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

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

This document includes evidence on the following topics:

- Individual symptoms
- Symptom combinations
- Investigation findings and how they relate to cancer diagnosis e.g. chest x-ray
- Safety netting those with signs and symptoms of lung cancer
- Risk stratification by demographics and smoking status
- Other topics where the evidence base is weaker but emerging

Background

Lung cancer is the most common cause of cancer death in the UK[1]. On average, between 2018-2019, 49% of lung cancer cases in Scotland were diagnosed at stage 4 each year (out of those with a known stage at diagnosis)[2]. Scottish survival by stage data is not publicly available, but England (2016-2020, followed up to 2021) data demonstrates large differences in survival dependent on stage for lung cancer. If diagnosed at the earliest stage, more than 6 in 10 (63%) will survive their disease for 5 years or more in England, compared to just 4% if diagnosed at the latest stage[3]. Data from Scotland's National Cancer Diagnosis Audit (2018-2019) demonstrates that emergency referrals are common for lung cancer (varying from ~20-40% of diagnoses via emergency referral by regional cancer networks)[4]. Variation exists in

[1] Cancer Research UK (2015). Lung Cancer Statistics. [online] Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-One.
[2] Public Health Scotland, Detect Cancer Early Staging Data. Summarised at: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/
[3] NHS England, Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021. Earliest stage = stage 1, latest stage = stage 4. Available at: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/.
[4] Public Health Scotland (2021). National Cancer Diagnosis Audit. [online] Available at: https://publichealthscotland.scot/media/8583/2021-08-03_ncda-2019-20_report.pdf.

guideline concordance (whether health professionals' decisions align with guideline recommendations) for suspected lung cancer[5] and inequalities exist in those most likely to present as an emergency[6] including women, older age groups, those from areas of higher deprivation and those with non-respiratory symptoms[7]. Scottish NCDA (2014 and 2018/19) data also found that GPs working in rural areas compared to urban differed in their frequency of ordering investigations, the length of primary care intervals and diagnostic intervals compared to those GPs working in urban areas [8]. Continued review of evidence underpinning referral guidelines and use of these to optimise pathways, will help ensure people are referred along the most appropriate route at the right time.

Search Strategy

Search terms: PubMed search for combinations of the following terms: lung, cancer, PPV, risk, prevalence, symptomatic, presentation, primary care, haemoptysis, dyspnoea, cough, chest x-ray, CT, direct access, recognition, referral, stage, investigation, routine, routes to diagnosis, comorbidity.

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

Peer-reviewed literature

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

Topic: Individual Symptoms
Summary: The evidence presented below largely supports the inclusion of symptoms in the current guidance.

[5] Koo, M.M., Mounce, L.T.A., Rafiq, M., Callister, M.E.J., Singh, H., Abel, G.A. and Lyratzopoulos, G. (2023). Guideline concordance for timely chest imaging after new presentations of dyspnoea or haemoptysis in primary care: a retrospective cohort study. Thorax, [online] p.thorax-2022-219509. doi:https://doi.org/10.1136/thorax-2022-219509.
[6] Newsom-Davis, T. (2017). The route to diagnosis: emergency presentation of lung cancer. Lung Cancer Management, 6(2), pp.67–73. doi:https://doi.org/10.2217/lmt-2017-0004.
[7] Mitchell, E.D., Pickwell-Smith, B. and Macleod, U. (2015). Risk factors for emergency presentation with lung and colorectal cancers: a systematic review. BMJ Open, 5(4), pp.e006965–e006965. doi:https://doi.org/10.1136/bmjopen-2014-006965.
[8] Maxwell, S., Pearce, C., Kynn, M., Anderson, L.A., Weller, D. and Murchie, P. (2023). The impact of rurality on patient experience and diagnostic pathway intervals in Scotland's cancer patients: Further results from a national cancer diagnosis audit. Cancer Epidemiology, [online] 86, p.102414. doi:https://doi.org/10.1016/j.canep.2023.102414.

- Paper 4 (below) stratifies 'low but not no risk' symptoms by smoking status, suggesting that some lower risk symptoms present more commonly in smokers e.g. dyspnoea and weight loss. This could help determine those eligible for CXR/more urgent investigation.
- In multiple studies, **back pain** was reported to present as often as some symptoms that are already included in guidelines and that may warrant a chest x-ray e.g. fatigue, loss of appetite.
- In current guidelines, **fatigue** alone warrants investigation with a CXR only in those who are current smokers. There are no estimates of PPV for fatigue specifically for patients who aren't current smokers, and there are no new PPV estimates for fatigue in all patients post-2015. Fatigue is reported in some studies as a relatively common presenting symptom for lung cancer. 41% of all cancer patients who present with fatigue are later diagnosed with lung cancer (paper 6), and 6% of those diagnosed with lung cancer present with fatigue (paper 7). 31% of those with fatigue (paper 6) were diagnosed at stage 4 and fatigue was not significantly associated with late stage diagnosis.
- It may be important to consider why **chest pain** is at greater risk of late-stage diagnosis and if guidelines have a role in expediting these referrals. Symptom lead time[9] (SLT) for chest pain is slightly shorter than for cough, but the study (paper 2) does not determine if this is significant or not.

Hoarseness is included as a symptom that warrants chest x-ray in SRG, which differs from NICE NG12 guidelines. There is no evidence from 2015 onwards investigating PPV for hoarseness and lung cancer, and limited evidence to support this from pre-2015 as well. Most evidence calculates odds or likelihood ratios, which provide a mixed picture on whether hoarseness should be included in guidelines (Iyen-Omofoman, 2012, Hippisley-Cox, 2011).

Paper number	Study	Summary	Notes
1	Chowienczyk, S., Price, S. and Hamilton, W. (2020) Changes in the presenting symptoms of lung cancer from 2000–2017: a serial cross-sectional study of observational records in UK primary care. British Journal of	This study aimed to (1) identify the first reported symptom of possible lung cancer and (2) assess whether the percentages of patients with each index symptom changed during 2000–2017. Between 2000-2017, the percentage of patients presenting with index symptoms of **dyspnoea** or **cough**	Cross-sectional study England data, Clinical Practice Research Datalink linked with cancer registration data N=27,795 patients with lung cancer included

[9] the time between symptoms caused by cancer and eventual diagnosis

	General Practice, 70(692), pp. e193-e199.	(alone or in combination with another symptom) increased from 20% to 33% and 27% to 33% respectively. Other index symptoms, most notably **chest pain**, **appetite loss**, **weight loss** and **haemoptysis** became less common between 2000-2017 (decreased 17% to 11%, 2% to <1%, 6% to 4% and 11% to 4% respectively).	**Limitation:** this study uses coded data only which is typically more likely to favour 'red flag' symptoms. This may underestimate the proportion of people presenting with non-specific symptoms.
2	Biswas M, Ades AE, Hamilton W. Symptom lead times in lung and colorectal cancers: what are the benefits of symptom-based approaches to early diagnosis? British Journal of Cancer. 2015;112(2):271–7.	This study aimed to estimate the symptom lead time (SLT) distribution for a range of potential symptom criteria for investigation. **Symptom lead time:** the time between symptoms caused by cancer and eventual diagnosis The mean (average) SLTs were between 4.7 and 6.0 months for lung cancer and the median was between 2.4 and 3.2 for lung cancer. SLTs were calculated for two lung cancer symptoms: chest pain and cough. Mean SLT for chest pain was 5.5 (95% CI 4.3-6.9) months, and median SLT was 2.5 (95% CI 1.9–4.0) months. For cough, mean SLT was 6.0 (95% CI 4.9–7.1), and median was 3.2 (95% CI 2.6–5.1). As the median is less than the mean, this means that a greater proportion of SLTs were less than 4.7-6 months. Timely public help-seeking and expedited recognition and referral routes would likely benefit those with	Secondary data analysis on a case-controlled study (ratio of controls:case 5:1) Data from Exeter, England between 1998-2002 N=247 **Limitation:** the study has a small sample size, is restricted to one area of England and uses relatively old data so may lack generalisability to current landscape in Scotland.

		suspected lung cancer, due to relatively short median symptom lead times. Over the period of observation, between 66%-83% of the occurrences of investigations for lung cancer were due to suspicion of lung cancer. Individual symptom sensitivity and specificity reported in this study: **Cough:** sensitivity 65%, specificity 71% **Chest pain:** sensitivity 56%, specificity 85% Any of the 7 symptoms included **(cough, dyspnoea, chest pain, fatigue, loss of weight, loss of appetite, and haemoptysis):** sensitivity 91%, specificity 53%	
3	Walter FM, Rubin G, Bankhead C, Morris HC, Hall N, Mills K, et al. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. British Journal of Cancer. 2015 Mar;112(S1):S6–13.	This study aimed to investigate symptoms and other clinical and sociodemographic factors associated with lung cancer diagnosis, time to diagnosis and stage at diagnosis. **Cough** (56%), **breathlessness** (41%) or worsening of either were the most commonly reported symptoms, as both first symptom or any noted symptom recognised within <2 years to diagnosis. **Haemoptysis** (14%) and **unexplained weight loss** (11%) were least frequently reported, but were the only two symptoms reported significantly more by those who had cancer compared to those who did not.	Prospective cohort study East and North East of England N=995 **Limitations:** this study utilised questionnaires to obtain symptom information which could lead to recall bias. The study also had relatively low return rate (19.5%).

		Haemoptysis was the first symptom recognised by participants in <5% of cases.	
4	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 Cohort Study in Primary Care. Cancers [Internet]. 2023 Aug 2;15(15):3936.	This study aimed to investigate the number and percentage of patients with a PPV ≥ 3% feature who also presented with a 2–2.99% or 1–1.99% feature in the preceding year. Of 818 patients with >3% risk symptom, 2.5% presented with a 2-2.99% PPV symptom, and 18.1% presented with a 1-1.99% PPV symptom in the previous year, suggesting earlier opportunities for recognition of lung cancer. Median time between presenting with 2-2.99% symptom and >3% symptom was 126 days (IQR: 37-230), and between 1-1.99% and >3% was 184 days (IQR: 99.5-293.5). **Weight loss in smokers** was the most common 2-2.99% symptom in year preceding 3% symptom (n=16) **Dyspnoea in smokers** was the most common 1-1.99% symptom in year preceding 3% symptom (n=71)	Cross-sectional study English primary care data from 2015-2016 N= 150,921 for all cancers combined N=7,108 patients with >3% risk symptom N= 818 lung cancer patients with >3% risk symptom **Note:** PPVs derived from a list of features of cancer from the systematic reviews published in NG12 2015 update for each of the cancer sites. **Limitation:** only coded data was used for this analysis, so there may be underestimation of threshold for symptoms, due to missing data in free text. Additionally, no definition of 'smoker' included in analysis.
5	Okoli GN, Kostopoulou O, Delaney BC. Is symptom-based diagnosis of lung cancer possible? A systematic review and meta-analysis of symptomatic lung cancer prior to diagnosis for	The aim of this study was to provide an evidence-based analysis of symptoms observed in lung cancer patients prior to diagnosis.	Systematic review N=13 studies included in analysis **Limitation:** 5 out of 13 studies investigated a small list of lung cancer symptoms with other

	comparison with real-time data from routine general practice. PLOS ONE. 2018 Nov 21;13(11):e0207686.	**Haemoptysis** had the greatest diagnostic value in the included studies, followed by **dyspnoea, cough** and **chest pain**. Pooled likelihood ratios from selected studies: Haemoptysis 5.968 (95% CI 3.18–11.19) Dyspnoea 2.138 (95% CI 1.35–3.39) Cough 1.748 (95% CI 1.29–2.37) Chest pain 1.756 (95% CI 0.95–3.24)	symptoms less commonly associated with lung cancer not assessed. Some included studies are relatively dated and may not reflect current practice
6	Koo MM, Swann R, McPhail S, Abel GA, Elliss-Brookes L, Rubin GP, et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. The Lancet Oncology. 2019 Nov;21(1).	There has been debate around whether symptoms present at an early enough stage for there to be the possibility for meaningful clinical intervention. This study aimed to examine associations between common presenting symptoms of cancer and stage at diagnosis. After adjusting for demographic factors, **chest pain** was the only lung cancer symptom associated with an increased odds (OR 2.12) of stage 4 disease as a single symptom, suggesting that most lung cancer symptoms have potential to be diagnosed at an earlier stage, where treatment outcomes are better. Proportions and odds ratios of diagnosis at stage 4 associated with symptoms when recorded alone: • Hoarseness: 31% (Adjusted OR 1·33 (95% CI 0·57–3·10)) • Fatigue: 31% (Adjusted OR 1·07 (95% CI 0·54–2·10)) • Weight loss: 38% (Adjusted OR 1·23 (95% CI 0·66–2·28))	Cross-sectional, population-based study England data using National Cancer Diagnosis Audit (NCDA) data (2014) N=7997 (for all cancers) N= 1715 (lung cancer only) **Limitation:** this study uses primary care records, which may be incomplete and prone to bias

		• Cough: 45% (Adjusted OR 0·99 (95% CI 0·59–1·65)) • Haemoptysis: 56% (Adjusted OR 1·51 (95% CI 0·78–2·92)) • Chest infection: 54% (Adjusted OR 1·40 (95% CI 0·73–2·66)) • Dyspnoea: 48% (Adjusted OR 1·22 (95% CI 0·70–2·12)) • Chest pain: 60% (Adjusted OR 2·12 95% CI (1·16–3·86)) Proportion of cancer patients who presented with *x* symptom who were subsequently diagnosed with lung cancer: • Chest infection: 95% • Cough: 93% • Haemoptysis: 91% • Dyspnoea: 86% • Chest pain: 86% • Weight loss: 44% • Fatigue: 41% • Back pain: (error in supp material: ~35%) • Hoarseness: 32% • Neck lump: 24% • Any other symptom: 20% • Abdominal pain: 8% • CIBH: 5% • Lower abdominal pain: 4% • Rectal bleeding: 1%	

7	Zakkak N, Barclay ME, Swann R, McPhail S, Rubin G, Abel GA, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. British Journal of Cancer [Internet]. 2024 Feb 1 [cited 2024 Feb 1];130(2):297–307.	This study aimed to (1) examine the relative frequency of presenting symptoms by cancer site (the 'symptom signature' of each cancer site), and (2) to examine the relative frequency of cancer sites by presenting symptom (the 'cancer site case-mix' of each symptom), among incident cancer cases. The mean number of symptoms present at lung cancer diagnosis was 1.7. The proportion of patients with lung cancer presenting with the following symptom groups was: • 55% respiratory • 23% non-specific • 21% no symptoms recorded • 8% upper abdominal • 6% musculoskeletal • 5% lower abdominal • 3% CNS • 1% breast, urological, lump/mass/lymph node. Of all patients diagnosed with lung cancer, the proportion that experienced *x* symptom are as follows: • 30% cough • 18% dyspnoea • 11% weight loss, chest infection • 10% chest pain • 7% haemoptysis • 6% fatigue, other • 5% back pain	Data from 2018 National Cancer Diagnosis Audit (England) N=55,122 (total cohort) N=7,608 (lung only) **Limitations:** this is a case-only analysis (only patients with diagnosis of cancer were included), so cannot make inferences about PPV

		• 4% loss of appetite • 2% nausea/vomiting, abdominal pain (NOS), hoarseness, bone pain • 1% fever, infection, night sweats, neck lump, dyspepsia, dysphagia, upper abdominal pain, CIHB, constipation, diarrhoea, distention, sore throat, headache, CNS function	

Topic: Symptom Combinations

Summary: Just under half of lung cancer patients diagnosed via the symptomatic route present with more than one symptom. Further research is needed to improve understanding of PPVs for symptom combinations, so this can eventually be reflected in guidelines. **Weight loss** and **thrombocytosis** combined has a relatively high PPV, which could indicate a symptom combination to refer straight onto urgent pathway rather than for CXR.

In current Scottish referral guidelines, symptom combinations are not included, which differs from NICE NG12 guidelines. Hamilton et al (2005) reported some symptom combinations which exceeded a >3% risk threshold. This included: dyspnoea and weight loss in smokers, dyspnoea and appetite loss in smokers, chest pain and weight loss in smokers, chest pain and appetite loss in smokers, chest pain and thrombocytosis in smokers, weight loss and appetite loss in smokers, and weight loss and thrombocytosis in all patients. This data has been referenced from NICE NG12 Evidence Review document, as the supplementary material for this study is no longer available online. It is important to note that this study was published in 2005.

Paper number	Study	Summary	Notes
8	Bradley SH, Hatton NLF, Aslam R, Bhartia B, Callister MEJ, Kennedy MPT, Mounce L, Shinkins B, Hamilton WT, Neal RD. Estimating lung cancer risk from chest x-ray and symptoms: a prospective	This study aimed to (1) establish the sensitivity and specificity of CXR requested by patients who are symptomatic; (2) determine the positive predictive value (PPV) of each presenting symptom of lung cancer following a negative CXR; (3) determine whether symptoms associated with lung cancer are different in	Prospective cohort study, data from 2011-2016 Based in Leeds, England N=8996 **Limitation:** insufficient cases were present to calculate PPVs for several

	cohort study. *British Journal of General Practice*, 2020, doi: 10.3399/bjgp20X713993	those who had a positive CXR result compared with those who had a negative CXR result. The study calculated PPV for the entire study population for **thrombocytosis,** as they were unable to calculate PPV following negative CXR due to small numbers: • 1.03 (95% CI = 0.00-2.45) in combination with **cough** • 2.17 (95% CI = 0.00-6.39) in combination with **chest pain** • 6.67 (95% CI = 0.00-15.59) in combination with **weight loss**. PPVs for other symptoms in the year following a negative self-referred CXR can be found in the 'Investigation Findings' table below.	symptom combinations. Also, the study cohort includes those who self-referred for CXR.
-	Biswas M, Ades AE, Hamilton W. Symptom lead times in lung and colorectal cancers: what are the benefits of symptom-based approaches to early diagnosis? British Journal of Cancer. 2015;112(2):271–7. This paper is also summarised above, see paper 2.	This study aimed to estimate the symptom lead time (SLT) distribution for a range of potential symptom criteria for investigation. Sensitivity and specificity for combinations of symptoms reported in this study: • Two different symptoms of any of the following (**cough, dyspnoea, chest pain, fatigue, loss of weight, loss of appetite, and haemoptysis**): sensitivity 74%, specificity 83% • Any 2 of the symptoms listed above in the past 3 months: sensitivity 81%, specificity 77%	See above.

-	Walter FM, Rubin G, Bankhead C, Morris HC, Hall N, Mills K, et al. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. British Journal of Cancer. 2015 Mar;112(S1):S6–13. This paper is also summarised above, see paper 3.	This study aimed to investigate the symptoms and other clinical and sociodemographic factors associated with lung cancer diagnosis, time to diagnosis and stage at diagnosis. Among the total cohort of lung cancer patients, only half had an isolated first symptom (n=475, 49%), 19% had two first symptoms, 9% had three and >10% reported four or more synchronous first symptoms.	See above.
-	Koo MM, Swann R, McPhail S, Abel GA, Elliss-Brookes L, Rubin GP, et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. The Lancet Oncology. 2019 Nov;21(1). This paper is also summarised above, see paper 6.	There has been debate around whether symptoms present at an early enough stage for there to be the possibility for meaningful clinical intervention. This study aimed to examine associations between common presenting symptoms of cancer and stage at diagnosis. After adjusting for demographic factors, **chest pain** (OR 1.45. 95% CI 1.06-1.98) and **dyspnoea** (OR 1.2. 95% CI 1.00-1.64) were associated with an increased odds of stage 4 disease when seen in combination with other symptoms.	See above. **Limitation:** 'Other symptoms' are not specified in supplementary material, so the exact symptom combinations associated with increased odds of stage 4 disease are unclear.

Topic: Investigation Findings
Summary:

• CXR sensitivity[10] estimates vary from 76-82%. The risk of having lung cancer after an initial negative CXR is low, but not no risk (0.56%-0.8% in the two years following CXR). Haemoptysis has a PPV of around 3% one year after a negative CXR, which supports the current guideline recommendation of urgent referral without CXR for those with haemoptysis. The PPVs for symptom combinations 1-year post CXR should be interpreted with caution, due to small numbers included in analysis. • Research conducted in Denmark reported increased use of CT improved proportion of stage 1 diagnosis, but found no impact of direct access to CT on diagnostic intervals or stage at diagnosis. • C-Reactive Protein (CRP, inflammatory marker) is independently predictive of lung cancer up to 12 months before diagnosis. Further research is required to determine how CRP might be useful in supporting management of patients with suspected lung cancer, particularly as raised CRP may be indicative of several other health conditions.			
Paper number	**Study**	**Summary**	**Notes**
9	Bradley SH, Abraham S, Callister M, Grice A, Hamilton W, Rodriguez Lopez R, Shinkin B, Neal R. Sensitivity of chest x-ray for detecting lung cancer in people presenting with symptoms: systematic review. *British Journal of General Practice*, 2019, doi: 10.3399/bjgp19X706853	The aim of this study was to estimate the sensitivity of chest X-ray for detecting lung cancer in symptomatic people. Pooled sensitivity: 77-80%.	Systematic review n=21 studies included Studies based in Northern Ireland, England and Denmark. **Limitations:** all studies included were considered relatively low quality, except for 3 which were used to generate sensitivity estimates.
-	Bradley SH, Hatton NLF, Aslam R, Bhartia B, Callister MEJ, Kennedy MPT, Mounce L, Shinkins B, Hamilton WT, Neal RD. Estimating lung cancer	The aim of this study was to (1) establish the sensitivity and specificity of CXR requested by patients who are symptomatic; (2) determine the positive predictive values (PPVs) of each presenting symptom of lung cancer following a negative CXR; (3) determine whether symptoms	See above.

[10] Sensitivity is the proportion of people with cancer that have a positive investigation. A test that is 100% sensitive means all cancers are correctly identified i.e. there are no false negatives.

	risk from chest x-ray and symptoms: a prospective cohort study. *British Journal of General Practice*, 2020, doi: 10.3399/bjgp20X713993 This paper is also summarised above, see paper 8.	associated with lung cancer are different in those who had a positive CXR result compared with those who had a negative CXR result. PPVs for symptoms and symptom combinations at 1-year following self-referred CXR (SR-CXR) in those with a negative self-referred CXR result: • Haemoptysis: only symptom alone that reached 3% (2.94%). • Haemoptysis and cough: 2.6% • Haemoptysis and breathlessness: 3.2% **(<5 cases)** • Haemoptysis and weight loss: 7.7% **(<5 cases)** • All other combinations were <2% risk. At 1 year following SR-CXR, a total of 114 patients (1.3%) were diagnosed with lung cancer, of whom 86 (75.4%) had a positive SR-CXR result; the remaining 28 (24.6%) had a negative SR-CXR result. The NPV for a diagnosis of lung cancer within 1 year was 99.7%. At 2 years following SR-CXR, a total of 154 patients (1.7%) were diagnosed with lung cancer, of whom 97 (63.0%) had a positive SR-CXR result; the remaining 57 (37.0%) had a negative SR-CXR result. 0.27% (95% CI: 0.13-0.55) of those who had a negative CXR were subsequently diagnosed with lung cancer in the	

		following year, and 0.56% (95% CI: 0.37-0.84) in the following two years, when adjusted for age, sex and smoking status.	
10	Bradley SH, Bhartia BS, Callister ME, Hamilton WT, Hatton NLF, Kennedy MP, Mounce L, Shinkins B, Neal R, et al. Chest X-ray sensitivity and lung cancer outcomes: a retrospective observational study. *British Journal of General Practice*, 2021. doi: 10.3399/BJGP.2020.1099	The aim of this study was to determine the sensitivity of CXR for lung cancer and to compare stage at diagnosis, time to diagnosis, and survival between those with CXR that detected, or did not detect, lung cancer. Only primary lung cancers included in ICD C34 were included, therefore any other intrathoracic malignancies e.g. mesothelioma were excluded. Overall sensitivity: 82.3%. Of the patients who had a CXR in the year before their diagnosis of lung cancer, those with positive results had a median duration to diagnosis of 43 days compared with 204 days for those with a negative initial CXR. There was no evidence of a statistically significant association between failure to detect lung cancer on CXR and stage at diagnosis or survival.	Retrospective observational study design Population: Leeds, England Data from 2008-2015, included all patients diagnosed with lung cancer in Leeds Teaching Hospitals NHS Trust N=4698 **Limitations:** The association between CXR result, stage, time to diagnosis and survival was not adjusted for potentially confounding factors such as smoking status, comorbidities.
11	Dwyer-Hemmings, L. and Fairhead, C. (2021). The diagnostic performance of chest radiographs for lung malignancy in symptomatic primary-care populations: A systematic review and meta-analysis. BJR|Open, 3(1), p.20210005.	The aim of this study was to synthesise existing evidence for the diagnostic accuracy of chest x-ray to detect lung malignancy in symptomatic patients presenting to primary care. Summary sensitivity: 81% (95% CI: 74-87%) Summary specificity: 68% (95% CI: 49-87%)	Systematic review of 10 studies, all performed in the UK or Northern Europe between 2006-2018 **Limitations:** 5 studies were judged to have high risk of bias

	doi:https://doi.org/10.1259/bjro.20210005.		
12	Bhartia, B.S.K., Hatton, N.L.F., Aslam, R., Bradley, S.H., Darby, M., Hamilton, W.T., Hurst, E., Kennedy, M.P.T., Mounce, L.T.A., Neal, R.D., Shinkins, B. and Callister, M.E.J. (2021). A prospective cohort evaluation of the sensitivity and specificity of the chest X-ray for the detection of lung cancer in symptomatic adults. European Journal of Radiology, [online] 144. doi:https://doi.org/10.1016/j.ejrad.2021.109953.	The aim of this study was to determine the diagnostic accuracy of CXR for the detection of non-small cell carcinoma (NSCLC) and all primary intrathoracic malignancies. 496 positive investigations led to a diagnosis of 101 patients with primary intrathoracic malignancy including 80 with NSCLC. Within two-years, a cumulative total of 168 patients with primary intrathoracic malignancies including 133 NSCLC were observed. Sensitivity NSCLC: 76% (95% CI 68–84) and Specificity NSCLC: 95% (95% CI 95–96) within 1-year Sensitivity NSCLC: 60% (95 %CI 52–69) and Specificity NSCLC: 95% (95 %CI 95–96) within 2-years. Within this symptomatic population a negative test reduced the 2-year risk of lung cancer to 0.8%.	Prospective cohort study Cohort of consecutive “self-request” CXR studies prospectively collated between January 2011 and October 2016 Based in Leeds, England N=8,948 CXR evaluated. **Limitations:** this study has a relatively small sample of those diagnosed with lung cancer.
13	McDonald L, Carroll R, Harish A, Tanna N, Mehmud F, Alikhan R, et al. Suspected cancer symptoms and blood test results in primary care before a diagnosis of lung cancer: a case–control	The aim of this study was to compare symptoms and blood test results prior to cancer diagnosis in individuals who were diagnosed lung cancer and those who were not. At 6 months prior to diagnosis, high CRP and platelet counts were reported to independently predict lung cancer, after	Nested case–control study, Clinical Practice Research Datalink UK data Data from: 1 January 1987–30 June 2018 26,379 patients and 92,125 matched controls

	study. Future Oncology. 2019 Nov;15(33):3755–62.	adjusting for other blood tests, symptoms and covariates (smoking status, BMI, Charlson comorbidity index). High CRP was also independently predictive of lung cancer diagnosis at every time point (every 2 months) up to at least 12 months before diagnosis. After adjustment for smoking status and Charlson comorbidity index, having a high CRP in conjunction with any other symptom was associated with increased odds of a lung cancer diagnosis (OR 4.62 (95% CI: 3.32–6.42)).	**Limitations:** the dataset was limited to patients recorded in CPRD, and as such some cancer diagnoses may have been missed or the date of first diagnosis may not have been accurately recorded
14	Louise Mahncke Guldbrandt, Morten Fenger-Grøn, Torben Valdbjørn Rasmussen, Rasmussen, F., Meldgaard, P. and Vedsted, P. (2015). The effect of direct access to CT scan in early lung cancer detection: an unblinded, cluster-randomised trial. 15(1). doi:https://doi.org/10.1186/s12885-015-1941-2.	This study aimed to evaluate the effect of direct access to low-dose computed tomography (LDCT) from general practice in early lung cancer detection on time to diagnosis and stage at diagnosis, in Denmark. **Intervention arm**: direct access LDCT and education session on LDCT **Control arm:** usual care (either CXR, routine referral, or fast-track referral) This study found no statistically significant difference in primary care or diagnostic intervals, stage or PPV between patients who underwent the control or the intervention.	Cluster-randomised, controlled trial including all lung cancer patients (in 19-month period) listed with general practice in the municipality of Aarhus (300,000 citizens), Denmark N=331 lung cancers diagnosed **Limitations:** this study was conducted in Denmark, which may limit the applicability to UK setting
15	Hyldgaard, C., Trolle, C., Harders, S.M.W., Engberg, H., Rasmussen, T.R. and Møller, H. (2022). Increased use of	This study aimed to understand the changes in referral pathways, patient characteristics and imaging procedures behind the observed increase in early-stage lung cancer in Denmark.	Retrospective analysis of data from Danish lung cancer registry, 2013–2018 N=547 lung cancer diagnosed

	diagnostic CT imaging increases the detection of stage IA lung cancer: pathways and patient characteristics. BMC cancer, [online] 22(1), p.464. doi:https://doi.org/10.1186/s12885-022-09585-2.	Stage 1A lung cancers increased between 2013-2018. The imaging procedures contributing to the increase in stage 1A was contrast enhanced CT, LDCT and X-ray followed by LDCT. 13.8% (34/247) of all lung cancers were diagnosed as stage 1A in 2013–2015, which increased to 28.3% (85/300) in 2016–2018. The proportion of stage 1A increased significantly from 12% (12/99) to 36% (47/129) for hospital referrals (significant increase) and from 17% (22/129) to 23% (38/165) for GP referrals (insignificant increase). These findings suggest increased use of CT leads to earlier diagnosis, but use in primary care referrals was less impactful than within-hospital referrals.	**Limitations:** this study was conducted in Denmark, which may limit the applicability to UK setting

Topic: Safety Netting			
Summary: Clear, actionable timeframes and advice are required within guidelines to advise how to safety net those who are symptomatic, but have a negative CXR. In the absence of high-quality evidence to support this, building clinical consensus on best practice may be a helpful approach. Those who have been investigated along the urgent suspicion of lung cancer pathway are at greater risk of being diagnosed with lung cancer in the next 1-5 years, but more evidence is needed to understand whether this could present an opportunity for earlier detection of lung cancer.			
Paper number	**Evidence Paper**	**Summary**	**Notes**
-	Bradley SH, Bhartia BS, Callister ME, Hamilton WT, Hatton NLF, Kennedy MP, Mounce L, Shinkins B, Neal R, et al. Chest X-ray sensitivity and lung cancer	The aim of this study was to determine the sensitivity of CXR for lung cancer and to compare stage at diagnosis, time to diagnosis, and survival between those with CXR that detected, or did not detect, lung cancer. Only primary lung cancers	See above.

	outcomes: a retrospective observational study. *British Journal of General Practice*, 2021. doi: 10.3399/BJGP.2020.1099 This paper is also summarised above, see paper 10.	included in ICD C34 were included, therefore any other intrathoracic malignancies e.g. mesothelioma were excluded. Median time from initial CXR to diagnosis for those with a 'positive' result was 43 days (IQR 27–78) compared with 204 days (IQR 105–287) for those who had a 'negative' CXR. Among patients diagnosed >6 weeks (42 days) after initial CXR (n=1,244), there was evidence that those with an initial negative CXR (n=350) were more likely to have stage 3 or 4 disease than those who had a positive initial CXR (n=894), but the analysis in this study suggested no differences in survival between these groups.	
16	Scott SE, Gildea C, Nicholson BD, Evans RE, Waller J, Smith D, et al. Future cancer risk after urgent suspected cancer referral in England when cancer is not found: a national cohort study. The Lancet Oncology [Internet]. 2023 Nov 1 [cited 2024 Jan 26];24(11):1242–51.	This study aimed to investigate the risk of cancer occurrence within 1-5 years of finding no cancer following an urgent suspected cancer referral. In years 1-5 post urgent referral for suspected lung cancer, people who were not diagnosed with lung cancer had a higher incidence rate of lung cancer than the rate expected in the general population (incidence ratio 3.00) Across all initial urgent referral pathways, lung cancer consistently comprised a substantial proportion of the subsequently diagnosed cancers.	National cohort study (England) Data from Cancer Waiting Times dataset and National Cancer Registration Dataset from April 2013 – March 2014 N= 63,112 subsequent cancers **Limitations:** Clinical context has changed since the data collection e.g. guideline changes which may limit the applicability of the results to current setting.

		The suspected lung cancer pathway had one of the highest absolute rates of same cancer diagnosis as the initial referral pathway.	

Topic: Risk Stratification
Summary: • The proportion of lung cancer cases in those who have never smoked, typically defined as having smoked <100 cigarettes in their lifetime, is increasing. Research has found increased risk of lung cancer in female never smokers is associated with non-white ethnicity, asthma diagnosis and taller stature. Generally, there is limited evidence on risk of lung cancer in people who have never smoked, but the available evidence does suggest that healthcare professionals may require further support and guidance to support management of this cohort. • Respiratory comorbidities may lead to delays in diagnosis due to masking of symptoms. Consideration should be taken in how to support health professionals with recognising lung cancer in these two cohorts and whether this is appropriate to be included in guidelines. • There is some evidence to suggest that the association of unexplained weight loss with lung cancer is stronger in men. There are differences in how symptoms are stratified between Scottish Referral Guidelines and NICE NG12 guidelines. There is a lack of evidence from 2015 onwards to support the differences in stratification, but some studies published pre-2015 which were included in the NICE NG12 evidence review investigate this. • Haemoptysis warrants an urgent referral for all patients aged >40 years in NICE NG12 guidelines, but only warrants an urgent referral for current/ex smokers aged >40 years in SRG. Pooled PPV from 3 studies (Jones, 2007, Hippisley-Cox, 2011, Iyen-Omofoman, 2013) found the PPV for haemoptysis in all patients was 3.5-3.8%, suggesting the PPV is high enough in all patients to warrant urgent referral. • All symptoms that warrant a CXR are stratified by age (>40 years) and smoking status in NICE NG12 guidelines. In SRG, only fatigue is stratified this way. Hamilton et al (2005) provides PPVs for individual symptoms for smokers and non-smokers in those aged >40 years in the supplementary information. This data has been taken from NICE NG12 evidence review document, as supplementary data for this paper is no longer available online. o For those who smoke, PPVs are as follows: cough (0.9%), fatigue (0.8%), dyspnoea (1.2%), chest pain (1.3), weight loss (2.1%), appetite loss (1.8%), thrombocytosis (4.2%).

<table>
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For non-smokers, PPVs are as follows: cough (0.4%), fatigue (0.4%), dyspnoea (0.6%), chest pain (0.8%), weight loss (1.1%), appetite loss (0.9%), thrombocytosis (1.6%).
For most symptoms, risk is relatively low for both smokers and non-smokers, except for weight loss, appetite loss and thrombocytosis.

Most studies investigating symptom risk include patients aged >40 years, which may explain the age thresholds used in NICE NG12 and Scottish Referral Guidelines.

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<tr><th>Paper number</th><th>Study</th><th>Summary</th><th>Notes</th></tr>
<tr><td>17</td><td>Black, G.B., Janes, S.M., Callister, M.E.J., van Os, S., Whitaker, K.L. and Quaife, S.L. (2024). The Role of Smoking Status in Making Risk-Informed Diagnostic Decisions in the Lung Cancer Pathway: A Qualitative Study of Health Care Professionals and Patients. Medical Decision Making: An International Journal of the Society for Medical Decision Making.</td><td>This study aimed to explore how clinicians make risk-informed diagnostic decisions for never-smokers.

In the absence of smoking history, clinicians reported more reliance on “rules of thumb” to weigh up potential harms and benefits, based on gut feeling, patient health state, and patient self-advocacy.

This study also found evidence of false over-reassurance from health professionals if the patient is a never smoker.

Based on the findings, the authors suggest risk tools and guidelines could be developed specifically to support management of people with potential lung cancer symptoms who have never smoked, and that guidelines could prompt healthcare professionals to ask patients about non-smoking related risk during consultations.</td><td>Qualitative study
Interviews with 10 lung cancer diagnosticians and 20 never-smoker lung cancer patients

Limitations: small sample size which may limit the representativeness of the wider population</td></tr>
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18	Pirie, K., Peto, R., Green, J., Reeves, G.K. and Beral, V. (2016). Lung cancer in never smokers in the UK Million Women Study. International Journal of Cancer, 139(2), pp.347–354. doi:https://doi.org/10.1002/ijc.30084.	This study aimed to assess the effects of various risk factors on lung cancer incidence among female never smokers. Of 34 risk factors analysed, 31 were not significantly related to risk. Lung cancer incidence was significantly associated with women of non-white ethnicity, of taller stature and for women with asthma requiring treatment.	Study included as part of the million women study: a population-based cohort study of women aged 50-64 in the UK N= 634,039 'never smokers' included in analysis **Limitations:** smoking data was obtained via survey, which may be prone to bias
-	Walter FM, Rubin G, Bankhead C, Morris HC, Hall N, Mills K, et al. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. British Journal of Cancer. 2015 Mar;112(S1):S6–13. This paper is also summarised above, see paper 3.	This study aimed to investigate the symptoms and other clinical and sociodemographic factors associated with lung cancer diagnosis, time to diagnosis and stage at diagnosis. When considering total diagnostic interval (TDI)*, certain symptoms e.g. haemoptysis, cough or decreased appetite were found to be significant predictors of shorter TDI for the total cohort. Having a respiratory comorbidity was associated with a longer TDI. *time from the first symptom/s to the date of diagnosis	See above.
19	Nicholson BD, Hamilton W, Koshiaris C, Oke JL, Hobbs FDR, Aveyard P. The association between unexpected weight loss and cancer diagnosis in	This study aimed to understand the cancer types detected in primary care patients with unexplained weight loss.	Retrospective matched cohort study (ratio of cases:controls 1:5) England and Wales data from Clinical Practice Research Datalink 2000-2014

	primary care: a matched cohort analysis of 65,000 presentations. British Journal of Cancer. 2020 Apr 15;122(12):1848–56.	Unexplained weight loss was associated with increased risk of lung cancer and demonstrated higher hazard ratios than for all cancers combined. The hazard ratio for men 0-3 months before lung cancer diagnosis is 5.93 (95% CI 4.43–7.94), 6 months before is 2.74 (95% CI 2.18–3.43) compared to controls. The hazard ratio for women 0-3 months before lung cancer diagnosis is 3.59 (95% CI 2.47–5.21) and 6 months is 1.82 (95% CI 1.36-2.44) compared to controls.	N=63,973 **Limitations:** data is relatively out of date and this study is unable to determine PPV

Emerging Topics

Prescription patterns: there is a growing body of evidence investigating prescription patterns that may be associated with greater or lesser risk of cancer. A study in England investigated patterns of relevant medications in patients who presented with dyspnoea in primary care and were subsequently diagnosed with lung cancer. This study reported that monthly prescribing rates for all medications (antibiotics, oral steroids, inhaled respiratory medications and oral analgesics) increased towards time of diagnosis and were highest in pre-existing COPD patients. Increases in prescribing activity were observed earliest in pre-existing COPD patients (5 months pre-diagnosis) for inhaled medications, antibiotics, and steroids[11]. A Swedish population-based study also found increased likelihood of recent history antibiotic prescriptions in people diagnosed with lung cancer[12]. Prescription data may be able to be utilised to recognise lung cancer earlier[13], but further research is required.

[11] Wickramasinghe, B., Renzi, C., Barclay, M., Callister, M., Rafiq, M. and Georgios Lyratzopoulos (2023). Pre-diagnostic prescribing patterns in dyspnoea patients with as-yet-undiagnosed lung cancer: A longitudinal study of linked primary care and cancer registry data. Cancer Epidemiology, 86, pp.102429–102429. doi:https://doi.org/10.1016/j.canep.2023.102429.

[12] Lukas Löfling, Shahram Bahmanyar, Kieler, H., Lambe, M. and Gunnar Wagenius (2021). Antibiotic use prior to a lung cancer diagnosis: a population-based study. Cancer Causes & Control, 32(6), pp.597–607. doi:https://doi.org/10.1007/s10552-021-01413-5.

[13] McDowell, R.D., Hughes, C., Murchie, P. and Cardwell, C. (2021). A systematic assessment of the association between frequently prescribed medicines and the risk of common cancers: a series of nested case-control studies. BMC medicine, [online] 19(1), p.22. doi:https://doi.org/10.1186/s12916-020-01891-5.

Risk prediction tools: most risk prediction tools for lung cancer are investigated and validated using asymptomatic cohorts. A systematic review compared some risk prediction models developed for primary care use (all based on UK primary care data), but concluded there is insufficient evidence to recommend any of the risk prediction tools as no tools had been externally validated at the time of publication[14].

Other insights:

Research insights from meeting with academic, February 2024:

- Stephen Bradley has published a few papers investigating variation in the use of CXR in English practices. One study[15] found higher practice scores for continuity and communication skills, and higher proportions of smokers, Asian and mixed ethnic groups, and patients aged >65 years were associated with increased CXR rates. Higher patient satisfaction scores for access and greater proportions of male patients and patients of Black ethnicity were associated with lower CXR rates.
- In recent conversations with the team, they've indicated that the forthcoming paper has found increased use of CXR does lead to improves outcomes for patients[16]. This work has built on Stephen Bradley's previous work, which found increased rates of chest x-ray are likely to contribute to earlier detection[17].

International Comparisons of lung cancer guidelines

- A journal article[18] identified and compared international primary care guidelines on first-line investigation for suspected lung cancer.
- The guidelines identified were all consistent in advocating CXR as the initial investigation, aside from Danish guidance.

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[14] Schmidt-Hansen, M., Berendse, S., Hamilton, W. and Baldwin, D.R. (2017). Lung cancer in symptomatic patients presenting in primary care: a systematic review of risk prediction tools. British Journal of General Practice, [online] 67(659), pp.e396–e404. doi:https://doi.org/10.3399/bjgp17x690917.

[15] Bradley, S.H., Barclay, M., Cornwell, B., Abel, G.A., Callister, M.E., Gomez-Cano, M., Round, T., Shinkins, B. and Neal, R.D. (2021). Associations between general practice characteristics and chest X-ray rate: an observational study. British Journal of General Practice, 72(714), pp.e34–e42. doi:https://doi.org/10.3399/bjgp.2021.0232.

[16] Bradley, S. (2023). Tackling the leading cause of cancer death – a GP's view on improving lung cancer survival. [online] Cancer Research UK - Cancer News. Available at: https://news.cancerresearchuk.org/2023/11/20/earlier-lung-cancer-diagnosis-improve-lung-cancer-survival/ [Accessed 15 Dec. 2023].

[17] Bradley, S.H., Kennedy, M.P.T. and Callister, M.E.J. (2022). Early-stage lung cancer associated with higher frequency of chest x-ray up to three years prior to diagnosis. Primary Health Care Research & Development, 23. doi:https://doi.org/10.1017/s1463423622000573.

[18] Bradley, S.H., Bhaskaran, D. and Bobby SK Bhartia (2023). How do the UK's guidelines on imaging for suspected lung cancer compare with other countries? British Journal of General Practice, 73(727), pp.84–86. doi:https://doi.org/10.3399/bjgp23x731985.

- Australian and Canadian (British Columbia) guidelines encourage immediate CT if there is a strong clinical suspicion of lung cancer. These guidelines, along with the US guidelines, also advocate follow-up investigation with CT if symptoms persist or are unexplained following the CXR.
- Australian and New Zealand guidelines recommend repeat CXR if symptoms persist, for example, beyond 6 weeks. Australian guidance gives autonomy to GPs in the selection of appropriate testing strategies based on clinical intuition that includes CT, and CXR with or without repeat imaging of either modality.
- None of the guidelines addressed how decisions about investigation for symptoms may be influenced by participation in lung cancer screening with CT.

Suspected Lung Cancer Referral Guidelines: NICE and SRG

NICE	SRG
Lung cancer **Refer people using a suspected cancer pathway referral for lung cancer if they:** • have chest X-ray findings that suggest lung cancer or • are aged 40 and over with unexplained haemoptysis. **Offer an urgent chest X-ray (to be done within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, or if they have ever smoked and have 1 or more of the following unexplained symptoms:** • cough • fatigue • shortness of breath • chest pain • weight loss • appetite loss.	**Urgent suspicion of cancer CXR:** **Any unexplained haemoptysis** Unexplained and persistent (more than 3 weeks): • change in cough or new cough • dyspnoea • chest/shoulder pain • loss of appetite • weight loss • chest signs • hoarseness (if no other symptoms present to suggest lung cancer refer via Head & Neck pathway) • fatigue in a smoker aged over 40 years New or not previously documented finger clubbing Persistent or recurrent chest infection

Consider an urgent chest X-ray (to be done within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following: • persistent or recurrent chest infection • finger clubbing • supraclavicular lymphadenopathy or persistent cervical lymphadenopathy • chest signs consistent with lung cancer • thrombocytosis. **Mesothelioma** **Refer people using a suspected cancer pathway referral for mesothelioma if they have chest X-ray findings that suggest mesothelioma.** **Offer an urgent chest X-ray (to be done within 2 weeks) to assess for mesothelioma in people aged 40 and over, if:** • they have 2 or more of the following unexplained symptoms, or • they have 1 or more of the following unexplained symptoms and have ever smoked, or • they have 1 or more of the following unexplained symptoms and have been exposed to asbestos: • cough • fatigue • shortness of breath • chest pain	Cervical and/or persistent supraclavicular lymphadenopathy* Thrombocytosis where symptoms and signs do not suggest other specific cancer** Any person who has consolidation on chest x-ray should have further imaging no more than 6 weeks later to confirm resolution * if CXR normal, refer via Head & Neck pathway ** if CXR normal, consider alternative diagnosis including other cancers **Urgent Suspicion of Cancer Referral** • Any unexplained symptoms or signs detailed above persisting for longer than six weeks despite a normal chest X-ray (other than isolated thrombocytosis or cervical and/or persistent supraclavicular lymphadenopathy) • Chest x-ray suggestive/suspicious of lung cancer (including pleural effusion, pleural mass and slowly resolving consolidation) • Persistent haemoptysis in smokers/ex-smokers over 40 years of age

• weight loss • appetite loss. **Consider an urgent chest X-ray (to be done within 2 weeks) to assess for mesothelioma in people aged 40 and over with either:** • finger clubbing or • chest signs compatible with pleural disease.	