size: 55,122 patients • N=55,122 • NCDA 2018 data, England only • Limitations: case-only analysis so cannot make inferences about PPV; surveys for GPs regarding the presenting symptoms were filled out retrospectively and therefore, could be prone to bias.

		• Night sweats was most common in Hodgkin's lymphoma (6%) and other haematological cancers (4%). • Loss of appetite was most common in pancreatic cancer (12%), stomach cancer (9%), cancer of the small intestine (8%), other HPB cancer (8%). • Nausea/vomiting was most common in cancer of the small intestine (16%), stomach cancer (12%), oesophageal cancer (12%), other HPB cancer (12%), pancreatic cancer (11%). • Abdominal pain (not otherwise specified) was most common in pancreatic cancer (20%), ovarian cancer (19%), other HPB cancer (16%), colon cancer (17%), liver cancer (12%), stomach cancer (10%). • Distention was most common in ovarian cancer (28%) and connective and soft tissue sarcoma (8%). • Back pain was most common in multiple myeloma (23%) and bone sarcoma (19%) • Bone pain was most common in bone sarcoma (29%) and multiple myeloma (9%). • Chest pain was most common in mesothelioma (20%) and lung cancer (10%). *Note: These symptoms could have occurred individually or in combination with other symptoms.*	
3	Moore SF, Price SJ, Bostock J, Neal RD, Hamilton W. Incidence of 'Low-Risk but Not No-Risk' Features of Cancer Prior to High-Risk Feature Occurrence: An Observational	This study explored whether patients who saw their GP with a high-risk cancer symptom had also seen their GP with a 'low risk but not no-risk' symptom in the previous year (defined as having a risk threshold between 1-2.99%). Only the non-specific symptoms are summarised below.	• Observational, descriptive, cross-sectional study • Clinical Research Practice Datalink (CPRD) data, England only

	Cohort Study in Primary Care. Cancers (Basel). 2023;15(15):3936. Published 2023 Aug 2. doi:10.3390/cancers15153936	The presence of 'low risk but not no risk' symptoms were most common for colorectal, lung, prostate and oesophago-gastric cancers. The paper does not provide further breakdown on percentage of people who experienced each non-specific symptom. • Colorectal cancer: 4.6% experienced a symptom with a risk threshold between 2-2.99, and 16.7% experienced a symptom with a risk threshold between 1-1.99 in the year prior to diagnosis. The non-specific symptoms experienced within this included appetite loss, abdominal tenderness/pain, and loss of weight. • Lung cancer: 2.6% experienced a symptom with a risk threshold between 2-2.99, and 18.1% experienced a symptom with a risk threshold between 1-1.99 in the year prior to diagnosis. The non-specific symptoms experienced within this included appetite loss, cough, fatigue, and weight loss. • Prostate cancer: 7.8% experienced a symptom with a risk threshold between 2-2.99, and 2.0% experienced a symptom with a risk threshold between 1-1.99 in the year prior to diagnosis. The non-specific symptom experienced within this included loss of weight. • Oesophago-gastric cancer: 0.9% experienced a symptom with a risk threshold between 2-2.99, and 30.7% experienced a symptom with a risk threshold between 1-1.99 in the year prior to diagnosis. The non-specific symptoms experienced within this included appetite loss, anaemia, weight loss, epigastric pain, thrombocytosis, nausea/vomiting, and abdominal pain.	• N=150,921 • Included data on patients 40 or older from 1 January 2015 to 31 December 2016

		• Kidney cancer: 5.7% experienced a symptom with a risk threshold between 1-1.99 in the year prior to diagnosis. The non-specific symptoms experienced within this included DVT and anaemia. • Bladder cancer: 6.0% experienced a symptom with a risk threshold between 1-1.99 in the year prior to diagnosis The non-specific symptom experienced within this included anaemia.	
FATIGUE			
4	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. Br J Cancer. 2022;126(11):1627-1636. Doi:10.1038/s41416-022-01733-6	This study explored the risk of cancer[5] in the 12 months after a patient presents with fatigue to a GP, and how risk changes in the months after initial presentation. The risk of cancer in men who presented with fatigue ranged from: • <1% in each age band from those aged 30–49 • 3–6% in age bands between 65–79 years • >6% for those aged 80+ The incidence risk of cancer in women who presented with fatigue ranged from: • <1% in those aged 30–59 years • >3% in those aged 80+ Cancer risk was at least 2 times greater in the cohort experiencing fatigue than that of the general population in men across all age groups, and from 1.5- to 1.7-times greater for women aged 60+.	• Retrospective cohort study • CPRD GOLD data, 2007-2013 • N=250,606 patients with fatigue included. • Women presented with fatigue more than men. • Note: no 'universal' definition of fatigue so codes included for new onset fatigue, chronic fatigue syndrome (CFS) and post viral fatigue syndrome (PVFS) • Limitations: estimates for rarer cancers (i.e., head and neck) may have lacked precision; variation in coding practices by GPs with evidence to suggest

[5]As this is a cohort study, calculation of symptom risk (PPV) by Bayesian methods is not possible. The methodology used in this cohort study to determine symptom risk is deemed comparable to PPV by Professor Willie Hamilton and provides helpful insight into symptom risk in primary care.

		Although risk of specific cancers did not exceed a 3% threshold, for men and women with fatigue, site-specific cancer risk was higher than expected (compared to general population expected rates) for 13 cancer sites, with prostate, lung, and colorectal cancers being the most common among men, and breast, lung and colorectal being the most common among women. Of note, leukaemia, pancreatic cancer, and brain cancers, were over-represented among patients with fatigue. Of the 4087 patients diagnosed with cancer within a year after their initial fatigue record, 47% were diagnosed in the first 3 months. Cancer risk was greatest in the 3 months following the initial presentation but returned to expected by 9 months.	that GPs are more likely to code alarm symptoms;
5	White B, Zakkak N, Renzi C, et al. Underlying disease risk among fatigued patients: a population-based cohort study in primary care. Br J Gen Pract. Published online July 31, 2024. Doi:10.3399/BJGP.2024.0093	This study aimed to contextualise disease risk in patients presenting with new-onset fatigue, identifying diseases with the strongest associations with fatigue. The researchers compared the cohort of people with a record of fatigue to a cohort of people without a record of fatigue but who had at least one consultation during 2011-2012. Fatigue was more likely to occur in women, although men with fatigue were more likely to be diagnosed with cancer. The risk of all cancers combined in men presenting with fatigue was 2.6% (95% CI = 2.5-2.7) which is double that of those not presenting with fatigue (1.2% (1.1-1.2)). In women presenting with fatigue, cancer risk was 1.4% (1.4-1.5), compared to 0.9% (0.9-0.9) in women without fatigue.	• CPRD GOLD linked with cancer registry and HES • Included patients presenting with 'new-onset fatigue' between Jan 2007-Dec 2017. • N=69,636 males and 384,098 females • Limitations: coding of fatigue varies; this study only considered people who visited a health care professional for fatigue and therefore, may not represent the wider community of people with fatigue.

		Risk of cancer increased with age. By 80 years old, cancer had the fourth highest excess risk in men with fatigue, and the 13th highest in women, relative to the non-fatigue cohort.	
WEIGHT LOSS			

6	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. Br J Gen Pract. 2018;68(670):e311-e322. doi:10.3399/bjgp18X695801	This study examined the diagnostic value of weight loss for cancer in primary care patients, and explored how predictive value varies by cancer type, stage, sex, and age. The included studies reported weight loss in association with colorectal, pancreatic, gastro-oesophageal, ovarian, lung, renal, myeloma, non-Hodgkin's lymphoma, biliary tree and prostate cancers.
		
		The diagnostic value of weight loss for cancer was as follows:
		• Sensitivity ranged from 2-47% across cancer types
		• Specificity ranged from 92% to 99% across cancer types.
		• Only studies reporting on colorectal and pancreatic cancer could be combined. The meta-analysis reported:
		  ○ Pooled sensitivity for colorectal cancer was 14% (95% CI = 6 to 30%) and pooled specificity was 97% (95% CI = 94 to 99%)
		  ○ Pooled sensitivity for pancreatic cancer was 13% (95% CI = 8 to 20%) and pooled specificity was 99% (95% CI = 98 to 99%)
		
		The authors calculated PPVs by age group. The more conservative estimates that used the lowest likelihood ratios were as follows:
			• Systematic review
			• N=25 studies included (most conducted in the UK)
			• Limitations: unclear how much weight loss is required to make cancer a probability **(weight loss was defined differently across studies);** variation in GP coding practices; studies included were of mixed methodological quality with some studies being affected by recall bias.

		• Female
		  ○ Aged 40-49: PPV 0.2
		  ○ Aged 50-59: PPV 0.8
		  ○ Aged 60-69: PPV 1.9
		  ○ Aged 70-79: PPV 3.5
		  ○ Aged 80-89: PPV 4.6
		  ○ Aged 90+: PPV 4.0
		• Male
		  ○ Aged 40-49: PPV 0.4
		  ○ Aged 50-59: PPV 2.2
		  ○ Aged 60-69: PPV 7.5
		  ○ Aged 70-79: PPV 13.0
		  ○ Aged 80-89: PPV 14.9
		  ○ Aged 90+: PPV 16.1
		Of note, no study in this review looked at weight loss and cancer stage.	

7	Nicholson BD, Hamilton W, Koshiaris C, Oke JL, Hobbs FDR, Aveyard P. The association between unexpected weight loss and cancer diagnosis in primary care: a matched cohort analysis of 65,000 presentations. Br J Cancer. 2020;122(12):1848-1856. doi:10.1038/s41416-020-0829-3	This study examined the association between unexpected weight loss (UWL) and cancer, and whether any association varies over time. In the first 3 months after first presentation, UWL was associated with an increased likelihood of pancreatic cancer, cancer of unknown primary, gastro-oesophageal, lymphoma, HPB, lung, bowel and renal tract compared with controls. However, UWL was associated with a decreased likelihood of breast and prostate cancer compared to controls. After the first 3 months, the risk of cancer was lower in patients with UWL than in those without UWL.	• Retrospective matched cohort study • CPRD data linked to registry, 2000-2014 • N=63,979 patients with UWL; N=1,375 diagnosed with cancer over 2 years of follow-up. • Limitations: <15% of cancers had complete staging data available.

		Men with UWL had an increasing risk of cancer starting at over 50 years old whereas for women, the risk of cancer was not increased until 70 years old. For both genders, UWL was associated with increased late-stage cancer diagnoses (most often stage IV, but also a higher likelihood for stage III and II in men).	
8	Martinez Gutierrez J, De Mendonca L, Ly P, et al. A scoping review of unexpected weight loss and cancer: risk, guidelines, and recommendations for follow-up in primary care. BJGP Open. Published online July 25, 2024. doi:10.3399/BJGPO.2024.0025	This review explored the evidence on the association between UWL and cancer and investigated the guidelines for follow-up for patients with UWL and risk of cancer. The narrative reviews that were included in this study illustrated evidence for an association between UWL and cancer, with prevalences ranging between 6-37%. The association between UWL and cancer was most pronounced in the first 3-6 months after recognition, and after 6 months, the risk decreases. PPVs for cancer in those with UWL increased with age and in the presence of certain abnormal blood tests (summarised in the 'Investigations' table below). Additionally, studies reported that the risk of cancer increased when UWL co-occurs with other cancer symptoms.	• Scoping review • N=25 studies included, most conducted in the UK or USA (Paper 6, 7 and 27 overlap with included studies in this review). • Limitations: scoping review only with results synthesised narratively.
ABDOMINAL SYMPTOMS			
9	Price SJ, Gibson N, Hamilton WT, King A, Shephard EA. Intra-abdominal cancer risk with abdominal pain: a prospective cohort primary care study. Br J Gen Pract. 2022;72(718):e361-e368.	This study aimed to quantify risk of intra-abdominal cancer (i.e., oesophagogastric, colorectal, liver, pancreatic, ovarian, uterine, kidney, and bladder cancer) after newly reported abdominal pain with or without other symptoms, signs, or abnormal blood tests indicative of cancer.	• Observational prospective cohort study • CPRD • England only • N=125 793 patients • Aged ≥40 years

	Published 2022 Apr 28. doi:10.3399/BJGP.2021.0552	In those with abdominal pain alone, the 1-year cumulative incidence of intra-abdominal cancer was higher for men than women and increased with age. For men aged 70+, the incidence of cancer reached 3.4% (95% CI = 3.0 to 3.7) and for women, it reached 2.3% (95% CI = 2.1 to 2.5). For all age groups, the risk was greatest for colorectal cancer, followed by pancreatic and oesophagogastric cancers (and ovarian cancer for women). Those who experienced abdominal pain had a higher risk of cancer than those in the general population. **Of note, in the SRG only abdominal pain when combined with weight loss is considered for an urgent referral for upper GI and oesophago-gastric cancers whereas in NICE NG12, those over 50 abdominal pain alone should be given a FIT and referred if above threshold.**	• Between 1 January 2009 and 31 December 2013. • Limitations: data is subject to accurate reporting/recording
10	Herbert A, Rafiq M, Pham TM, et al. 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;18(8):e1003708. Published 2021 Aug 2. doi:10.1371/journal.pmed.1003708	This study aimed to estimate the PPV of common abdominal symptom presentations in primary care for cancer, inflammatory bowel disease (IBD), and the combination of cancer or IBD. Abdominal symptoms that were included were abdominal bloating/distention, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding. Only findings related to non-specific symptoms and cancer are covered in this summary. Rectal bleeding, change in bowel habit, and dysphagia are more specific symptoms and are not considered in this summary. Across the 6 symptoms, 1.41% (95% CI: 1.36% - 1.46%) to 4.64% (4.45% - 4.84%) of men and 1.03% (0.99% - 1.07%) to 2.46%	• Retrospective population-based cohort study • Data from the Health Improvement Network primary care database between 2000-2017 • N=102,785 for abdominal bloating/distension; N=909,451 for abdominal pain; N=108,698 for change in bowel habit; N=528,428 for dyspepsia; N=87,971 for dysphagia; N=240,253 for rectal bleeding

		(2.37% - 2.55%) of women were diagnosed with cancer in the year following their symptom presentation.
		
		The PPV for cancer for each symptom, regardless of other co-occurring symptoms was:
		• Abdominal bloating/distention:
		  ○ Men - 1.65 (95% CI 1.50-1.80)
		  ○ Women - 1.33 (95% CI 1.25-2.42).
		• Abdominal pain:
		  ○ Men – 1.77 (95% CI 1.73-1.82)
		  ○ Women – 1.20 (95% CI 1.17-1.23)
		• Dyspepsia:
		  ○ Men – 1.41 (95% CI 1.36-1.46)
		  ○ Women – 1.03 (95% CI 0.99-1.07)
		
		PPVs were higher in men and older people. Men were more likely to have cancer than IBD across all abdominal symptoms whereas in women, IBD was more likely than cancer.
			• Limitations: Variation in doctors recording patient symptoms; Cancer diagnoses were collected through primary care records as opposed to linked cancer registration data.

11	Holtedahl K, Hjertholm P, Borgquist L, et al. Abdominal symptoms and cancer in the abdomen: prospective cohort study in European primary care. Br J Gen Pract. 2018;68(670):e301-e310. doi:10.3399/bjgp18X695777	This study evaluated the predictability of abdominal symptoms for new cancers of the abdomen within 180 days from first presentation. Of the 175 patients with abdominal cancer diagnosed within 6 months of consultation, 43.4% had abdominal symptoms and 22.3% had multiple abdominal symptoms.[6] Among patients	• GP practices in Norway, Denmark, Sweden, the Netherlands, Belgium, and Scotland • February 2011-July 2011, with GPs reporting back 8 months after study registration.

[6] These included abdominal pain (upper and lower), constipation, diarrhoea, distended abdomen/bloating, increased belching, acid regurgitation, rectal bleeding, unexpected genital bleeding, macroscopic haematuria, increased urinary frequency, other abdominal problems

		with at least one abdominal symptom, non-specific symptoms occurred in 38.2% of patients with cancer. The hazard ratios[7] (HRs) for single symptoms compared to those without symptoms for cancer were: • Abdominal pain (upper): 4.8 (1.9-11.8) • Abdominal pain (lower): 5.8 (2.4-14.3) • Constipation: 6.7 (2.1-21.8) There were a broad range of cancers affected by abdominal pain, with colorectal cancer being the cancer with the most variety of symptoms displayed by the cohort.	• N=61,802; 175 abdominal cancers diagnosed and 132 non-abdominal cancers diagnosed within 6 months. • Limitations: Symptoms presenting before diagnosis but after initial consultation do not appear in the cross-sectional data; small sample size of cancers diagnosed; confidence intervals wide.

12	Rafiq M, Renzi C, White B, et al. Predictive value of abnormal blood tests for detecting cancer in primary care patients with nonspecific abdominal symptoms: A population-based cohort study of 477,870 patients in England. PLoS Med. 2024;21(7):e1004426. Published 2024 Jul 30. doi:10.1371/journal.pmed.1004426	This paper quantified the PPV of 19 abnormal blood tests[8] for detecting cancer in patients with non-specific abdominal pain or abdominal bloating.
		
		The PPV of abdominal pain or bloating for any cancer in the following 12 months was 2.2% overall.
		
		For abdominal pain, the PPV for any cancer by age and sex was:
		• Men
		  ○ Overall: 2.8 (CI 2.7-2.9)
		  ○ 30-49: <1
		  ○ 50-59: 1.9 (CI 1.8-2.1)
			• CPRD data linked to cancer registry
			• 2007-2016
			• N=425,549 patients with a new episode of abdominal pain and N=52,321 patients with new abdominal bloating.
			• Limitations: population includes patients who had already been selected by GPs to have testing which means that estimates may be lower for the broader

[7] HRs express the risk for cancer being diagnosed at any point in time during the study period when a patient had presented with an abdominal symptom, compared with when no symptom had been presented.

[8] Included blood tests were: PSA; acute phase reactants (platelets, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), ferritin and total white blood cell count (WBC)); markers of iron deficiency or anaemia (ferritin and haemoglobin); liver, renal or bone profile tests (bilirubin, albumin, AST, ALT, ALP, calcium, and creatinine); glycosylated haemoglobin (HbA1c).

		○ 60-69: 4.2 (CI 4.0-4.5) ○ 70-79: 6.9 (CI 6.5-7.2) ○ 80+: 8.6 (CI 8.0-9.1) • Women: ○ Overall: 1.9 (CI 1.8-1.9) ○ 30-49: <1 ○ 50-59: 1.5 (CI 1.4-1.6) ○ 60-69: 3.1 (CI 2.9-3.3) ○ 70-79: 4.4 (CI 4.1-4.6) ○ 80+: 5.1 (CI 4.8-5.5) For abdominal bloating, the PPV for any cancer by age and sex was: • Men: ○ Overall: 2.6 (CI 2.3-2.8) ○ 30-49: <1 ○ 50-59: 1.6 (CI 1.2-2.2) ○ 60-69: 3.0 (CI 2.5-3.7) ○ 70-79: 6.3 (CI 5.3-7.5) ○ 80+: 6.7 (CI 5.3-8.4) • Women: ○ Overall: 2.1 (CI 1.9-2.2) ○ 30-49: <1 ○ 50-59: 1.6 (CI 1.3-1.9) ○ 60-69: 3.5 (CI 3.1-4.0) ○ 70-79: 4.7 (CI 4.1-5.4) ○ 80+: 4.6 (CI 3.9-5.5) The most common cancer sites in males were colon, prostate, and pancreas, and in females were colon, breast,	population of people presenting with abdominal pain or bloating.

		ovary, and pancreas, however all had individual PPVs <1% for both abdominal symptoms.	
ANAEMIA, THROMBOCYTOSIS, MIRCOCYTOSIS			
13	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 [published correction appears in Br J Gen Pract. 2021 Sep 30;71(711):445. doi: 10.3399/bjgp21X717173]. Br J Gen Pract. 2017;67(659):e405-e413. doi:10.3399/bjgp17X691109	This paper examined risk of cancer in patients with thrombocytosis. The 1-year cancer incidence in males with thrombocytosis was 11.6% (95% CI = 11.0 to 12.3) and in females, was 6.2% (95% CI = 5.9 to 6.5). This is compared to a 1-year cancer incidence of 4.1% in males (95% CI = 3.4 to 4.9) and 2.2% in females (95% CI = 1.8 to 2.6) with a normal platelet count. The risk of cancer increased with increasing platelet count. Of those with thrombocytosis subsequently diagnosed with cancer, 49.2% were diagnosed at an early stage and 50.8% were diagnosed at a late stage. Those with thrombocytosis subsequently diagnosed with cancer were more likely to be diagnosed at a late stage than those with normal platelet counts who were subsequently diagnosed with cancer. Lung and colorectal cancer were the most diagnosed cancers among those with thrombocytosis. Of those diagnosed with lung cancer, 35.7% had no other symptoms that were noted in NICE NG12 guidance for urgent referral. Similarly, of those diagnosed with colorectal cancer, 32.9% had no other symptoms that were noted in NICE NG12 guidance for urgent referral.	• Prospective cohort study • CPRD linked to cancer registry • N=31,261 patients with thrombocytosis and N=7,969 patients with a normal platelet count • 'Thrombocytosis' defined as a platelet count of >400 × 10^9/L, • Limitations: Registry staging data was incomplete so stage results should be interpreted with caution; reason for blood test was unknown.
14	Mounce LT, Hamilton W, Bailey SE. Cancer incidence following a high-	This study examined cancer incidence in those with platelet counts at the upper end of the normal range (defined as	• Prospective cohort study

	normal platelet count: cohort study using electronic healthcare records from English primary care. *Br J Gen Pract*. 2020;70(698):e622-e628. Published 2020 Aug 27. doi:10.3399/bjgp20X710957	326–400 × 10^9/l – known as 'high-normal' cohort) compared with those who had low-normal platelet counts (defined as 150–325 × 109/l – known as the 'low-normal' cohort). Among males with high-normal platelet count, the 1-year incidence of cancer was 2.7% (95% CI 2.6-2.9). Among females, the 1-year incidence of cancer was 1.4% (95% CI 1.3-1.5). In comparison, among males with low-normal platelet count, the 1-year incidence of cancer was 2.1% (95% CI 2.0-2.3) and for females, it was 1.1% (95% CI 1.0-1.1). Incidence of cancer in all age-cohorts for females never surpassed the 3% risk threshold used in NICE guidance. In contrast, all men with high-normal platelet count aged ≥60 years met the NICE threshold for referral, however, note that all men 70+ regardless of high-normal or low-normal platelet count met the 3% risk threshold. For men aged 60+ in the high-normal group, the most common cancers within 1 year were prostate, colorectal and lung. Bladder and oesophagogastric cancers also appeared to have an association with platelet counts >400 x 10^9/l. The OR for lung cancer in those with platelet counts between 376–400 × 10^9/l was 4.68 (95% CI 2.79-7.87) compared to those patients in the lower-normal group. Similarly, for colorectal cancer the OR was 3.93 (95% CI 3.12-4.97). Of males in the high-normal groups aged 60+, 74.7% of those diagnosed with lung cancer, and 68.9% of those diagnosed with colorectal cancer, had no recorded alarm features of cancer prior to their platelet count test. After controlling for	• CPRD GOLD data linked to cancer registry • May 2005 – April 2013 • N=226,262 patients with high-normal platelet counts and N=69,050 patients with lower-normal platelet count • Limitations: Prostate cancer incidence was higher in those who were tested than in registry recorded data for the general population, irrespective of platelet count, suggesting no association between high platelet count and prostate cancer; uncertainty about the link to clinically significant prostate cancer as Gleason Grade was not analysed; unknown why GPs requested blood test.

		age, sex, and smoking status, a high-normal count represented an increase of nearly 50% in the odds of advanced stage at diagnosis (OR 1.5; 95% CI = 1.22 to 1.97).	
15	Bailey SE, Ukoumunne OC, Shephard E, Hamilton W. How useful is thrombocytosis in predicting an underlying cancer in primary care? a systematic review. Fam Pract. 2017;34(1):4-10. doi:10.1093/fampra/cmw100	This systematic review aimed to investigate whether those with thrombocytosis in primary care are at greater risk of cancer compared to those with normal platelet counts. Four studies which performed multivariable analyses found a statistically significant association between thrombocytosis and the specific cancer site evaluated in each study. The adjusted ORs in the studies were: • Lung cancer: 9.3 (95% CI 3.4-26) • Kidney cancer: 2.2 (95% CI 1.7-2.7) • Oesophago-gastric cancer: 2.4 (95% CI 2.0-2.9) • Uterine cancer: 1.50 (95% CI 1.00-2.25) The authors calculated likelihood ratios for each cancer site using the individual studies' raw data. Likelihood ratios were highest for ovarian, lung, kidney, colorectal, and oesophago-gastric cancer. The only non-significant likelihood ratio was for breast cancer.	• Systematic review • N=9 studies, all from the UK (all were site-specific studies so no overlap in any studies included elsewhere in this evidence review). • Limitations: potential for publication bias; the definition of thrombocytosis varied depending on the local laboratory definition but was either 400 or 450×10^9/l in the studies included.
16	Hopkins R, Bailey SE, Hamilton WT, Shephard EA. Microcytosis as a risk marker of cancer in primary care: a cohort study using electronic patient records. Br J Gen Pract. 2020;70(696):e457-e462. Published 2020 Jun 25. doi:10.3399/bjgp20X709577	This study analysed cancer incidence in patients with microcytosis (smaller than normal red blood cells), with and without accompanying anaemia. Those with microcytosis (with or without accompanying anaemia) had a 1-year cancer incidence of 4.0% (CI = 3.7 to 4.4) compared to 2.0% (CI 1.9-2.1) in the normal mean cell volume (MCV) group. For those with microcytosis, cancer incidence was higher in males than females (6.21% vs. 2.66%,	• Cohort study • CPRD linked to cancer registry • N=85,439; N=12,289 with microcytosis and N=73,150 with a normal MCV • Microcytosis was defined as an upper threshold of 85 fL • Limitations: unknown reason for blood test; the tested

		respectively), and in those 70+ compared to those <69 years (2.69% vs. 4.87%, respectively). The most common cancers diagnosed were colorectal (23%), lung (13%), lymphoma (5%), kidney (4%) and stomach (3%). In those with microcytosis without accompanying anaemia, the incidence of cancer was 3.3% (CI = 2.6 to 4.0) in males and 2.0% (CI = 1.6 to 2.4) in females. The most common cancer sites diagnosed were prostate, lung and colorectal in males, and colorectal, lung and breast in females.	population is expected to be more ill than the untested population; the researchers note that the threshold of 85 fL for microcytosis was a conservative choice but reflects what is commonly used in the UK.

Topic: Combinations of signs, symptoms, and clinical features			
Summary: The PPV of symptoms is higher for non-specific symptoms where they are experienced in combination with other non-specific symptoms. Particularly, in men 60+, the PPV surpassed 3% for most symptom combinations, with some variation reported across studies. The PPV for symptom combinations for women were usually lower overall, but paper 14 notes that certain combinations in women surpassed 3% particularly in older age groups, such as fatigue and weight loss in those 65+, fatigue and abdominal pain in those 79+ and fatigue and abdominal bloating in those 80+.			
Paper number	Study	Summary	Notes
FATIGUE COMBINATIONS			
17	White B, Renzi C, Barclay M, Lyratzopoulos G. Underlying cancer risk among patients with fatigue and other vague symptoms: a population-based cohort study in primary care. Br J Gen Pract. 2023;73(727):e75-e87. Published 2023 Jan 26. Doi:10.3399/BJGP.2022.0371	This study estimated the risk of cancer (excluding non-melanoma skin cancer) in patients who present with fatigue in combinations with other presenting vague symptoms, but not alongside alarm symptoms.	• Retrospective cohort study • CPRD GOLD data, 2007-2015 • England only • N=239,846 patients with fatigue without anaemia or other alarm symptoms. • Limitations: Study population does not represent the broader population that experiences fatigue; differences in coding

		38% of people with fatigue (but no alarm symptoms or anaemia) experienced ≥1 other vague symptom(s)[9]. 26% of people had only one additional vague symptom and 12% had ≥2. For patients with ≥2 different additional vague symptoms in combination with fatigue, cancer risk was: • Males: 2.5%, 95% CI = 2.2 to 2.9% • Females: 1.3%, 95% CI = 1.2 to 1.5 For patients with 1 additional vague symptom in combination with fatigue, cancer risk was: • Males: 1.5%, 95% CI = 1.4 to 1.7 • Females: 0.8%, 95% CI = 0.8 to 0.9 After adjusting for age, cancer risk was highest for the following additional symptoms: • Weight loss (males & females) • Abdominal pain (males & females) • Constipation (males & females) • Other upper GI symptoms (males & females) • Abdominal bloating (females) • Dyspnoea (females). For males, cancer risk exceeded 3% for the following symptom combinations and age groups:	practices among GPs; did not stratify by other factors such as multiple combinations or morbidity status.

[9] Other vague symptoms included: musculoskeletal pain, cough, back pain, urinary tract infections, lower respiratory infections, dyspnoea, abdominal pain, headache, other upper GI symptoms, upper respiratory infection, chest pain, diarrhoea, constipation, thromboembolic, abdominal bloating, weight loss, testicular pain, night sweats and pelvic pain.

		• Fatigue–weight loss (from 59 years) • Fatigue–abdominal pain (from 65 years) • Fatigue–constipation (from 67 years) • Fatigue–other upper GI symptoms (from 67 years). For females, risk exceeded 3% for the following symptom combinations and age groups: • Fatigue–weight loss (from 65 years) • Fatigue–abdominal pain (from 79 years) • Fatigue–abdominal bloating (from 80 years).	
ABDOMINAL SYMPTOMS COMBINATIONS			
9	Price SJ, Gibson N, Hamilton WT, King A, Shephard EA. Intra-abdominal cancer risk with abdominal pain: a prospective cohort primary care study. Br J Gen Pract. 2022;72(718):e361-e368. Published 2022 Apr 28. doi:10.3399/BJGP.2021.0552	This study aimed to quantify risk of intra-abdominal cancer (i.e., oesophagogastric, colorectal, liver, pancreatic, ovarian, uterine, kidney, and bladder cancer) after newly reported abdominal pain with or without other symptoms, signs, or abnormal blood tests indicative of cancer. At least one additional feature (including abdominal mass, change in bowel habit, diarrhoea/constipation, nausea/vomiting, weight loss, haematuria/UTI, low haemoglobin/raised platelets) accompanied abdominal pain in 12.9%, 19.2%, and 34.6% of men, and in 21.0%, 25.7%, and 39.7% of women aged 40–59, 60–69, and ≥70 years, respectively. Risk exceeded 3% for the following additional symptoms (in specific age cohorts or sexes):	• Observational prospective cohort study • CPRD • England only • N=125 793 patients • Aged ≥40 years • Between 1 January 2009 and 31 December 2013. • Limitations: data is subject to accurate reporting/recording

		• Abdominal mass in women aged 40-59 increased colorectal, ovarian, oesophagogastric, or liver cancer risk to 7% (95% CI 2.0-17) • Weight loss increased risk of colorectal, ovarian, pancreatic, or oesophagogastric cancer to 4% in women and men (95% CI 1-9 in women and 2-9 in men). • Nausea/vomiting increased risk of pancreatic or oseophagogastric cancers to 4% (CI 2-7) in men aged 60-69 and 3.6% (CI 2.2-5.4) in men aged 70+.	
10	Herbert A, Rafiq M, Pham TM, et al. 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;18(8):e1003708. Published 2021 Aug 2. doi:10.1371/journal.pmed.1003708	This study aimed to estimate the PPV of common abdominal symptom presentations in primary care for cancer, inflammatory bowel disease (IBD), and the combination of cancer or IBD. Abdominal symptoms that were included were abdominal bloating/distention, abdominal pain, change in bowel habit, dyspepsia, dysphagia, and rectal bleeding. Only findings related to non-specific symptoms and cancer are covered in this summary. Rectal bleeding, change in bowel habit, and dysphagia are more specific symptoms and are therefore, only considered in combination with non-specific symptoms. The PPVs for non-specific symptom combinations that surpassed 3% were: • Abdominal bloating/distention + dysphagia in men (PPV=3.91) • Abdominal pain + dysphagia (PPV=3.15) in men	• Retrospective population-based cohort study • Data from the Health Improvement Network primary care database between 2000-2017 • N=102,785 for abdominal bloating/distension; N=909,451 for abdominal pain; N=108,698 for change in bowel habit; N=528,428 for dyspepsia; N=87,971 for dysphagia; N=240,253 for rectal bleeding • Limitations: Variation in GPs recording patient symptoms; Cancer diagnoses were collected through primary care records as opposed to linked cancer registration data.

		• Change in bowel habit + abdominal bloating/distention (PPV=3.29) or abdominal pain (PPV=4.78) in men; • Dysphagia + abdominal pain (PPV=5.10) and dyspepsia (PPV=5.69) in men; The PPVs for non-specific symptom combinations that were between 2-2.99% were: • Abdominal bloating / distension + abdominal pain in men (PPV=2.53). • Abdominal pain + abdominal bloating / distention in men (PPV=2.86) or dyspepsia (PPV=2.02) in men • Change in bowel habit + dyspepsia in men (PPV=2.95); Change in bowel habit + abdominal bloating distension (PPV=2.12) or abdominal pain (PPV=2.10) in women. • Dyspepsia + change in bowel habit (PPV=2.16) or dysphagia (PPV=2.31) in men; • Dysphagia + abdominal bloating / distention (PPV = 2.25) in men; Dysphagia + abdominal pain (PPV=2.00) or dyspepsia (PPV=2.37) in women. • Rectal bleeding + abdominal bloating/distention (PPV=2.97) or abdominal pain (PPV=2.94) or dyspepsia (PPV=2.45) in men; Rectal bleeding + abdominal bloating / distention (PPV=2.04) in women. The PPVs for non-specific symptom combinations that were between 1-1.99% were: • Abdominal bloating / distention + dyspepsia (PPV=1.45) in men; Abdominal bloating / distention +	

		abdominal pain (PPV=1.68) or dyspepsia (PPV=1.05) in women; • Abdominal pain + abdominal bloating / distention (PPV=1.86) or dyspepsia (PPV=1.54) in women. • Change in bowel habit + dyspepsia (PPV=1.91) in women. • Dyspepsia + abdominal bloating / distention (PPV=1.48 in men, 1.10 in women) or abdominal pain (PPV=1.67 in men, 1.16 in women). • Dysphagia + abdominal bloating / distention (PPV=1.59) in women. • Rectal bleeding + abdominal pain (PPV=1.98) or dyspepsia (PPV=1.80) in women. No symptom combinations had PPV <1%. In general, PPVs increased significantly if the initial symptom was combined with change in bowel habit (among those presenting with any of the other 5 symptoms) or with rectal bleeding (among those presenting with abdominal bloating/distension and change in bowel habit). The highest PPV was seen among those presenting with change in bowel habit combined with rectal bleeding or vice versa. Among patients subsequently diagnosed with cancer, the percentage of those with more than 1 symptom recorded in the same consultation or the following year was highest for abdominal bloating/distension (56%) and dyspepsia (13%).	

11	Holtedahl K, Hjertholm P, Borgquist L, et al. Abdominal symptoms and cancer in the abdomen: prospective cohort study in European primary care. Br J Gen Pract. 2018;68(670):e301-e310. doi:10.3399/bjgp18X695777	This study evaluated the predictability of abdominal symptoms for new cancers of the abdomen within 180 days from first presentation.
		
		The HR for different combinations of symptoms compared to patients without any abdominal symptoms (ref group) was:
		• Abdominal pain, upper part + lower part
		  ○ HR male: 6.7; HR female: 11.1
		• Abdominal pain, upper part + constipation
		  ○ HR male: 19.8; HR female 26.1.
		• Abdominal pain, upper part + diarrhoea
		  ○ HR male: 17.6; HR female: 8.8.
		• Abdominal pain, upper part + distended abdomen
		  ○ HR male: 12.4; HR female: 19.9.
		• Abdominal pain, upper part + increased belching
		  ○ HR male: 21.1; HR female: 26.1.
		• Abdominal pain, upper part + acid regurgitations
		  ○ HR male: 16.6; HR female: 12.9.
		• Abdominal pain, upper part + rectal bleeding
		  ○ HR male: 57.5; HR female: 100.5.
		• Abdominal pain, upper part + other abdominal problem
		  ○ HR male: 19.6; HR female: 24.2.
		• Abdominal pain, lower part + constipation
		  ○ HR male: 9.2; HR female: 19.7.
		• Abdominal pain, lower part + distended abdomen
		  ○ HR male: 7.1; HR female: 9.6.
		• Abdominal pain, upper part + lack of appetite
		  ○ HR male: 14.9; HR female: 22.4
		• Abdominal pain, upper part + unusual tiredness
			• GP practices in Norway, Denmark, Sweden, the Netherlands, Belgium, and Scotland
			• February 2011-July 2011, with GPs reporting back 8 months after study registration.
			• N=61,802; 175 abdominal cancers diagnosed and 132 non-abdominal cancers diagnosed within 6 months.
			• Limitations: Symptoms presenting before diagnosis but after initial consultation do not appear in the cross-sectional data; small sample size of cancers diagnosed; confidence intervals wide.

		○ HR male: 13.4; HR female: 23.3. • Abdominal pain, upper part + UWL ○ HR male: 30.8; HR female: 18.2.	
ANAEMIA, THROMBOCYTOSIS, OR MICROCYTOSIS COMBINATIONS			
16	Hopkins R, Bailey SE, Hamilton WT, Shephard EA. Microcytosis as a risk marker of cancer in primary care: a cohort study using electronic patient records. Br J Gen Pract. 2020;70(696):e457-e462. Published 2020 Jun 25. doi:10.3399/bjgp20X709577	This study analysed cancer incidence in patients with microcytosis (smaller than normal red blood cells), with and without accompanying anaemia. Of those with microcytosis, 45.1% of males and 32.5% of females also had anaemia. In these patients, 9.8% of males and 4.0% of females were diagnosed with cancer. The most common cancer site among these patients was colorectal cancer.	• Cohort study • CPRD linked to cancer registry • N=85,439; N=12,289 with microcytosis and N=73,150 with a normal MCV • Microcytosis was defined as an upper threshold of 85 fL • Limitations: unknown reason for blood test; the tested population is expected to be more ill than the untested population; the researchers note that the threshold of 85 fL for microcytosis was a conservative choice but reflects what is commonly used in the UK. .

Topic: GP 'gut feeling'
Summary: GP 'gut feeling' is known as a feeling that GPs experience when they suspect a patient may have a serious condition but may not necessarily present with alarm/red flag signs or symptoms. Within each UK nations' non-specific symptom pathways (such as the RCDSs in Scotland), GPs can refer solely based on gut feeling (regardless of signs and symptoms), and there is evidence to support the use of GP gut feeling as a referral criterion for cancer. Qualitative evidence suggested that GPs felt that gut feeling helped them to navigate the 'grey area' between what is normal and abnormal for their patient. GPs also

mentioned that using gut feeling helped them to interpret referral guidance or prompt further investigation or safety netting. Most GPs were supportive of gut feeling being used as a referral criterion, however there was some concern expressed in cases where a GP's experience was limited.
Quantitatively, one meta-analysis, paper 19, showed that the odds of a patient being diagnosed with cancer were 4 times higher in GPs that had a gut feeling compared to when GPs did not have a gut feeling. Diagnostic accuracy was correlated with skills, training, and years of experience as a GP as well as how well the GP knew the patient.
In England, advice and guidance (A&G) services exist which allow primary care professionals to seek advice from other clinicians (usually specialists) prior to, or instead of, referral. These services may be helpful for clinicians to sense-check gut feeling and get advice from other experienced specialists. Services such as these might be useful in Scotland to help ensure gut feeling is being acted on appropriately.

Paper number	Study	Summary	Notes
18	Smith CF, Kristensen BM, Andersen RS, Hobbs FR, Ziebland S, Nicholson BD. GPs' use of gut feelings when assessing cancer risk: a qualitative study in UK primary care. Br J Gen Pract. 2021;71(706):e356-e363. Published 2021 Apr 29. doi:10.3399/bjgp21X714269	This study explored the role of gut feeling in primary care clinical decision making by conducting interviews with GPs who had recently referred patients to a pathway for non-specific symptoms of cancer based on gut feelings (the SCAN pathway in Oxfordshire). Some GPs noted discomfort with 'gut feeling' being 'unscientific' but many felt that it was a marker of clinical experience. They stressed the importance of obtaining broad clinical experience before gut feelings could be considered reliable. Gut feelings were felt to require an ability to identify patterns and use observational skills, empathy and self-awareness. Many GPs shared that they felt they were uniquely placed in the health system to understand their patient as a whole person and to go beyond formalised medical knowledge and training to navigate the 'grey area' (the space between what is 'normal' and what is 'abnormal'). They also stated that clinical judgement is required to interpret referral guidance, especially for patients whose presentations may not fit entirely well. Gut feelings were also used to prompt further clinical investigations or gain a second	• Qualitative interview study with 19 GPs in Oxfordshire • Limitations: The study focused on GPs who had made a referral based on gut feeling. This group of GPs may differ from other GPs and may have different views on gut feeling. There is also a risk of recall bias.

		opinion. In most cases, GPs felt use of gut feelings were valuable in their clinical practice.	
19	Smith CF, Drew S, Ziebland S, Nicholson BD. Understanding the role of GPs' gut feelings in diagnosing cancer in primary care: a systematic review and meta-analysis of existing evidence. Br J Gen Pract. 2020;70(698):e612-e621. Published 2020 Aug 27. doi:10.3399/bjgp20X712301	This systematic review and meta-analysis aimed to (1) examine the current evidence on GP gut feelings of cancer (2) collate factors that are thought to prompt use of gut feelings (3) explore how gut feelings are used in primary care, and (4) establish the diagnostic utility of gut feelings. Many GPs struggled to articulate what gut feelings were but described it as largely an 'uneasy' feeling. Both verbal and non-verbal patient cues contributed to gut feelings, as well as GPs' knowledge and experience. In most cases, gut feeling served as a prompt to re-examine the patient's narrative, think beyond the most likely clinical explanation, and request further testing or specialist referral. In cases where GPs do not refer, they reported managing gut feelings through safety netting or watchful waiting. The researchers performed a meta-analysis with 4 studies to quantify the diagnostic value of gut feelings. The results showed that the odds of a patient being diagnosed with cancer were 4 times higher than when no gut feeling was recorded (OR 4.24, 95% CI 2.26-7.94).	• Systematic review and meta-analysis • N=12 studies included (4 from the UK, and the rest from Europe). Overlap with Donker et al., study included below. • The cohort and cross-sectional study included were noted as high risk of bias, but the qualitative papers were of better methodological quality. • Limitations: Variation in terminology used; no objective measure of gut feelings; imbalance in study populations related to age, sex, and years of GP experience.
20	Smith CF, Kristensen BM, Andersen RS, Ziebland S, Nicholson BD. Building the case for the use of gut feelings in	This study explored the patient perspective for those that had been referred to a non-specific symptoms pathway based on a gut feeling.	• Qualitative interview study • N=21 patients • Oxfordshire, UK

	cancer referrals: perspectives of patients referred to a non-specific symptoms pathway. Br J Gen Pract. 2021;72(714):e43-e50. Published 2021 Dec 31. doi:10.3399/BJGP.2021.0275	Most patients felt that GP gut feeling was comprised of clinical knowledge, experience, and empathy, and was also impacted by the relationship between the GP and the patient. Longer and more continuous relationships between patients and GPs would lead to more reliable gut feelings and better communication in consultations. Most felt that gut feeling is justified as a referral criterion, however some felt that referrals should only be made based on gut feeling if they were supported by concerning clinical symptoms. For many patients, the presence of concern in a GP, with training, skills, and experience, and the potential to rule out or diagnose serious disease earlier, provided legitimacy for the use of gut feelings. Patients also noted the issue of the 'grey area' in primary care and that gut feeling can help navigate the distinction between serous and non-serious illness and inform further investigations.	• Limitations: all patients were White British which limits understanding of ethnic perspectives; interviews were conducted via telephone which may limit visual cues and quality.
21	Donker GA, Wiersma E, van der Hoek L, Heins M. Determinants of general practitioner's cancer-related gut feelings-a prospective cohort study. BMJ Open. 2016;6(9):e012511. Published 2016 Sep 13. doi:10.1136/bmjopen-2016-012511	This study aimed to quantitatively assess GP gut feeling of cancer. Of 366 patients, 35% had a cancer diagnosis after 3 months. The PPV of gut feeling of cancer was related to how long the GP knew the patient and the patient's age. The odds for an accurate gut feeling increased with a factor of 1.04 (95% CI 1.01-1.06, p=0.004) for every year the GP knew the patient and with a factor of 1.02 (95% CI 1.00-1.03, p=0.03) for every year a patient becomes older. The GPs age and years of experience also influenced the PPV of gut feeling. The odds for an accurate gut feeling increased with a factor of 1.04 (95% CI 1.01-1.07, p=0.007) for every year a GP becomes older and a factor of 1.04 (95% CI 1.01-1.08, p=0.002) for every year of additional experience. When	• Prospective cohort study • Netherlands • Data collected from the Sentinel Practices of NIVEL Primary Care database • January 2010 to December 2013, including 44 general practices • N=366 questionnaires on different patients completed by 59 different GPs • Limitations: Small sample size per GP; no control group; large variation in the number of gut feelings GPs reported, likely linked

		the researchers conducted a multivariate analysis, only the patient's age and GP's age remained significant, with the odds increasing by a factor of 1.02 for every year a patient becomes older and a factor of 1.03 every year a GP becomes older. Weight loss (24%), rare GP visits (this was not defined in the study) (22%), and duration of symptoms (19%) were the most frequent triggers for GP gut feeling. These triggers resulted in a cancer diagnosis in 25-28% of the patients after 3 months. Most GPs acted immediately on gut feeling by referring to specialist (64%), requesting a lab test (32%), X-ray (21%), or ultrasound examination (13%), while 5% decided to engage in watchful waiting.	to the fact that gut feeling can be subconscious and therefore, under reported; variation in what 'gut feeling' is; may not be appliable to a UK population.
22	Yao M, Kaneko M, Watson J, Irving G. Gut feeling for the diagnosis of cancer in general practice: a diagnostic accuracy review. BMJ Open. 2023;13(8):e068549. Published 2023 Aug 11. doi:10.1136/bmjopen-2022-068549	This review summarises the evidence on the diagnostic accuracy of gut feeling for the diagnosis of cancer. The diagnostic accuracy for gut feeling was: • Sensitivity = 0.40 (SE 0.06, 95% CI 0.28 o 0.53) • Specificity = 0.85 (SE 0.04, 95% CI 0.75 to 0.92) The researchers found that when the prevalence of cancer in the symptomatic population presenting to primary care exceeds 1.15%, then the PPV of gut feeling for cancer reaches 3%. They note that in the UK, the prevalence of symptomatic cancer is ~3.5% and is increasing over time.	• Review and meta-analysis of studies of diagnostic accuracy • N=4 studies included, mostly European (also in Smith CF, 2020 review) • One study was of high risk of bias, and all other studies had at least one unclear risk which limits methodological quality. • Limitations: small number of studies; high level of heterogeneity between studies due to range of definitions of 'gut feeling' and differences in populations studied; patient

			characteristics or GP characteristics (i.e., level of experience, etc.) was not considered; did not look at specific cancer sites.
23	Oliva-Fanlo B, March S, Gadea-Ruiz C, Stolper E, Esteva M; CORap group. Prospective Observational Study on the Prevalence and Diagnostic Value of General Practitioners' Gut Feelings for Cancer and Serious Diseases. J Gen Intern Med. 2022;37(15):3823-3831. doi:10.1007/s11606-021-07352-w	This study assessed the prevalence and determinants of gut feelings in general practice, explored how patients are managed if a GP experiences gut feeling, and quantified the diagnostic value of gut feelings for serious disease. The researchers used the Gut Feelings Questionnaire (GFQ) in the study to assess whether a GP had a gut feeling during a consultation. GPs experienced an alarming gut feeling in 21.7% of consultations. A sense of alarm was more common in consultations where GPs employed more analytical reasoning skills, as well as with older patients, when a patient presented with at least one cancer-associated symptom, in rural areas, or when the native language of the patient differed. If a GP experienced an alarming gut feeling, they were more likely to order lab tests, radiological investigations, or other primary care procedures, as well as refer to outpatient or emergency services. Patients also visited their GP more frequently after GPs raised a sense of alarm. The odds that a patient would receive a new diagnosis of cancer or other serious disease within 2 months or 6 months	• Prospective observational study • Spain • The GFQ has been validated in a Dutch context and has since been translated into 7 languages. • N=155 GPs reporting on 1,487 patients • Limitations: Data lacked the power needed to draw conclusions about diagnostic value of gut feeling related only to cancer; COVID-19 impacted follow-up; Spanish study so may not be entirely generalisable to UK.

		were higher after GP sense of alarm (adjusted OR=5.3 and 3.6, respectively.) After 2 months, the sense of alarm for cancer or a serious disease had a sensitivity of 59.3%, specificity of 79.4%, a PPV of 12.2%, an NPV of 97.5%. After 6 months, the PPV was 18.3% and the NPV was 94.5%.	

Topic: Investigation findings			
Summary: Prior to referral in Scotland's RCDSs, filter function tests must be completed in primary care. These tests can include a full blood count (FBC), C-reactive protein blood test (CRP), erythrocyte sedimentation rate (ESR), liver function tests (LFTs), ferritin and iron studies, thyroid function tests (TFTs), HbA1c, bone biochemistry, FIT, prostate-specific antigen (PSA) test (men), and CA125 (women). Evidence supports the use of FBC, CRP, ESR, LFTs, ferritin and iron studies, HbA1c, and FIT within cohorts of people with certain non-specific symptoms and within the RCDSs in Scotland. Most studies showed that abnormal blood test results in combination with non-specific symptoms in older adults had a PPV >3% for cancer, with the PPV typically being higher in men than in women. Based on this finding, including these tests in tumour-site specific pathways in addition to RCDSs should be considered. Studies also showed that for patients with non-specific symptoms, these tests were more often requested, supposedly because they help support clinical assessment and are easy to complete and low risk. There could be opportunity to encourage use of these tests more often in this cohort of patients. Some more specific tests, such as bone profiles and serum electrophoresis appear to be more requested for patients with back or bone pain only, and amylase tests were more common among people with abdominal pain. There was no evidence on the diagnostic accuracy of TFTs, urinalysis, chest X-ray, CA-125 or PSA test in patients with only non-specific symptoms such as fatigue, weight loss, abdominal pain/bloating, nausea, loss of appetite, or bone pain.			
Paper number	Study	Summary	Notes
BLOOD TESTS (INCL. TUMOUR BIOMARKER TESTS)			
24	Cranfield BM, Abel GA, Swann R, et al. Pre-Referral Primary Care Blood Tests and Symptom Presentation before Cancer Diagnosis: National Cancer Diagnosis Audit Data. Cancers	This study analysed data on the use of blood tests in primary care in patients subsequently diagnosed with cancer to understand how often and when blood tests were used. Blood tests were most frequently ordered for patients experiencing non-specific symptoms such as fatigue, weight	• NCDA 2018 • N=39,751 incident cancer cases • Data on the following blood tests: ○ Generic: full blood count (FBC), urea and

	(Basel). 2023;15(14):3587. Published 2023 Jul 12. doi:10.3390/cancers15143587	loss, change in bowel habit, and abdominal pain. The most common tests were FBC, U&E, LFTs, and (to a slightly lesser extent) inflammatory markers (IMs). Ferritin and bone profile were used less frequently to generic blood tests but were more common among those with non-specific symptoms. Specifically, bone profile and serum electrophoresis were more commonly used in patients with back pain or bone pain, and amylase tests were more common for patients with upper abdominal pain. Men with urological symptoms most commonly had a PSA test, although PSA test use was also high among men presenting with back pain (35%) and bone pain (47%) as well. CA125 testing was most common in patients with non-specific abdominal or urinary symptoms, however 1 in 5 women presenting with loss of appetite or weight loss also had CA125 testing. Blood testing occurred in 51-52% of patients presenting with a symptom that has a PPV of 0.01–1.99% and increased to 64% when presenting with a symptom that has a PPV of2.00-2.99%. However, in patients presenting with symptoms with a PPV > 3%, testing declined.	electrolytes (U&E), liver function tests (LFTs), and inflammatory markers (IM), ○ Organ-specific blood tests: cancer biomarkers, serum protein electrophoresis, ferritin, bone profile, and serum amylase. • Limitations: time frame between symptom and blood test is not captured in the NCDA; case-only analysis so could not compare to those who presented with same symptoms but did not have cancer.
12	Rafiq M, Renzi C, White B, et al. Predictive value of abnormal blood tests for detecting cancer in primary care patients with nonspecific abdominal	This paper quantified the PPV of 19 abnormal blood tests[10] for detecting cancer in patients with non-specific abdominal pain or abdominal bloating.	• CPRD data linked to cancer registry • 2007-2016 • N=425,549 patients with a new episode of abdominal pain and

[10] Included blood tests were: PSA; acute phase reactants (platelets, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), ferritin and total white blood cell count (WBC)); markers of iron deficiency or anaemia (ferritin and haemoglobin); liver, renal or bone profile tests (bilirubin, albumin, AST, ALT, ALP, calcium, and creatinine); glycosylated haemoglobin (HbA1c).

	symptoms: A population-based cohort study of 477,870 patients in England. PLoS Med. 2024;21(7):e1004426. Published 2024 Jul 30. doi:10.1371/journal.pmed.1004426	Patients with any abnormal blood test results had elevated cancer risk than those with all-normal blood test results. All abnormal blood tests in men aged 60+ had a PPV greater than 3%. Specifically, in men: • Anaemia and raised PSA both had a PPV >3% in all age cohorts, with risk increasing with age. • Raised platelets, raised calcium, and raised ALP had a PPV > 3% in age cohorts >40. • Low albumin and low ferritin had a PPV > 3% in those 30-39 and over 50 years old only. • Raised CRP, raised ESR, raised total white blood cells (WBCs), and raised ferritin all had a PPVs >3 % in age cohorts 50 and over only. • Raised alanine aminotransferase (ALT), low total WBCs, low platelets, raised bilirubin, raised creatinine, and raised HbA1c all had a PPV >3% in those over 60 only. In women, all abnormal blood tests had a PPV greater than 3% in those aged 70+, and most had a PPV greater than 3% in those aged 60+. Specifically, in women: • Raised CA125 had a PPV >3% in all age cohorts, with risk increasing with age. • Raised platelets and low albumin had a PPV >3% in age cohorts 40 and older only. • Anaemia, raised CRP, raised total WBCs, raised ferritin, and raised creatinine all had a PPV >3% in age cohorts 50 and older only.	N=52,321 patients with new abdominal bloating. • Limitations: population includes patients who had already been selected by GPs to have testing which means that estimates may be lower for the broader population of people presenting with abdominal pain or bloating.

		• Raised calcium, raised AST, raised ESR, raised ALT, raised bilirubin, and raised HbA1c all had a PPV >3% in age cohorts 60 and over only. • Low ferritin and low platelets had a PPV >3% in age cohorts 70 and over only. The researchers created a model to explore how many more urgent referrals could be generated if blood test results were additionally considered in referral criteria. This model indicated that for every 1,000 patients with abdominal bloating who had blood tests, 74 additional urgent referrals could be generated, and 10 referrals could be avoided. For abdominal pain the respective numbers were up to 68 additional referrals and 2 referrals avoided. This is assuming guidelines are fully adhered to.	
25	Cranfield BM, Koo MM, Abel GA, et al. Primary care blood tests before cancer diagnosis: National Cancer Diagnosis Audit data. Br J Gen Pract. 2023;73(727):e95-e103. Published 2023 Jan 26. doi:10.3399/BJGP.2022.0265	This study examined how often patients diagnosed with cancer were investigated using common blood tests (i.e., FBC, U&E, or LFTs) in primary care as part of their initial presentation. 41% of patients had at least one common blood test in primary care before being diagnosed with cancer. The odds of getting a blood test varied by symptom group: • Non-alarm symptom alone – OR 2.75 (95% CI = 2.61 to 2.89) compared to alarm symptom alone. • Both alarm and non-alarm symptom - OR 3.68 (95% CI = 3.44 to 3.93) compared to alarm symptom alone. Cancer-sites had varying levels of testing:	• NCDA 2018 • N=39,752 • Limitations: time frame between symptom and blood test is not captured in the NCDA; presented symptoms may be under-recorded.

		• For pancreatic, myeloma, liver, colon, stomach, and leukaemia, FBCs, U&E, and LFTs were ordered in over 50% of patients. • Biomarker tests were most frequently used in patients diagnosed with prostate (86%) and ovarian cancer (47%). • Inflammatory markers were more frequent in those diagnosed with myeloma (49%), pancreatic cancer (42%), liver cancer (37%), carcinoma of unknown primary (36%), non-Hodgkin lymphoma (35%), leukaemia (33%), and colon cancer (33%). • 53% of patients diagnosed with myeloma had serum protein tests and 36% had bone profile tests. • 34% of patients diagnosed with colon cancer and 28% of those diagnosed with stomach cancer had ferritin tests • 17% of patients diagnosed with pancreatic cancer had amylase tests.	
26	Næser E, Møller H, Fredberg U, Frystyk J, Vedsted P. Routine blood tests and probability of cancer in patients referred with non-specific serious symptoms: a cohort study. BMC Cancer. 2017;17(1):817. Published 2017 Dec 4. doi:10.1186/s12885-017-3845-9	This study examined the diagnostic value of blood tests when cancer is suspected in patients with non-specific serious symptoms. The median number of abnormal blood tests was 7 for patients diagnosed with cancer compared to 3 for patients not diagnosed with cancer. Probability of cancer increased with 6 or more abnormal blood tests. Post-test cancer probability was highest for the following abnormal blood tests: • High human chorionic gonadotropin (hCG) – 44.4% • High M protein - 37.4%	• Prospective cohort study • Denmark • N=1,499 patients referred by GP to blood test panel at Silkeborg Regional Hospital in Denmark between Feb 2011 and December 2013 • Limitations: did not include information of comorbidity; reference ranges were compared to the Department of Clinical Biochemistry and not specific to cancer; Danish study

		• High CA-125 – 36.8% Cancer was also diagnosed in more than 25% of patients with high bilirubin, low immunoglobulin A (IgA), high calcium, high metamyelocyte count, high alkaline phosphatase, high neutrophil count or low platelet count.	so may not be as applicable to the UK population.
27	Watson J, Salisbury C, Banks J, Whiting P, Hamilton W. Predictive value of inflammatory markers for cancer diagnosis in primary care: a prospective cohort study using electronic health records. *Br J Cancer*. 2019;120(11):1045-1051. doi:10.1038/s41416-019-0458-x	This study aimed to quantify the PPV of inflammatory markers (i.e., CRP, ESR, or plasma viscosity (PV)) for cancer diagnosis in primary care. 3.53% (95% CI 3.37-3.70) of those with a raised inflammatory marker were diagnosed with cancer compared to 1.50% (95% CI 1.43-1.58) of those with normal inflammatory markers (p<0.001). The diagnostic accuracy of abnormal inflammatory marker tests were: • CRP: sensitivity 46.1% (95% CI 44-48.1), specificity 75.4% (95% CI 75.1-75.6), diagnostic odds ratio 2.29 (95% CI 2.12-2.46) • ESR: sensitivity 43.6% (95% CI 41.4-45.9), specificity 75.6% (95% CI 75.3-75.9), diagnostic odds ratio 1.98 (95% CI 1.83-2.15) • PV: sensitivity 49.7% (95% CI 44.0-55.4), specificity 72.1% (95% CI 71.4-72.8), diagnostic odds ratio 1.69 (95% CI 1.43-1.99) The PPV was >5% for those with raised inflammatory markers associated with cough, back pain, nausea and vomiting, and chest pain. In general, risk of cancer exceeded 3% in men over 50 and women over 60 years with a raised inflammatory marker. Of	• CPRD linked to cancer registry • N=155,646 patients; of these 71.6% had a CRP test, 58.1% had an ESR test, and 10.1% had a PV test. • Limitations: lack of full data on the reason for inflammatory marker testing.

		note, those who tested normal have higher incidence than those entirely untested but still lower than those with raised tests. In particular, men over 60 with normal inflammatory markers had a cancer incidence higher than 3%. The paper provides a breakdown of types of cancer sites diagnosed in those with generally raised inflammatory markers, however they do not break this down further by abnormal CRP, ESR, and PV. Also note that some sample sizes are quite small, but that more data exists for sites such as lung and colorectal.	
28	Nicholson BD, Oke JL, Aveyard P, Hamilton WT, Hobbs FDR. Individual inflammatory marker abnormalities or inflammatory marker scores to identify primary care patients with unexpected weight loss for cancer investigation? Br J Cancer. 2021;124(9):1540-1542. doi:10.1038/s41416-021-01282-4	This study investigated whether inflammatory marker scores (modified Glasgow prognostic score (mGPS), the neutrophil-lymphocyte score (NLS), and the platelet-lymphocyte score (PLS)) could be used to select patients with UWL for further cancer investigation as opposed to using individual inflammatory marker abnormalities (including albumin, CRP, lymphocyte count, neutrophil count, and platelet count). The PPV for individual inflammatory marker tests were: • Low albumin: ○ ≥18 years old: 7.06 (95% CI 5.43-8.99) ○ 40-59: 3.81 (1.05-9.47) ○ 60-79: 10.6 (7.65-14.20) ○ ≥80: 4.94 (2.90-7.79) • Raised CRP: ○ ≥18 years old: 6.26 (5.34-7.29) ○ 40-59: 3.27 (1.75-5.53) ○ 60-79: 7.71 (6.21-9.43) ○ ≥80: 7.01 (5.31-9.05) • Raised neutrophils:	• The mGPS combines low albumin and raised CRP, the NLS combines neutrophils and lymphocytes, and the PLS combined platelets and lymphocytes. The researchers derived the following scores to be used in this analysis: ○ mGPS = 2 (CRP > 10 mg/l and albumin < 35 g/l) ○ NLS = 2 (NC > 7.5×10^9/l and LC < 1.5×10^9/l) ○ PLS = 2 (PC > 400×10^9/l and LC < 1.5×10^9/l). • N=12,024 people with UWL and complete inflammatory markers recorded. • Limitations: Population of people tested are normally at higher risk of cancer compared to

		○ ≥18 years old: 6.14 (4.93-7.54) ○ 40-59: 3.02 (1.39–5.66) ○ 60-79: 7.36 (5.38–9.79) ○ ≥80: 9.07 (6.28–12.56) • Low lymphocytes: ○ ≥18 years old: 2.90 (2.37–3.52) ○ 40-59: 1.91 (1.02–3.24) ○ 60-79: 3.74 (2.80–4.89) ○ ≥80: 3.26 (2.29–4.49) • Raised platelets: ○ ≥18 years old: 8.56 (6.42–11.13) ○ 40-59: 6.87 (3.19–12.64) ○ 60-79: 9.62 (6.49–13.61) ○ ≥80: 10.08 (5.32–16.95) The PPV for the inflammatory marker scores were: • mGPS=2: ○ ≥18 years old: 8.85 (7.01–10.99) ○ 40-59: 5.32 (1.75–11.98) ○ 60-79: 12.27 (9.12–16.02) ○ ≥80: 6.87 (4.40–10.12) • NLS=2: ○ ≥18 years old: 9.60 (6.98–12.80) ○ 40-59: 8.00 (2.22–19.23) ○ 60-79: 11.05 (6.88–16.55) ○ ≥80: 10.24 (6.08–15.89) • PLS=2: ○ ≥18 years old: 10.67 (6.55–16.17) ○ 40-59: 20.83 (7.13–42.15) ○ 60-79: 12.36 (6.33–21.04)	those untested; could not stratify by cancer site and stage.

		○ ≥80: 5.36 (1.12–14.87) For most age-groups with unexpected WL, the PPV for a single abnormal inflammatory marker or a raised score was above 3%.	
FAECAL IMMUNOCHEMICAL TEST (FIT)			
29	Bailey SER, Abel GA, Atkins A, et al. Diagnostic performance of a faecal immunochemical test for patients with low-risk symptoms of colorectal cancer in primary care: an evaluation in the South West of England. Br J Cancer. 2021;124(7):1231-1236. doi:10.1038/s41416-020-01221-9	This study evaluated the diagnostic performance of FIT in general practice for those with low-risk symptoms* of possible colorectal cancer. Low-risk symptoms included: • Those 50+ with unexplained abdominal pain or weight loss • Those aged 50-60 with a change in bowel habit or iron-deficiency anaemia • Those aged 60+ with anaemia even without iron deficiency. A f-Hb ≥10 μg Hb/g faeces (test positive) was recorded for 618 patients (15.9%). The diagnostic accuracy of FIT for cancer in this population of patients presenting with 'low risk' symptoms was: • PPV: 7.0% (95% CI 5.1-9.3) • NPV: 99.8% (95% CI 99.5-99.9) • Sensitivity: 84.3% (95% CI 71.4-93.0) • Specificity: 85.0% (95% CI 83.8-86.1). The most common cancer diagnosed was colorectal, but a small number oesophago-gastric and pancreatic cancers were diagnosed as well. A f-Hb level of 37 μg Hb/g faeces corresponded to an individual's colorectal cancer risk of 3%. *at the time this study was conducted, these 'low-risk' symptoms were the only symptoms that warranted a FIT prior to referral, as	• Southwest of England • June 2018 – December 2018 • N=3,890; 41.6% aged ≥50 years with abdominal pain or weight loss; 30.7% aged <60 years with changes in bowel habit or iron-deficiency anaemia; 23.9% aged >60 years and with anaemia (in absence of iron deficiency). • A threshold value of ≥10 μg Hb/g faeces defined a positive test • Limitations: Only tests that were completed and returned were considered; symptom data could not be verified; small number of cancers may have been missed.

		per NICE DG30 guidelines. These guidelines have since been updated.	

Topic: Evidence from non-specific symptom pathways			
Summary: Non-specific symptom referral pathways have been created across the UK. Service evaluations have been published in Scotland, England, and Wales. Most of these pathways show a cancer conversion rate between 7-12% which is higher than conversion rates seen in most urgent suspected referral pathways. For Scotland specifically, evaluations have shown a conversion rate of between 11-12%, with lung and upper GI HPB being most diagnosed. Most cancers are diagnosed at a late stage, however for rarer cancers such as pancreatic, kidney or non-Hodgkin's lymphoma 20-25% of early-stage cancers are diagnosed. A significant number of serious non-cancer conditions are also diagnosed within these pathways. Qualitative findings show positive reflections from both patients and professional staff. Areas of improvement include ensuring GPs are aware of referral criteria, ensuring timely access to onward referral pathways, and more guidance for patients who exit the pathway with no diagnosis or explanation for symptoms. Overall, service evaluations are limited by the fact that they do not report on patient outcomes yet, nor do they provide a sense of how the pathway is working in relation to other cancer pathways (such as site-specific urgent referral pathways). The evaluations also do not compare to a patient's journey before these pathways existed, so it is difficult to tease out the pathway's impact. Note that one systematic review which summarises a large body of evidence from Denmark has been included to supplement insights (paper 37).			
Paper number	Study	Summary	Notes
30	University of Strathclyde Glasgow. Interim Report of the Evaluation of Rapid Cancer Diagnostic Services. 2022.	This report details the interim evaluation of the RCDSs in Scotland. This is a fast-track referral and diagnostic pathway for patients with non-specific symptoms. The evaluation involved a quantitative and qualitative analysis on 3 RCDS centres: NHS Ayrshire & Arran, NHS Dumfries & Galloway and NHS Fife. **Quantitative analysis** • Overall cancer incidence of 12.1%; non-cancer diagnosis in 33.8%; 54% had no diagnosis.	• Qualitative sample had only 8 patient responses included; only 10 professionals included. • Majority of qualitative sample was White British or White Scottish and mostly male. • No patients interviewed had received a cancer diagnosis.

		• The mean age of cancer diagnosed was 73.9 years • The most common cancer sites diagnosed were lung (~19%), upper GI HPB (~16%), urological (~10%), haematological (~8%), and colorectal (~8%). • The most common symptoms/signs experienced by patients referred to the pathway who were subsequently diagnosed with cancer was unexplained weight loss (80%), GP 'gut feeling' (~70%), fatigue (~70%), new unexplained pain (abdominal/back/bone) (~60%), and new unexplained laboratory results (~60%). • Most patients subsequently diagnosed with cancer presented with 3 or more non-specific symptoms. • The mean time from RCDS referral to outcome was 14 days. **Qualitative analysis** The qualitative analysis included interviews with patients who have been through the pathway and professionals working in the pathway. • Most patients reported extremely positive perceptions regarding the pathway and pathway timings. Most felt they had clarity on the pathway, were able to ask questions and request more information, and felt like they had a clear contact. • Some patients felt frustration with timeliness and access to onward referral pathways in secondary care or had limited/no follow-up with their GP after being discharged back to them after receiving no diagnosis of cancer. • Professionals working in the service were overall positive and satisfied with the pathway.	

		• Only 66% of primary care professionals felt familiar with referral criteria, meaning referral criteria could be clearer.	
31	University of Strathclyde Glasgow. NHS Scotland Rapid Cancer Diagnostic Services (RCDS). Evaluation Summary. 2024.	This was the final full evaluation of the RCDS in Scotland. This evaluation included the following RCDS sites: NHS Ayrshire & Arran, NHS Dumfries & Galloway, NHS Fife (all launched in 2021 and included in the interim report as well), NHS Lanarkshire and NHS Borders (launched in April 2023 and only evaluated in this report). The cancer conversion rate was 11.9%. A non-cancer diagnosis was given to 40.7% of patients. Most patients who were not diagnosed with cancer were redirected back to primary care. The most common cancers diagnosed were lung and HPB cancers. Unexplained weight loss was the most common symptom. Additionally, unexpected lab results, GP 'gut feeling' and nausea/appetite loss were more common in patients subsequently diagnosed with cancer. Qualitative findings were very similar to those found in the interim report (summarised above).	• 22 professional staff interviewed; 50 staff surveyed. • 32 patients interviewed; 601 patients surveyed. • Limitations: No interviews conducted with those who had a resultant cancer diagnosis
32	Wales Cancer Network. Rapid diagnosis clinic programme evaluation – Final report. 2023.	This report details the final evaluation of the Rapid Diagnosis Clinics (RDCs) programme in Wales. This is the fast-track diagnostic pathway for patients with non-specific symptoms. Six of seven health boards in Wales had implemented RDCs at the time of this evaluation, with the remaining area of Powys being referred to RDCs in neighbouring health boards.	• Data for conversion rates mainly calculated from 2022-2024 data • The national programme for RDCs was started in December 2020

		Quantitative analysis • Cancer conversion rate of 7%; 34% significant non-cancer diagnoses referred to secondary care; 23% non-cancer diagnoses referred back to GP; 35% no diagnosis referred back to GP. **Qualitative reflections** • High level of job satisfaction reported by RDC staff • There was improved communication between primary and secondary care staff and improved collaboration and networking between Health Boards and RDC teams • There was sometimes inconsistent quality of referrals from GPs.	
33	Dolly SO, Jones G, Allchorne P, et al. The effectiveness of the Guy's Rapid Diagnostic Clinic (RDC) in detecting cancer and serious conditions in vague symptom patients. Br J Cancer. 2021;124(6):1079-1087. doi:10.1038/s41416-020-01207-7	This paper evaluated the Guys' and St. Thomas RDC for patients with non-specific symptoms in order to establish cancer detection rate. The most commonly reported symptoms were weight loss (53.7%), pain (47.2%) and abdominal symptoms (36.1%). Most patients reported multiple symptoms (median = 3) and multiple comorbidities (i.e., 20% were current smokers, 42% had polypharmacy). Patients subsequently diagnosed with cancer were more likely to be male, older, and present with recent weight loss. There was also an increased rate of anaemia (43 vs 27%), thrombocytosis (18 vs 6%), raised CRP (68 vs 36%) and liver dysfunction (18 vs 8%) in cancer vs non-cancer groups.	• Data included from patients referred to the Guys' and St. Thomas RDC for non-specific symptoms between December 2016 – June 2019 • Note that Guys' and St Thomas RDC began in 2016. • N=1,341

		The cancer conversion rate was 7.3%, with lung (16.1%), haematological (12.9%) and colorectal (11.8%) being the most common sites. 40% of cancers were metastatic. 35.8% of people were diagnosed with a serious benign condition and were referred onward to a secondary care specialist.	
34	Vasilakis C, Forte P. Setting up a rapid diagnostic clinic for patients with vague symptoms of cancer: a mixed method process evaluation study. BMC Health Serv Res. 2021;21(1):357. Published 2021 Apr 17. doi:10.1186/s12913-021-06360-0	This was an evaluation study of the Cwm Taf UHB RDC in Wales. Approximately 30% of patients had 3 or more vague symptoms. Weight loss was the most common symptom, with 100 patients also concordantly presenting with lack of appetite as well. 10.3% of patients were referred onwards to a specialist cancer pathway, while an additional 1.9% had a suspected cancer with further investigations needed. 22.3% had a non-cancer diagnosis and were referred to secondary care, while 13.6% had a non-cancer diagnosis but were referred back to their GP. The most common cancer site to be diagnosed with was gastro-oesophageal (21.4%), urological (16.7%), lung (16.7%), unknown primary (14.3%), colorectal (11.9%), and haematological (11.9%). Qualitatively, GP interviews showed positive support for RDCs, including comments on the ease of referral and diagnostic testing, speed of diagnosis, and reduction of stress for GPs to be able to refer patients for vague symptoms. However, GPs recommended continued awareness of RDCs, more data collection such as waiting times and outcomes, and reviewing the requirement for pre-RDC tests for patients.	• N=574 • The RDC was launched in 2017 • Data from patients attending the RDC between July 2017 – March 2019
35	Chapman D, Poirier V, Vulkan D, et al. First results from five	This study evaluated the Accelerate, Coordinate, Evaluate (ACE) Programme's pilot Multi-disciplinary Diagnostic Centres (MDCs),	• N=2961

	multidisciplinary diagnostic centre (MDC) projects for non-specific but concerning symptoms, possibly indicative of cancer. Br J Cancer. 2020;123(5):722-729. doi:10.1038/s41416-020-0947-y	and reported on patient characteristics, cancer diagnoses and stage at diagnosis. Of the patients referred, 40% had some degree of physical impairment and 27% had moderate or severe comorbidities. 28% of patients had 3 or more previously primary care consultations. The most common symptom was weight loss, followed by GP gut feeling. 55% reported symptom duration of 3 months or more. 8% of patients referred were diagnosed with cancer, with most being upper GI (22%) or lung (22%). 13% had haematological, 13% had lower GI, 13% had urological, 6% had breast, 3% had sarcoma, 8% had other, and 1% had an unknown primary cancer. Majority of cancers were stage III or IV, however there were still significant proportions for stage I and II for upper GI and lung (Upper GI: 4.3% stage 1 and 21.3% stage 2; Lung 25.5% stage I and 8.5% stage 2).	• The ACE MDC programme had 10 operating pilot centres in England (Airedale, Greater Manchester (×2), Leeds, London (×5) and Oxford) launched in 2016-2017. These pathways were for patients with non-specific symptoms of cancer and allowed more rapid diagnosis testing. The ACE MDC programme was the foundation for the non-specific symptoms pathway later rolled out throughout England. • Limitations: no comparison group; time-limited evaluation; cannot comment on long term patient outcomes; local variation between sites; over 50% of stage data missing for haematological cancers.
36	Chapman D, Poirier V, Fitzgerald K, Nicholson BD, Hamilton W; Accelerate Coordinate Evaluate Multidisciplinary Diagnostic Centre projects. Non-specific symptoms-based pathways for diagnosing less common cancers in primary care: a service evaluation. Br J Gen	This study was a service evaluation of the MDC pilot projects. The researchers aimed to examine the less common cancers identified during the MDC pilots. The overall cancer conversion rate was 7% with 4% of the cancers diagnosed being of less common cancer types (most common were kidney cancer, non-Hodgkin's lymphoma, and pancreatic cancer). 79% of less common cancers were diagnosed at late stage, however for some cancer types, earlier	• Service evaluation • December 2016-March 2019 • N=5134 • Limitations: relatively small numbers of some individual less common cancers; no comparison group.

	Pract. 2021;71(712):e846-e853. Published 2021 Oct 28. doi:10.3399/BJGP.2020.1108	stages were still notable (i.e., kidney – 29% early stage; non-Hodgkin's lymphoma – 25% early stage; pancreas – 23% early stage). Patients with less common cancers were more likely to be older and slightly more likely to experience GP gut feeling than those with more common cancers. 68% of patients diagnosed with less common cancers presented with ≥2 non-specific symptoms, with the most common pairings being 'weight loss and nausea', and 'weight loss and GP gut feeling.	
37	Jensen E, Kristensen JK, Bjerglund RT, Johnsen SP, Thomsen JL. The pathway and characteristics of patients with non-specific symptoms of cancer: a systematic review. BMC Cancer. 2022;22(1):574. Published 2022 May 23. doi:10.1186/s12885-022-09535-y	This review aimed to summarize the physical, mental, and socioeconomic characteristics of patients with non-specific symptoms as well as how patients seek and obtain access to the health care system. Between 11-35% of people referred to a non-specific symptoms diagnostic centre or who triggered GP gut feeling were later diagnosed with cancer. Four studies showed haematological cancers as the most frequent diagnosis, whereas others showed breast, lung, or upper gastrointestinal as being most frequent. One-year mortality was between 28-44% for patients with a cancer diagnosed compared to 2-3% for patients not diagnosed with cancer. Danish studies found that time from referral to last visit day in the diagnostic centre ranged from 7-10 days whereas the Swedish study found that time from first GP contact to diagnosis was median 37 days.	• Systematic review • N=12 studies included (n=6 from Denmark, 1 from Sweden, 2 from UK, and 1 from Netherlands) ○ All papers except the Netherlands investigated patients with non-specific symptoms who were referred to a diagnostic centre for investigation (non-specific symptoms pathway in most cases). • Studies were of good methodological quality. • This review particularly summarises the Danish evidence base well. • Overlap with over studies included in this review: Dolly SO,

		The most common symptom was weight loss, with fatigue, pain and loss of appetite also being frequently reported. Four Danish studies described comorbidities, with cardiovascular and lung diseases, as well as diabetes or previous cancer being the most common. One study showed that 10% of patients had a weekly consumption of alcohol over the national guidelines, and two studies showed that 61-70% of patients were former or current smokers.	et al (2021); Donker GA (2016), Chapman D (2020). • Limitations: Study populations were diverse and outcomes/characteristics reported varied across studies.

Emerging Topics

Blood test trend for cancer detection (BLOTTED) studies

Funded by CRUK, the BLOTTED studies are a combination of studies, led by Brian Nicolson and team at Oxford, that will use population-level primary care data to (1) describe trends in blood testing by cancer site, and overall (2) examine the association between blood test trends and cancer incidence, and (3) develop prediction models that use patient-level trends to quantify risk of cancer.[11,12] A systematic review has been published following objective 1,[13] and more studies on objective 2 and 3 are anticipated. These studies may provide valuable evidence for the consideration of blood test trends in patients suspected of cancer who present with non-specific symptoms.

PinPoint test

The PinPoint Test is a decision support tool for clinicians to aid in triaging that uses a machine learning algorithm to assess blood samples and determine a person's risk of having cancer, and subsequently provide faster diagnosis. The test algorithm has been developed for the

[11] BLOod Test Trend for cancEr Detection (BLOTTED): an observational and prediction model development study using English primary care electronic health records data. Available from: https://www.phc.ox.ac.uk/research/research-themes/cancer/projects/blotted
[12] Virdee PS, Bankhead C, Koshiaris C, et al. BLOod Test Trend for cancEr Detection (BLOTTED): protocol for an observational and prediction model development study using English primary care electronic health record data. Diagn Progn Res. 2023;7(1):1. Published 2023 Jan 10. doi:10.1186/s41512-022-00138-6
[13] Virdee PS, Collins KK, Friedemann Smith C, et al. The Association between Blood Test Trends and Undiagnosed Cancer: A Systematic Review and Critical Appraisal. Cancers (Basel). 2024;16(9):1692. Published 2024 Apr 26. doi:10.3390/cancers16091692

following pathways: breast, lower GI, upper GI, gynaecological, urological, lung, haematological, head and neck, and skin.[14] Because the test was designed to work with existing NHS technology and pathology laboratories, there is potential for fast rollout across the UK. Humber & North Yorkshire Cancer Alliance is investigating the potential of the PinPoint Test for use in non-site-specific pathways in Mid-Yorks Hospitals Trust and Leeds Teaching Hospitals Trust. A full evaluation needs to be completed and results awaited ahead of further testing and implementation.

Multi-cancer tests (MCTs) – SYMPLIFY Trial

The SYMPLIFY trial was an observational study to evaluate the performance of the Galleri test in symptomatic patients within the NHS in England and Wales. The Galleri test is an MCT developed by GRAIL that analyses a single blood sample in search of markers for multiple types of cancer. Results of the trial indicate a use for MCTs for direct investigation in people with non-specific symptoms or to aid in the decision-making of referral onto urgent cancer pathways.[15] However, a lot more research is needed to further understand the use of MCTs in symptomatic settings before implementation.

Other insights:

We've contacted Brian Nicholson (researcher and GP) to obtain unpublished results from a paper on the diagnostic accuracy of weight loss for cancer. This paper was originally published in the BMJ[16], but the authors submitted an expression of concern to the journal due to a selection bias that they identified in their approach to the research during external validation. This is why the original paper has not been included in the evidence review tables above. The authors have been working with the BMJ so that an updated manuscript will be published. Please note these have been shared in confidence prior to publication. The key study methods and findings are as follows:

- **Study aim:** to establish the PPV of UWL for cancer (overall, and by site) stratified by patient age, sex, smoking status, concurrent symptoms, signs and blood test results.
- **Data & population:** CPRD linked to NCRAS; N=326,240 identified with a code for UWL.

[14] Savage R, Messenger M, Neal RD, et al. Development and validation of multivariable machine learning algorithms to predict risk of cancer in symptomatic patients referred urgently from primary care: a diagnostic accuracy study. BMJ Open. 2022;12(4):e053590. Published 2022 Apr 1. doi:10.1136/bmjopen-2021-053590
[15] Nicholson BD, Oke J, Virdee PS, et al. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. Lancet Oncol. 2023;24(7):733-743. doi:10.1016/S1470-2045(23)00277-2
[16] Nicholson BD, Aveyard P, Price SJ, Hobbs FR, Koshiaris C, Hamilton W. Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study. BMJ. 2020;370:m2651. Published 2020 Aug 13. doi:10.1136/bmj.m2651

- **Results:**
  - The PPV of unexplained weight loss alone across cancers surpassed 3% in men aged 50+ and in women aged 60+, regardless of smoking status.
  - The following table summarises which signs/symptoms/test results, in combination with UWL, exceeded a risk of 3% and therefore, may warrant further investigation:

Age (years)	Men and women	Men	Women
>18		Anaemia, lymphadenopathy, hypoalbuminaemia, thrombocytosis, raised C-reactive protein level.	
≥40	Anaemia, abdominal mass, vomiting, hypoalbuminaemia, raised alkaline phosphatase, raised C-reactive protein level, thrombocyctosis.	Abdominal pain, appetite loss, constipation, dyspepsia, haempotysis, IDA, jaundice lymphadenopathy, leucocytosis, raised erythrocyte sedimentation rate.	Dysphagia
≥50		All[17]	Anaemia, abdominal mass, abdominal pain, appetite loss, chest signs, dysphagia, hypoalbuminaemia, iron deficiency anaemia, jaundice, leucocytosis, lymphadenopathy, nausea, pelvic mass, raised alkaline phosphatase, raised C-reactive protein level, raised

[17] For men, 'all' included: abdominal pain, appetite loss, back pain, constipation, dyspepsia, dysphagia, fatigue, haemoptysis, hoarse voice, itch, vomiting, weakness, abdominal mass, abnormal prostate exam, chest signs, anaemia, jaundice, lymphadenopathy, venous thromboembolism, low albumin, raised alkaline phosphate, raised bilirubin, low haemoglobin, raised platelets, raised WBCs, raised CRP, raised ESR, raised creatinine

			erythrocyte sedimentation rate, reflux, thrombocytosis, venous thromboembolism, vomiting.
≥60		All	All[18]

These results suggest that in men aged over 50 years old and women aged over 60 years old with UWL, and in younger adults when UWL occurs with additional symptoms, signs, or blood test abnormalities, referral for further investigation may be justified.

Suspected Cancer Referral Guidelines: NG12 and SRG

NG12	SRG
Symptoms of concern in children and young people 1.13.1 Take into account the insight and knowledge of parents and carers when considering making a referral for suspected cancer in a child or young person. Consider referral for children if their parent or carer has persistent concern or anxiety about the child's symptoms, even if the symptoms are most likely to have a benign cause. [2015] **Symptoms of concern in adults** 1.13.2 For people with unexplained weight loss, which is a symptom of several cancers including colorectal, gastro-oesophageal, lung, prostate, pancreatic and urological cancer: • carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely and • offer urgent investigation or a suspected cancer pathway referral. [2015] 1.13.3	The SRG currently do not have specific guidance divided up just for non-specific symptoms. Instead, non-specific symptoms may be included within guidance for specific cancer sites. For example, the guidance for an urgent suspicion of cancer chest X-ray for lung cancer includes unexplained and persistent loss of appetite and weight loss.

[18] For women, 'all' included abdominal pain, appetite loss, back pain, dysphagia, fatigue, nausea, reflux, vomiting, abdominal mass, chest signs, anaemia, jaundice, lymphadenopathy, pelvic mass, rectal mass, venous thromboembolism, low albumin, raised alkaline phosphate, raised ALT/AST, raised bilirubin, low haemoglobin, raised platelets, raised WBCs, raised CRP, raised ESR, raised creatinine

For people with unexplained appetite loss, which is a symptom of several cancers including lung, oesophageal, stomach, colorectal, pancreatic, bladder and renal cancer: • carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely and • offer urgent investigation or a suspected cancer pathway referral. [2015] 1.13.4 For people with deep vein thrombosis, which is associated with several cancers including urogenital, breast, colorectal and lung cancer: • carry out an assessment for additional symptoms, signs or findings that may help to clarify which cancer is most likely and • consider urgent investigation or a suspected cancer pathway referral. [2015] NG12 also has guidance organised by symptom, with a non-specific symptoms section and associated recommendations here.	

Appendix A:

Background on non-specific symptom pathways across the UK and how they compare to each other

In Scotland and Wales, each nation's non-specific symptoms pathways have similar referral criteria including unexplained weight loss, severe unexplained fatigue, unexplained laboratory findings, persistent nausea or appetite loss, new atypical pain (i.e., abdominal pain or bone pain), or GP 'gut feeling' of cancer. Patients must also understand the process, be well enough to go through the pathway, and there must be no other urgent cancer pathway for their clinical scenario. Prior to referral, GPs must request pre-referral tests, also known as filter function tests. In Scotland, these tests can include a FBC, CRP blood test, ESR, LFTs, ferritin and iron studies, TFTs, HbA1c, bone biochemistry, FIT, PSA test (men), and CA125 (women).

In England, referral criteria are largely the same, however unexplained weight loss is preferred to be documented as >5% over three months or with strong clinical suspicion, and symptoms such as nausea, fatigue, abdominal pain, and progressive pain (such as bone pain) should have occurred for four weeks or more. England also includes symptoms such as malaise and bloating and includes a chest X-ray as part of

its filter function tests. It should also be noted that pathways in all UK countries may have local variation in referral criteria or filter function tests.

Appendix B: Malignant spinal cord compression

Search terms: "malignant spinal cord compression", "spinal metastasis", "metastatic spinal cord compression", "spinal cord compression", "back pain", "spinal pain", pain, "progressive pain", walking, neurologic*, "bowel dysfunction", "bowel symptom", "bladder dysfunction", "bladder symptom", weakness, symptom, recognition, diagnosis, referral, "primary care", "general practice", risk

Background

Malignant spinal cord compression (also called metastatic spinal cord compression) can occur when cancer presses on or spreads to the spine.[19] Pressure on the spinal cord limits the ability of nerve function which can cause symptoms such as back pain, limb weakness, and difficulty walking. Spinal cord compression is considered an 'oncologic emergency' and must be treated quickly. To diagnose spinal cord compression, the standard imaging method is an MRI scan of the whole spine, but patients might also get a CT scan. Spinal cord compression is more common in cancers that commonly spread to the bone, including prostate, lung and breast cancer.

Evidence review

A foundational piece of evidence in this space was a prospective study was conducted between 1998-1999 at three Scottish cancer centres where the authors aimed to examine the diagnosis, management and outcomes of patients with malignant spinal cord compression and considered the patient, hospital clinician, and GP perspective.[20] This paper highlighted many of the symptoms that exist in the SRG today and it also prompted the creation of NICE guidance on malignant spinal cord compression.

[19] Cancer Research UK. Spinal cord compression. 2024. Available from: https://www.cancerresearchuk.org/about-cancer/coping/physically/spinal-cord-compression/about
[20] Levack P, Graham J, Collie D, et al. Don't wait for a sensory level--listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. Clin Oncol (R Coll Radiol). 2002;14(6):472-480. doi:10.1053/clon.2002.0098

While there is some older evidence in this space, no recent (post-2015) UK-based studies on symptom presentation or predictive values for patients subsequently diagnosed with malignant spinal cord compression were identified in this review or in 2023 evidence review by NICE on metastatic spinal cord compression.[21]

There were some more recent (post-2015) studies found in the 2023 NICE evidence review on symptoms that suggest spinal metastasis, however all studies were conducted outside the UK and within secondary or tertiary care.[22] Some of these studies provide information on recognition for spinal metastasis. For example, one recent retrospective study based in China found the most common symptoms were local pain (15.50%), loss of sphincter control (14.96%), and weight loss (14.16%). The highest sensitivity (76.2%) and NPV (96.79%) was found for local pain, while night-aggravating pain had the highest specificity (99.4%) and PPV (92.42%).[23] Overall, the NICE evidence review found that low back pain was not a useful indicator of spinal metastasis in primary care.

No other relevant evidence was found in this evidence review.

[21] National Institute for Health and Care Excellence (NICE). Spinal metastases and metastatic spinal cord compression [E] Evidence reviews for recognition – MSCC. 2023. Available from: https://www.nice.org.uk/guidance/ng234/evidence/e-recognition-mscc-pdf-13134698177
[22] National Institute for Health and Care Excellence (NICE). Spinal metastases and metastatic spinal cord compression [E] Evidence reviews for recognition – spinal metastases. 2023. https://www.nice.org.uk/guidance/ng234/evidence/d-recognition-spinal-metastases-pdf-13134698176
[23] He S, Ye C, Gao X, et al. Distribution and predictive value of initial presenting symptoms in spinal metastases from primary cancer patients. Eur Spine J. 2020;29(12):3148-3156. doi:10.1007/s00586-020-06425-4