



Australian Government  
Cancer Australia

*Evidence report for*  
Investigating symptoms of  
lung cancer: a guide for all  
health professionals

May 2020

*Evidence report for Investigating symptoms of lung cancer: a guide for all health professionals* was prepared and produced by:

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## Foreword

Lung cancer is the fifth most commonly diagnosed cancer and the leading cause of cancer death in Australia.<sup>1</sup> Over half of lung cancers are diagnosed at an advanced stage, contributing to the low five-year relative survival rate of 17%.<sup>1</sup>

We know that diagnosis at an earlier stage of lung cancer leads to better survival outcomes for patients. However, diagnosing lung cancer can be challenging. Symptoms are often non-specific, which can impact on both patient and health professional awareness. Furthermore, the association of lung cancer with smoking can cause patients to feel stigmatised, contributing to delays in help-seeking for symptoms, and imaging results are not always definitive, which may cause uncertainty for health professionals to know what step to take next.

Not only is it important for all health professionals to be aware of the risk factors, symptoms and signs of lung cancer, but also understanding the recommended steps for investigating lung cancer in symptomatic patients will help ensure that patients are referred as quickly as possible into the multidisciplinary diagnostic pathway.

*Investigating symptoms of lung cancer: a guide for all health professionals* (the Guide) is an update of Cancer Australia's 2012 resource *Investigating symptoms of lung cancer: a guide for GPs*. We have expanded the target audience to include all health professionals, to encompass the diverse primary care workforce and to acknowledge the role of other health professionals, such as nurses and Aboriginal Health Workers, in the identification of lung cancer. Expanding the audience will support timely diagnosis for all Australians, including those living in rural, regional and remote settings.

The Guide reflects current, high-quality best-practice evidence. It provides health professionals with a systematic pathway for the appropriate investigation and referral of people with symptoms or signs of lung cancer. The Guide includes the optimal timeframes for action at each step in the pathway because timeliness is critical in the diagnosis of lung cancer.

This accompanying Evidence Report supports the recommendations in the Guide. It includes detailed information on lung cancer in Australia, risk factors for lung cancer, symptoms and signs consistent with lung cancer, and the importance of multidisciplinary teams in the management of patients with lung cancer. There are also additional recommendations to facilitate referral and patient support, while the inclusion of information about stigma reinforces the need for continued psychosocial support for those affected by lung cancer in Australia.

We anticipate that awareness and uptake of the recommendations in the Guide will promote our goal of improving outcomes for all people affected by lung cancer across Australia.



Professor Dorothy Keefe PSM MD  
Chief Executive Officer  
Cancer Australia

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## Acknowledgments

Cancer Australia gratefully acknowledges the support of the many individuals and organisations that contributed to the development of *Investigating Symptoms of Lung Cancer: a guide for all health professionals*, and this supplementary Evidence Report.

We would like to recognise the guidance and expertise of Cancer Australia's *Investigating Symptoms of Lung Cancer* Expert Reference Group, in particular, the consumer representatives who, in sharing their experiences of lung cancer, confirmed the need for this resource. See Appendix A for membership details.

We also acknowledge the input from the group of academic staff and health professionals at the Department of General Practice, Monash University who focus tested the Guide.

We appreciate the constructive feedback received during the external consultation of the Guide from individual health professionals, colleges, organisations and Cancer Australia's Lung Cancer Advisory Group. Through this consultation we captured valuable perspectives from primary care, cancer nursing, respiratory and surgical specialities, rural and remote healthcare sectors, Indigenous health professionals and lung cancer consumers.

Finally, we acknowledge the following colleges and organisations that support the Guide through endorsement or recognition as an Accepted Clinical Resource.

Australian College of Rural and Remote Medicine (ACRRM)  
Australian Primary Health Care Nurses Association (APNA)  
Cancer Nurses Society of Australia (CNSA)  
Consumers Health Forum of Australia (CHF)  
CRANaplus  
Lung Foundation Australia (LFA)  
National Aboriginal and Torres Strait Islander Health Workers Association (NATSIHWA)  
Royal Australasian College of Surgeons (RACS)  
Royal Australasian College of Physicians (RACP)  
The Royal Australian College of General Practitioners \*  
The Royal Australian and New Zealand College of Radiologists (RANZCR)  
The Thoracic Society of Australia and New Zealand (TSANZ).

\* The Guide has been officially recognised as an Accepted Clinical Resource by The Royal Australian College of General Practitioners.



# Part 1: Investigating symptoms of lung cancer: a guide for all health professionals

## Investigating symptoms of lung cancer

Lung cancer is the leading cause of cancer death in Australia. Symptoms of lung cancer can often be non-specific which may hinder early diagnosis and treatment.

### Risk factors for lung cancer

**Lifestyle factors**

- current or former tobacco smoking

**Environmental or occupational factors**

- passive smoking
- occupational exposures e.g. radon, asbestos, diesel exhaust, silica
- air pollution

**Personal factors**

- Increasing age
- family history of lung cancer
- chronic lung disease e.g. chronic obstructive pulmonary disease (COPD), pulmonary fibrosis
- personal history of cancer e.g. lung cancer, head and neck cancer, bladder cancer

### Risk of lung cancer in different populations

- ▶ While smoking is the largest single cause of lung cancer, **people who have never smoked may also be diagnosed with lung cancer.** About 90% of lung cancer in males and 65% in females is estimated to be a result of tobacco smoking.<sup>1</sup>
- ▶ Aboriginal and Torres Strait Islander people are twice as likely to be diagnosed with and die from lung cancer<sup>2</sup> and have lower 5-year survival<sup>3</sup> compared with non-Indigenous Australians.
- ▶ Incidence and mortality increase with remoteness and are highest for those living in lower socioeconomic areas.<sup>3</sup>
- ▶ The association of lung cancer with smoking can lead to lung cancer patients feeling stigmatised, contributing to delays in help-seeking for symptoms<sup>4,5</sup> and psychological distress.<sup>6</sup>

### Symptoms and signs of lung cancer

- ▶ Symptoms can present in a similar manner to other conditions such as COPD, chronic heart failure and coronary heart disease.<sup>7</sup>
- ▶ Please refer to the flow chart overleaf for symptoms and signs of lung cancer, recommended investigations and referrals, and timeframes for referral.

## a guide for all health professionals

May 2020

This guide has been developed to assist all health professionals to investigate **symptomatic** people with suspected lung cancer and support their early and rapid referral into the diagnostic pathway. This is a general guide to appropriate practice to be followed subject to the clinician's judgement in each individual case. The guide is based on the best available evidence and expert consensus.

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### Early detection and diagnosis of lung cancer improves chances of survival<sup>8</sup>

- ▶ Health professionals working in primary care are integral to early detection, as the majority of patients with cancer first present to primary care settings.<sup>9</sup> In the three months leading up to diagnosis, patients often see a GP ≥ 4 times before a diagnosis of lung cancer is made.<sup>10</sup>

#### Stage at diagnosis and 5-year survival of lung cancer<sup>11,12</sup>

Category	Proportion of lung cancer cases by stage in 2011 (%)	5-year relative survival by stage 2011-2016 (%)
Stage 1	10	68
Stage 2	10	32
Stage 3	10	17
Stage 4	40	3
Unknown stage	28	14
Lung cancer overall 5-yr survival	-	17
All cancers combined 5-yr survival	-	69

### Optimal imaging modalities for lung cancer

- ▶ Chest CT scans should be offered when there is a strong clinical suspicion of lung cancer. They should be delivered with contrast unless contraindicated.
- ▶ Low-dose CT (LDCT) scans have a lower radiation dose compared to conventional chest CT scans, provide good clinical information and are more sensitive than chest X-ray in the diagnosis of lung cancer.<sup>13</sup>
- ▶ There is ongoing national and international research into the role of LDCT screening for lung cancer in asymptomatic people. For more information on the potential role of screening for asymptomatic patients, visit [Cancer Australia's lung cancer screening enquiry information centre](#).

### Multidisciplinary care is the best practice approach to providing evidence-based cancer care<sup>14</sup>

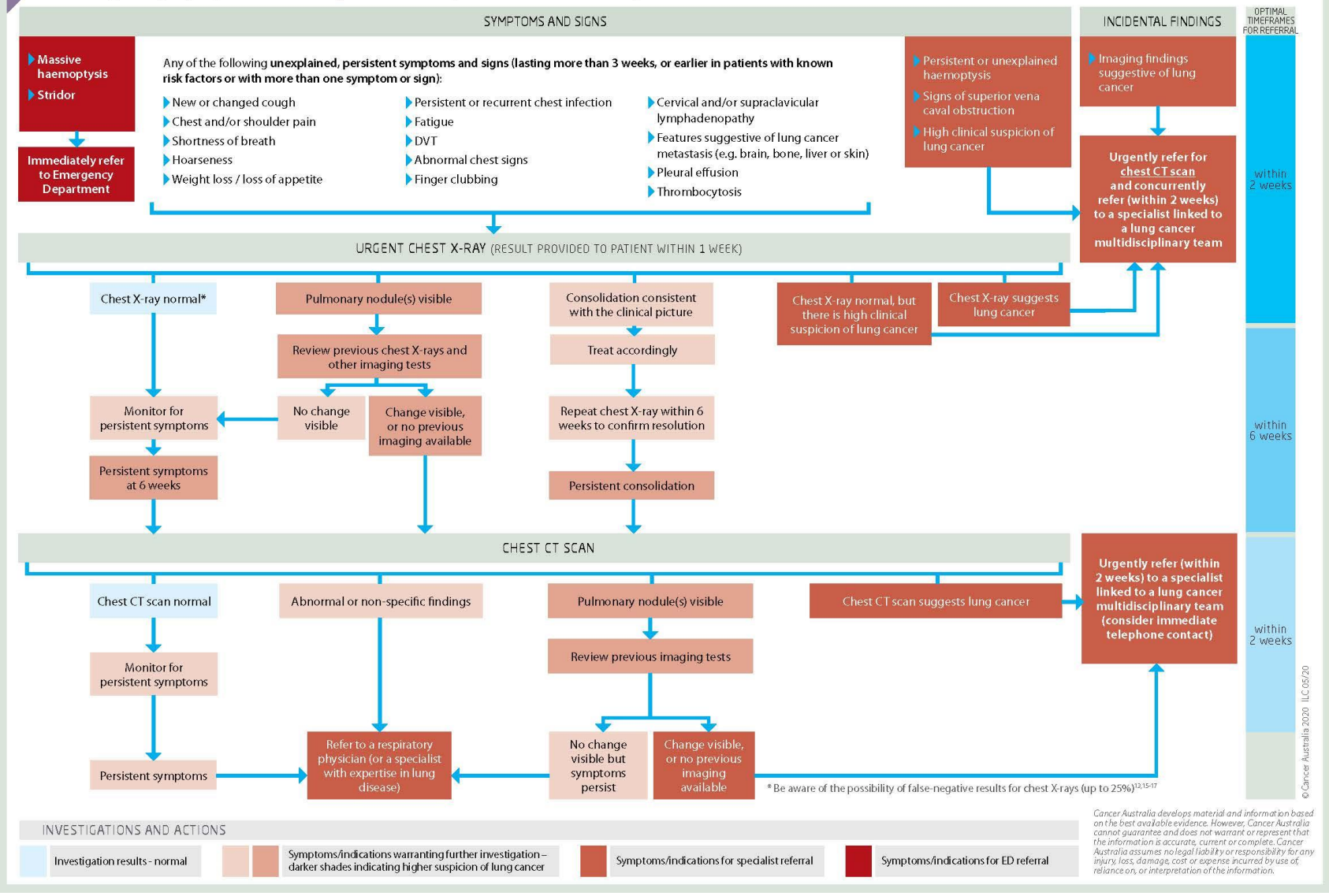
- ▶ All patients with suspected lung cancer should be referred to a specialist with expertise in lung cancer who is affiliated with a multidisciplinary team (MDT).
- ▶ Ensure referrals are made in a timely manner; the first specialist appointment should take place within two weeks of referral.
- ▶ Lung Foundation Australia's MDT directory provides useful information about MDTs with expertise in lung cancer, visit [lungfoundation.com.au/lung-cancer-mdt/](http://lungfoundation.com.au/lung-cancer-mdt/)

For the full recommendations, the evidence underpinning this guide and reference list, visit [canceraustralia.gov.au](http://canceraustralia.gov.au)

Accepted Clinical Resource: Australian College of Rural & Remote Medicine

Endorsed by:

# Investigating symptoms of lung cancer - a guide for all health professionals





## Part 2: Background

### 2.1 Introduction

Lung cancer is the fifth most commonly diagnosed cancer in Australia and is the leading cause of cancer death and cancer burden.<sup>1</sup> Early diagnosis leads to improved survival.<sup>2</sup> Nationally, 18% of lung cancers are diagnosed at an early stage and 53% at an advanced stage.<sup>1</sup> The five-year survival for lung cancers diagnosed an early stage (stage 1 and stage 2) are 68% and 32% respectively compared to 17% and 3% for those diagnosed at an advanced stage (stage 3 and stage 4).<sup>1</sup>

Non-specific lung cancer symptoms can make both patient awareness and primary care diagnosis difficult.<sup>3</sup> Many of the symptoms of lung cancer are commonly encountered in primary care but are often non-specific, such as cough and chest pain, which can hinder early diagnosis and treatment.<sup>4,5</sup> Lung cancer presentations can also be complex, due to co-morbidities or plausible alternative diagnoses.<sup>6</sup> Lung cancer symptoms can present in a similar manner to other conditions such as chronic obstructive pulmonary disease (COPD), chronic heart failure and coronary heart disease.<sup>7</sup> Therefore, it is important to increase awareness of lung cancer symptoms and risk factors, and to provide all health professionals with the most recent evidence to assist in the appropriate investigation of people with suspected lung cancer and the early and rapid referral into the diagnostic pathway.

### 2.2 The 2012 Guide

Cancer Australia resource *Investigating symptoms of lung cancer: a guide for GPs (2012)* (The Guide)<sup>8</sup> was first published by Cancer Australia in 2012 to provide guidance on the appropriate investigation of people with symptoms that are consistent with lung cancer, and to support their early and rapid referral into the cancer care pathway. The Guide was developed using an evidence-based systematic approach<sup>9</sup> and was endorsed by the Royal Australian College of General Practitioners. The Guide included guidance (24 recommendations) in relation to symptoms of lung cancer, investigations in patients with suspected lung cancer and referral pathways for people with suspected lung cancer.

A flow chart to assist general practitioners (GPs) was developed based on the 24 recommendations and included in the Guide. The algorithm presents the recommendations as part of a flow chart based on symptoms and signs, various outcomes of primary care investigations and referral pathways. The Guide has been a key resource for GPs seeking guidance on the pathway for investigation and referral of patients who present with symptoms and signs suggestive of lung cancer.

### 2.3 Purpose and scope

The purpose of this Report is to outline the methodology undertaken to revise and update The Guide. The Guide is intended to be a concise, easily accessible and evidence-based tool to assist all health professionals to investigate symptomatic people with suspected lung cancer and support their early and rapid referral into the diagnostic pathway. This is a general guide to appropriate practice to be followed subject to the clinician's judgement in

each individual case. The Guide is based on the best available evidence and expert consensus.

The Evidence report and the Guide provides information and guidance about:

- lung cancer in Australia
- the importance of multidisciplinary teams (MDTs)
- risk factors for lung cancer
- symptoms and signs consistent with lung cancer
- initial investigations and diagnosis
- referral pathways
- patient support and information for patients and carers.

The Guide provides information to assist all health professionals in the appropriate assessment/ investigation and referral of adult patients who present to primary care with symptoms or signs consistent with lung cancer.

The Guide does not provide advice on the following:

- adults with mesothelioma
- adults with lung metastases arising from primary cancer originating outside the lung
- children (younger than 18 years) with lung cancer
- adults with rare lung tumours
- adults with benign lung tumours, and
- adults being screened for lung cancer. For more information on the potential role of screening for asymptomatic patients, visit [Cancer Australia's lung cancer screening enquiry information centre](#).

## Part 3: Methodology

### 3.1 Development process (2012 Guide)

The 2012 Guide was developed using the ADAPTE framework for guideline adaptation.<sup>10</sup> A multidisciplinary Expert Advisory Panel (EAP) was convened to oversee the development of the Guide. A search to identify relevant guidelines was conducted in May 2011 and a short-list of 13 identified guidelines were assessed using the AGREE process.<sup>11</sup> Three guidelines with the highest overall AGREE scores were selected for further consideration:

- New Zealand Guidelines Group (NZGG) guidelines, "*Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities*"<sup>12</sup>
- National Institute of Clinical and Health Excellence (NICE) guidelines, "*The diagnosis and treatment of lung cancer*"<sup>13</sup>
- American College of Chest Physicians guidelines, "*Diagnosis and Management of Lung Cancer*" (ACCP 2007).<sup>14-20</sup>

The majority of the recommendations from the 2012 Guide were adapted or endorsed from these three guidelines.

For the complete development process of the 2012 Guide, refer to previous *Evidence relevant to the guide for the investigation of symptoms of lung cancer* (November 2012).<sup>9</sup>

### 3.2 Update of the Guide

The update of Cancer Australia's 2012 Guide followed an evidence-based systematic approach to ensure that the Guide reflects current and high-quality best-practice evidence in the appropriate investigation and referral of people with symptoms or signs that are consistent with lung cancer.

#### 3.2.1 Recommendation update methods

The following categorisation and approach to updating was used to inform the updated content and recommendations of the Guide:

- A. Updated or new recommendations informed by consensus opinion and agreement
- B. Updated or new recommendations informed by high quality national and international guidelines and evidence-based resources
- C. Updated or new recommendations informed by targeted evidence review
- D. No amendments required; original 2012 recommendation accepted.

#### **Category A – Updated or new recommendations informed by consensus opinion and agreement**

Members considered revised wording for recommendations where insufficient evidence was available to support a new or updated recommendation. Potential amended wording was

circulated to members for their input and support. Consensus agreement was achieved when the final wording was agreed as acceptable to at least 75% of the members.

### **Category B – Updated or new recommendations informed by high quality national and international guidelines and evidence-based resources**

Where there was sufficient evidence identified in high quality national and international resources, previous recommendations were amended or new recommendations were developed based on these resources. Sources were identified from review of international guidelines, recent publications by peak national/international agencies and government reports and resources (see section 3.2.2).

### **Category C – Updated or new recommendations informed by targeted evidence review**

Members agreed that some recommendations should be updated based on relevant national and international studies identified through a targeted evidence review. For update method C, three areas were identified where a targeted evidence review was required to inform and support updated or new recommendations.

A summary of the results of the targeted evidence review are provided in Appendix B.

### **Category D – No update required**

Where no amendments were required to the original recommendation from the 2012 Guide, these were considered as method D.

## **3.2.2 Review of national and international guidelines**

Cancer Australia commissioned a preliminary assessment of the Guide to assess the currency of the resource compared to other comparable national and international guidelines and high-level evidence reviews (i.e. systematic reviews and meta-analyses). This assessment identified areas that required an update and opportunities for the incorporation of new information into the Guide. A search to identify the relevant guidelines was conducted in June 2018 using the following websites:

- AHRQ EPC Reports
- American College of Chest Physicians (ACCP)
- American College of Radiology (ACR)
- American Society of Clinical Oncology (ASCO)
- Cancer Care Ontario (CCO)
- Cancer Council Australia
- Centre for Reviews and Dissemination (CRD)
- Cochrane Library
- European Association for Cardio-Thoracic Surgery (EACTS)
- European Society for Medical Oncology (ESMO)
- Google Scholar
- Institute for Clinical Systems Improvement
- International Guidelines Library (G-I-N)
- National Comprehensive Cancer Network (NCCN)
- National Guideline Clearinghouse (AHRQ)
- National Institute for Health and Care Excellence (NICE)
- New Zealand Ministry of Health (includes New Zealand Guidelines Group)
- NHMRC Guideline Portal

- Scottish Intercollegiate Guidelines Network (SIGN)
- The Royal Australian College of General Practitioners (RACGP)
- US Preventive Services Task Force.

A search in PubMed was also conducted using various combinations of terms, including “lung cancer”. Both searches were restricted to guidelines and reviews published from January 2012 to May 2018 and yielded a total of 49 results.

A short-list of 27 guidelines and 16 evidence reviews were compared with the Cancer Australia 2012 Guide to determine similarities/differences and identify more recent evidence references in the later guidelines. Short-listed clinical practice guidelines were assessed using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) tool<sup>30</sup>. The AGREE II tool assesses the following domains on a 7-point scale (1-strongly disagree to 7-strongly agree):

- Domain 1. Scope and purpose
- Domain 2. Stakeholder involvement
- Domain 3. Rigour of development
- Domain 4. Clarity of presentation
- Domain 5. Applicability
- Domain 6. Editorial independence

The following guidelines assessed as the highest quality included:

- Scottish Intercollegiate Guidelines Network (SIGN) Management of lung cancer (2014)
- National Institute for Health and Care Excellence (NICE) Suspected cancer: recognition and referral (2015)
- American College of Chest Physicians (ACCP) Diagnosis and management of lung cancer, 3rd Ed. (2013)
- Belgian Health Care Knowledge Centre (KCE) Non-small cell and small cell lung cancer: diagnosis, treatment and follow-up (2013)
- British Thoracic Society (BTS) guidelines for the investigation and management of pulmonary nodules (2015) and guideline for diagnostic flexible bronchoscopy in adults (2013).

Other resources that provide guidance but are not official clinical practice guidelines, such as clinical standards and Optimal Care Pathways were assessed narratively using the same domains as above, however formal scores were not applied as these resources are not designed as guidelines. The care pathways were considered to be of high quality with regards to domains such as scope and purpose, stakeholder involvement and clarity of presentation, however it was often unclear regarding the rigour of development domain as there was no mention of systematic reviews supporting the pathways and limited primary evidence was referenced. Systematic reviews were appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2)<sup>43</sup>, with nine considered ‘moderate’ quality reviews, five considered ‘low’ quality reviews and one considered ‘critically low’. Almost all reviews (except for one Cochrane review) did not perform a comprehensive search according to the AMSTAR 2 criteria.

Each guideline was reviewed and compared with the Cancer Australia 2012 Guide to determine whether the more recent guidelines were consistent and/or provided new evidence in comparison to the 2012 Guide.

Key resources identified in the preliminary assessment that were considered most relevant, and provided additional information for the update of the Guide were the Australian *Optimal Care Pathway for people with lung cancer* (2016),<sup>21</sup> the NICE guidelines for

*Suspected cancer: recognition and referral* (2015).<sup>22</sup> and the Cancer Care Ontario Guidelines for *Referral of suspected lung cancer by family physicians and other primary care providers* (2019)<sup>23</sup>. The NICE guidelines were supported by evidence reviews (including evidence published up to August 2014), however for some topic areas, no clinical evidence was identified and therefore, recommendations were made by expert opinion.

Of the 27 guidelines and 16 evidence reviews identified, the following sources were used to inform new or updated recommendations:

- the [Cancer Care Ontario Guidelines for Referral of suspected lung cancer by family physicians and other primary care providers \(2019\)](#)<sup>23</sup>
- the [AIHW Cancer in Australia 2019 report](#)<sup>1</sup>
- the [Cancer Australia Lung Cancer Framework \(2018\) \(Lung Cancer Framework\)](#)<sup>24</sup>
- the [Optimal Care Pathway for Aboriginal and Torres Strait Islander people with cancer \(2018\)](#)<sup>25</sup>
- the [Optimal Care Pathway for people with lung cancer \(2016\)](#)<sup>21</sup>
- the [National Institute for Health and Care Excellence Suspected cancer: recognition and referral guidelines \(NICE 2015\)](#)<sup>22</sup>
- the [Cancer Australia Risk factors for lung cancer review \(2014\)](#)<sup>26</sup>

For those recommendations where national and international evidence was not available, targeted evidence reviews were undertaken to inform and support new or updated recommendations.

### **3.2.3 Targeted evidence reviews**

Three research questions for the targeted systematic evidence reviews were determined in consultation with the Expert Reference Group (ERG). The research questions were:

- 1) What is the effectiveness of first-line investigations for patients presenting to primary care with symptoms and signs consistent with lung cancer?
- 2) What strategies are effective to assess and follow-up patients who present in primary care with persistent symptoms/signs who are either considered at low-risk of lung cancer or who have had previous normal/negative imaging results?
- 3) Are there combinations of signs, symptoms and/or risk factors that are more likely to predict lung cancer?

Literature searches were undertaken in February 2019 in electronic databases PubMed and OVID (EMBASE, Medline and PsycINFO). Individual targeted search strategies were performed for each research question (see Appendix B). The searches were limited to publication date 2012-2019 and English language.

Articles identified in the search were screened for eligibility based on their title and abstract (first round) and full text (second round) by two independent reviewers. Any queries were discussed with Cancer Australia and resolved with a third reviewer. Data extraction and critical appraisal of the included studies was performed by one reviewer and checked by another reviewer for accuracy.

Critical appraisal of the included studies was conducted using a variety of available tools:

- Systematic reviews were appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2).<sup>27</sup>
- Primary studies (including RCTs, cohorts, case-control studies, and qualitative studies) were appraised using checklists developed by the UK Critical Appraisal Skills Programme (CASP).<sup>28</sup>

For primary studies which were not included in the CASP checklists, the following tools were used:

- Mixed methods studies were appraised using the Mixed Methods Appraisal Tool (MMAT)<sup>29</sup>
- Cross-sectional studies were appraised using the AXIS tool.<sup>30</sup>

A summary of the results of the targeted evidence reviews is provided in Appendix B.

### 3.2.4 Expert Reference Group

A multidisciplinary Expert Reference Group (ERG) was established to oversee and provide high-level expert advice to the update of the Guide (see Appendix A for membership). The ERG comprises representatives with clinical, academic and consumer knowledge and experience. Colleges with representation on the ERG include the Royal Australian College of General Practitioners (RACGP), the Royal Australian and New Zealand College of Radiologists (RANZCR), the Royal Australasian College of Surgeons (RACS), the Royal Australasian College of Physicians (RACP), the Australian Indigenous Doctors' Association (AIDA), the Thoracic Society of Australia and New Zealand (TSANZ) and the Cancer Nurses Society of Australia (CNSA).

The ERG was supported by the Cancer Australia project team who provided project management and technical support for the development of the Guide.

All members of the Expert Reference Group completed statements on their conflicts of interest. No conflicts of interest were identified.

Based on discussions at the ERG meetings held in November 2018, May 2019 and September 2019, the content and recommendations in the Guide were updated by the most appropriate categorisation and method to update, as agreed by consensus agreement with the ERG members. Many of the original recommendations have been retained with some amendments to ensure consistency with recent national and international resources. Where there are differences in the wording of endorsed recommendations, these have been updated by the ERG to ensure consistency of wording in the updated Guide. The ERG agreed that only those recommendations and supporting content that provides the most direct and relevant guidance for supporting best practice care for the investigation of lung cancer should be included in the Guide. For completeness, other recommendations, including those that facilitate referral and patient support, have been retained in the Evidence report.

## 3.3 External review and consultation process

The updated Guide was focus tested with a group of primary care health professionals and academic staff at Monash University, Melbourne in October 2019. The Guide was circulated to professional colleges, cancer organisations and key individual stakeholders for external consultation during October to November 2019. Feedback was considered by the ERG in November 2019 and amendments incorporated based on consensus.

## **Part 4: Investigating symptoms of lung cancer - recommendations**

### **4.1 Recommendations**

The 2020 Guide recommendations are provided in Table 1.

Recommendations are grouped into the following topic areas:

- signs and symptoms
- investigations
- referral (includes recommendations to facilitate referral and patient support).



**Table 1 Summary of original and updated recommendations, and method for update**

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
<b>Signs and symptoms</b>			
<p>1 Investigate symptoms of lung cancer in patients with the following risks:</p> <p>lifestyle factors:</p> <ul style="list-style-type: none"> <li>• tobacco smoking, former tobacco smoking.</li> </ul> <p>environmental factors:</p> <ul style="list-style-type: none"> <li>• passive smoking</li> <li>• radon exposure</li> <li>• occupational exposure, e.g. previous exposure to asbestos, diesel exhaust</li> <li>• air pollution.</li> </ul> <p>personal factors:</p> <ul style="list-style-type: none"> <li>• age</li> <li>• family history of lung cancer</li> <li>• smoking-related chronic obstructive pulmonary disease</li> <li>• previous lung diseases</li> <li>• history of cancer especially head and neck cancer</li> </ul>	<p>International expert opinion, NZGG 2009</p> <p>Adapted to include risks identified in AIHW 2011 and IARC 2012</p>	<p>1* Consider possible risk factors when investigating patients with signs or symptoms consistent with lung cancer. Risk factors for lung cancer include:</p> <ul style="list-style-type: none"> <li>• lifestyle factors: <ul style="list-style-type: none"> <li>– Current or former tobacco smoking</li> </ul> </li> <li>• environmental or occupational factors: <ul style="list-style-type: none"> <li>– passive smoking</li> <li>– occupational exposure, e.g. radon (including underground workers in poorly ventilated environments, such as underground miners), asbestos, diesel exhaust, silica</li> <li>– air pollution</li> </ul> </li> <li>• personal factors: <ul style="list-style-type: none"> <li>– age</li> <li>– family history of lung cancer</li> <li>– chronic lung disease, e.g. chronic obstructive pulmonary disease (COPD), pulmonary fibrosis</li> <li>– personal history of cancer e.g. lung cancer, head and neck cancer, bladder cancer</li> </ul> </li> </ul>	<p>Method for update: Category B</p> <p>Reworded to group "environmental or occupational factors" together to be consistent with Cancer Australia <i>risk factors for lung cancer</i> report (2014). Amendments to personal factors as agreed by consensus by the ERG.</p>
<p>2 Urgently refer a patient for a chest X-ray if they have:</p> <ul style="list-style-type: none"> <li>• unexplained haemoptysis</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• any of the following unexplained, persistent symptoms and signs (lasting more than 3 weeks or less</li> </ul>	<p>International expert opinion, NZGG 2009</p> <p>Reworded to include "new or changed" cough, "unresolved chest infection" and "signs of pleural</p>	<p>2* Urgently refer a patient for a chest X-ray if they have:</p> <ul style="list-style-type: none"> <li>• any of the following unexplained, persistent symptoms and signs (lasting more than 3 weeks, or earlier in patients with known risk factors or with more than one symptom or sign):</li> </ul>	<p>Method for update: Category B</p> <p>Reworded to include "persistent or recurrent chest infection", "fatigue", "deep vein thrombosis (DVT)" and</p>

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
<p>than 3 weeks in patients with known risk factors):</p> <ul style="list-style-type: none"> <li>• new or changed cough</li> <li>• chest and/or shoulder pain</li> <li>• shortness of breath</li> <li>• hoarseness</li> <li>• weight loss/loss of appetite</li> <li>• unresolved chest infection</li> <li>• abnormal chest signs</li> <li>• finger clubbing</li> <li>• cervical and/or supraclavicular lymphadenopathy</li> <li>• features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin)</li> <li>• signs of pleural effusion.</li> </ul>	<p>effusion”.</p>	<ul style="list-style-type: none"> <li>– new or changed cough</li> <li>– chest and/or shoulder pain</li> <li>– shortness of breath</li> <li>– hoarseness</li> <li>– weight loss/loss of appetite</li> <li>– persistent or recurrent chest infection</li> <li>– fatigue</li> <li>– deep vein thrombosis (DVT)</li> <li>– abnormal chest signs</li> <li>– finger clubbing</li> <li>– cervical and/or supraclavicular lymphadenopathy</li> <li>– features suggestive of lung cancer metastasis (for example, in brain, bone, liver or skin)</li> <li>– signs of pleural effusion</li> <li>– thrombocytosis</li> </ul>	<p>“thrombocytosis” as these are included in 2015 NICE guidelines.</p> <p>Included earlier referral for patients with more than one symptom as agreed by consensus with the ERG.</p>
<b>Investigations</b>			
<p>3 Review previous chest X-rays and other relevant imaging tests in every patient with a pulmonary nodule(s) that is visible on chest X-ray.</p>	<p>Level III-3, ACCP 2007</p>	<p>3* Review previous chest X-rays and other relevant imaging tests in every patient with a pulmonary nodule(s) that is visible on chest X-ray.</p>	<p>Method for update: Category D</p>
<p>4 Refer any patient with risk factors for lung cancer, who has clinical and chest X-ray features of pneumonia for a repeat chest X-ray within 6 weeks to confirm resolution.</p>	<p>International expert opinion, NZGG 2009 Reworded to include “has clinical and chest X-ray features of pneumonia”.</p>	<p>4* If chest X-ray shows consolidation consistent with the clinical picture, treat accordingly and repeat chest X-ray within 6 weeks. If persistent consolidation, refer to chest CT scan.</p>	<p>Method for update: Category A</p> <p>Reworded to be consistent with recommendation as presented in Guide algorithm.</p>
<p>5 After urgent referral for chest X-ray, ensure the chest X-ray is completed, reported and reviewed</p>	<p>International expert opinion, NZGG 2009</p>	<p>5* After urgent referral for chest X-ray, ensure the chest X-ray is completed, reported and reviewed as soon as</p>	<p>Method for update: Category B</p>

\* Recommendation included in the Guide

<b>Recommendation (2012 Guide)</b>	<b>Original evidence base and source (2012)</b>	<b>Recommendation amendment (2020 Guide)</b>	<b>Method for update, additional evidence base and source (2020 Guide)</b>
as soon as possible.	Reworded to replace "the chest X-ray should be completed and reported within one week", with "ensure the chest X-ray is completed, reported and reviewed as soon as possible".	possible. Test results should be provided to the patient within one week.	Reworded to include "Test results should be provided to the patient within one week." Expert opinion, OCP for lung cancer 2016.
6 Perform chest computed tomography (CT) in every patient with a pulmonary nodule(s) that shows change on chest X-ray or if no previous imaging is available.	Level III-3, ACCP 2007  Reworded from "indeterminate single pulmonary nodule" to "a pulmonary nodule(s) that shows change on chest X-ray or if no previous imaging is available".	6* Perform chest CT scan in every patient with a pulmonary nodule(s) that shows change on chest X-ray or if no previous imaging is available.	Method for update: Category A
7 Review previous imaging tests in every patient with a pulmonary nodule(s) that is/are visible on chest CT scan.	Level III-3, ACCP 2007  Reworded from "indeterminate single pulmonary nodule" to "pulmonary nodule(s)".	7* Review previous imaging tests in every patient with a pulmonary nodule(s) that is/are visible on chest CT scan.  Urgently refer to a specialist linked to a lung cancer multidisciplinary team for patients with a pulmonary nodule(s) that shows change on chest CT scan or if no previous imaging is available for review. If no change is visible and symptoms persist, refer to a respiratory physician (or a specialist with expertise in lung disease).	Method for update: Category A  Reworded to be consistent with recommendation as presented in Guide algorithm, minor amendments made as agreed by consensus by the ERG.
8 In the general practice setting sputum cytology is not recommended for the investigation of lung cancer due to its low	International expert opinion, NZGG 2009  Reworded to qualify this	8 In the general practice setting sputum cytology is not recommended for the investigation of lung cancer due to its low sensitivity and increased risk of delay.	Method for update: Category D  Nil amendments.

\* Recommendation included in the Guide

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Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
sensitivity and increased risk of delay.	statement to relate to the general practice setting and include limitations of the test.		
9 If a chest X-ray is normal and symptoms persist, refer the patient for a chest CT scan.	New recommendation Australian local expert advisory panel consensus statement.	9* If a chest X-ray is normal, monitor for persistent symptoms. Advise the patient to return for referral for a chest CT scan if symptoms persist at 6 weeks.	Method for update: Category A  Australian local ERG consensus statement.
10 If a chest CT scan is normal and symptoms persist, refer the patient to a respiratory physician (or a designated specialist with expertise in lung disease)	New recommendation Australian local expert advisory panel consensus statement.	10* If a chest CT scan is normal, monitor for persistent symptoms. If symptoms persist, refer the patient to a respiratory physician (or a specialist with expertise in lung disease). i. If chest CT scan findings are abnormal or non-specific, and not suggestive of lung cancer, refer the patient to a respiratory physician (or a specialist with expertise in lung disease).	Method for update: Category D  Reworded to include "monitor for persistent symptoms" to be consistent with recommendation as presented in the Guide algorithm.
<b>Referral</b>			
11 Immediately refer a patient to an emergency department if any of the following are present: • massive haemoptysis • stridor.	International expert opinion NICE 2011, with adaptations by the Australian local expert advisory panel consensus  Reworded to recommend immediate referral to emergency department for symptoms of massive haemoptysis and stridor, regardless of smoking status.	11* Immediately refer a patient to an emergency department if any of the following are present: • massive haemoptysis • stridor.	Method for update: Category D  Nil amendments.

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
<p>12 Urgently refer a patient to a specialist linked to a lung cancer multidisciplinary team, while awaiting results of a chest CT, if the patient has:</p> <ul style="list-style-type: none"> <li>• persistent haemoptysis and are smokers or former smokers aged 40 years or older or who have other risk factors,</li> <li>• signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure), or</li> <li>• a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation).</li> </ul>	<p>International expert opinion, NZGG 2009</p> <p>International expert opinion, NICE 2011</p> <p>Reworded to include "specialist linked to a lung cancer Multidisciplinary team".</p>	<p>12* Urgently refer (within 2 weeks) a patient to a specialist linked to a lung cancer multidisciplinary team, while awaiting results of a chest CT, if the patient has:</p> <ul style="list-style-type: none"> <li>• persistent or unexplained haemoptysis</li> <li>• signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure), or</li> <li>• imaging findings suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)</li> <li>• high clinical suspicion of lung cancer.</li> </ul>	<p>Method for update: Category A</p> <p>"unexplained haemoptysis" added to be consistent with NICE 2015 guidelines, however without addition of risk factors as agreed by consensus by the ERG.</p> <p>"chest X-ray" reworded to "imaging findings" as agreed by consensus by the ERG.</p> <p>"high clinical suspicion of lung cancer" included as agreed by consensus by the ERG.</p>
<p>13 Urgently refer a patient to a specialist linked to a lung cancer multidisciplinary team if a chest X-ray or CT scan suggests lung cancer (including pleural effusion and slowly resolving consolidation).</p>	<p>International expert opinion, NICE 2011</p> <p>Reworded to include "specialist linked to a lung cancer multidisciplinary team".</p>	<p>13* Urgently refer (within 2 weeks) a patient to a specialist linked to a lung cancer multidisciplinary team if imaging suggests lung cancer (including pleural effusion and slowly resolving consolidation).</p>	<p>Method for update: Category A</p> <p>Minor amendments made to the original recommendation as agreed by consensus by the ERG.</p>
<p>14 Urgently refer a patient to a specialist linked to a lung cancer multidisciplinary team, while awaiting results of a chest CT scan, if the patient has a normal chest X-ray, but there is a high suspicion of</p>	<p>International expert opinion, NZGG 2009</p> <p>Reworded to replace "referral to specialist" with "referral to a specialist linked</p>	<p>14* Urgently refer (within 2 weeks) a patient for chest CT scan and concurrently refer to a specialist linked to a lung cancer multidisciplinary team, if the patient has a normal chest X-ray, but there is a high clinical suspicion of lung cancer.</p>	<p>Method for update: Category A</p> <p>Minor amendments made to the original recommendation as agreed</p>

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
lung cancer.	to a lung cancer multidisciplinary team, while awaiting the results of a chest CT scan"		by consensus by the ERG.
15 Consider immediate telephone contact with an appropriate specialty service when the patient has a high index of suspicion of lung cancer.	International expert opinion, NZGG 2009  Reworded to include reference to lung cancer	15* Urgently refer (within 2 weeks) to a specialist linked to a lung cancer multidisciplinary team (consider immediate telephone contact) when there is a high index of suspicion of lung cancer.	Method for update: Category A  Minor amendments made to the original recommendation to be consistent with recommendation as presented in the Guide algorithm as agreed by consensus by the ERG.
<i>Recommendations to facilitate referral and patient support</i>			
16 Ensure referrals: • are made in a timely manner, and • provide relevant and sufficiently detailed information to the specialist, including the most appropriate way to contact the patient.	International expert opinion, NZGG 2009	16* Ensure referrals provide relevant and sufficiently detailed information to the specialist, including: • the most appropriate way to contact the patient • all relevant clinical information and investigations • notification if an interpreter service is required.  Ensure referrals are made in a timely manner, the first specialist appointment should take place within two weeks of referral.	Method for update: Category B  Amendments informed by OCP for lung cancer 2016 and agreed by consensus by the ERG.
17 Ensure that the patient is aware of the timeframes, where available,	International expert opinion, NZGG 2009	17 When a patient presents with signs or symptoms suggestive of lung cancer,	Method for update: Category B

\* Recommendation included in the Guide

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Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
for: <ul style="list-style-type: none"> <li>receiving an acknowledgment of the referral, or</li> <li>being seen by a specialist or an investigation service.</li> </ul>		provide information that clearly describes: <ul style="list-style-type: none"> <li>why and where they are being referred and how to obtain information about lung cancer</li> <li>by whom the patient will be seen and who to contact if they have any questions about their appointment</li> <li>what a patient can expect from the specialty service</li> <li>the expected timeframes for appointments and when they will be seen by a specialist or an investigation service</li> </ul>	Amendments informed by OCP for lung cancer 2016, and NICE 2015 guidelines and agreed by consensus by the ERG.
18 When a patient presents with signs or symptoms suggestive of lung cancer, provide information that clearly describes: <ul style="list-style-type: none"> <li>where the patient is being referred</li> <li>by whom the patient will be seen</li> <li>what a patient can expect from the speciality service.</li> </ul>	International expert opinion, NZGG 2009  Reworded to include reference to lung cancer.		
19 Advise patients to carry their previous imaging results when they attend for a new chest X-ray or chest CT scan.	New recommendation, Australian local EAP consensus statement.	18 Advise patients to carry all relevant imaging and results, where possible, when they attend for a chest X-ray or chest CT scan.	Method for update: Category A  Minor amendments made to the original recommendation as agreed by consensus by the ERG.
20 Advise patients to stop smoking, and advise the patient why this is important.	Level III-3, NICE 2011  Reworded to remove "as soon as the diagnosis of lung cancer is suspected".	19 All current smokers should be offered smoking cessation advice and support to quit.	Method for update: Category B  Consensus statement, OCP for lung cancer 2016.
21 Offer nicotine replacement therapy and other therapies to assist patients to stop smoking.	Level III-3, NICE 2011		
22 Address the patient's need for continuing support while the patient is waiting for a referral appointment(s). Include inviting the	International expert opinion, NZGG 2009	20 Address the patient's need for continuing support while the patient is waiting for a referral appointment(s). Include inviting the patient to contact the	Method for update: Category B  Added supportive care

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
patient to contact the GP again if the patient has concerns or further questions before their specialist appointment.		GP and GPN again if the patient has concerns or further questions before their specialist appointment. Assess supportive and palliative care needs and refer to appropriate health professionals or organisations.	statement to be consistent with OCP for lung cancer 2016.
23 Where possible, provide culturally-appropriate information and support.	International expert opinion, NZGG 2009  Reworded to replace "enquire about a person's ethnicity to ensure that the person's health care preferences can be met" with "provide culturally appropriate information and support".	21 Provide information that is appropriate for the person in terms of language, health literacy and culture, recognising the potential for different cultural meanings associated with the possibility of cancer.	Method for update: Category B  International expert opinion, NICE 2015 Reworded "ability" to "health literacy".
		<ul style="list-style-type: none"> <li>Every patient will have different communication needs, including cultural and language differences. The <i>Lung cancer framework</i> and the <i>Optimal Care Pathway for people with lung cancer</i> provide further information regarding communication and coordination of care strategies.</li> </ul>	Added to be consistent with OCP for lung cancer 2016.
		<ul style="list-style-type: none"> <li>Some Aboriginal and Torres Strait Islander people may have personal or cultural factors that affect the presentation and investigative pathway. Refer to the <i>Optimal Care Pathway for Aboriginal and Torres Strait Islander people with cancer</i> for detailed information.</li> </ul>	Added to be consistent with OCP for Aboriginal and Torres Strait Islander people with cancer 2018.
24 Share information between healthcare professionals about:	Level IV, NICE 2011	22 Share information between healthcare professionals about:	Method for update: Category D

\* Recommendation included in the Guide



Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
<ul style="list-style-type: none"> <li>• the management plan</li> <li>• what the patient has been told</li> <li>• what the patient has understood (where possible)</li> <li>• the involvement of other agencies and healthcare professionals</li> <li>• any advance decision made by the patient with regard to end-of-life care</li> <li>• other relevant patient information</li> </ul>	<p>Reworded to include “other relevant patient information” and exclude “any problems the patient has”.</p>	<ul style="list-style-type: none"> <li>• the management plan</li> <li>• what the patient has been told</li> <li>• what the patient has understood (where possible)</li> <li>• the involvement of other agencies and healthcare professionals</li> <li>• any advance decision made by the patient with regard to end-of-life care</li> <li>• other relevant patient information</li> </ul>	<p>Nil amendments</p>
		<p>23 Ensure that the results of investigations are reviewed and acted upon appropriately, with the healthcare professional who ordered the investigation taking, or explicitly passing on, responsibility for this. Be aware of the possibility of false-negative results for chest X-rays.</p> <p>Consider a review for patients with any symptom that is consistent with an increased risk of lung cancer, but who do not meet the criteria for referral or other investigative action. The review may be:</p> <ul style="list-style-type: none"> <li>• planned within a time frame agreed with the patient or</li> <li>• patient-initiated if new symptoms develop, the patient continues to be concerned or their symptoms recur, persist or worsen.</li> </ul>	<p>International expert opinion, NICE 2015</p> <p>Reworded to be lung cancer specific; after chest X-rays removed “and tests for occult blood in faeces”; modified “person(s)” to “patient(s)” and “associated” to “consistent”.</p>

ERG= Expert Reference Group; LDCT= low-dose computed tomography; OCP= Optimal Care Pathway

\* Recommendation included in the Guide

*Evidence report for Investigating symptoms of lung cancer: a guide for all health professionals*

## 4.2 Supporting evidence and information for updated content and recommendations

The following section outlines the content and recommendations from the 2012 Guide followed by the amended 2020 content and recommendations. The original evidence base and source that informed the 2012 Guide recommendations is listed, as well as the method for update, additional evidence base and sources used to update the recommendations for the amended 2020 content.

### 4.2.1 Title of resource, target audience and aim

#### 2012 Guide

##### **Investigating symptoms of lung cancer: a guide for GPs**

This guide was developed to assist GPs to manage people who have or may have lung cancer and support the early and rapid referral into the cancer care pathway. This is a general guide to appropriate practice to be followed subject to the clinician's judgement in each individual case. The guide is based on the best available evidence and expert consensus. August 2012

#### 2020 Guide

##### **Investigating symptoms of lung cancer: a guide for all health professionals**

This guide has been developed to assist all health professionals to investigate people with suspected lung cancer and support their early and rapid referral into the diagnostic pathway. This is a general guide to appropriate practice to be followed subject to the clinician's judgement in each individual case. The Guide is based on the best available evidence and expert consensus. February 2020.

#### *Rationale for amendment: Title, aim, target audience*

- The title has been retained as 'Investigating symptoms' to limit the scope of the Guide to symptomatic people. However, a change has been made to the aim of the Guide, to reflect 'suspected lung cancer' with the indications to raise suspicion including signs, symptoms and radiological findings.
- The target audience of the Guide has been expanded to all health professionals to assist in consistency of messaging and implementation across disciplines, to encompass the diverse primary care workforce and to acknowledge the role of other health professionals such as nurses and Aboriginal Health Workers who may use the Guide.
- The term 'cancer care pathway' has been amended to 'diagnostic pathway' to reflect the sequential nature of cancer diagnosis preceding cancer care and to emphasise the purpose of the Guide.

## 4.2.2 Lung Cancer in Australia

2012 Guide

### Lung cancer in Australia<sup>31</sup>

- Lung cancer is the fourth most commonly diagnosed invasive cancer in Australia. Around 6000 men and 3800 women were diagnosed with lung cancer in Australia in 2007.
- Lung cancer is the leading cause of cancer death, for both non-Indigenous and Indigenous men and women.
- Only 14% of those diagnosed with lung cancer survive five years after diagnosis.<sup>32</sup>
- The incidence of lung cancer is strongly related to age, with over 80% of new lung cancers diagnosed in people aged 60 years and older.
- While tobacco smoking is the largest single cause of lung cancer, people who have never smoked may also be diagnosed with lung cancer.<sup>33</sup> About 90% of lung cancer in males and 65% in females is estimated to be a result of tobacco smoking.
- Indigenous people are about 1.7 times as likely to be diagnosed with lung cancer as non-Indigenous people. This difference may be partly explained by higher rates of smoking by Indigenous adults.

2020 Guide

### Lung cancer in Australia

- Lung cancer is the fifth most commonly diagnosed cancer, the leading cause of cancer burden and the leading cause of cancer death in Australia.<sup>1</sup>
- Only 17% of those diagnosed with lung cancer survive five years after diagnosis.<sup>1</sup>
- Variations in lung cancer outcomes exist across populations:
  - Indigenous Australians are approximately twice as likely to be diagnosed with and to die from lung cancer<sup>34</sup> and have lower 5-year survival<sup>1</sup> compared with non-Indigenous Australians
  - Incidence and mortality increase with remoteness<sup>1</sup>
  - Incidence and mortality rates are highest for those living in living in lowest socioeconomic areas<sup>1</sup>
- Whilst tobacco smoking is the largest single cause of lung cancer, people who have never smoked can also be diagnosed.
  - 90% of cases in males and 65% of cases in females are estimated to be caused by tobacco smoking.<sup>31</sup>
- The association of lung cancer with smoking can lead to lung cancer patients feeling stigmatised, contributing to delays in help-seeking for symptoms<sup>35, 36</sup> and psychosocial distress.<sup>37</sup>
- Health professionals working in primary care are integral to early detection, as the majority of patients with cancer first present to primary care settings, often seeing a GP four or more times before a diagnosis is made.<sup>38, 39</sup>
- Patients with suspected lung cancer may also present at emergency departments or be identified in other healthcare settings through incidental findings.<sup>39</sup>
- Early diagnosis increases chances of survival.<sup>2</sup> Nationally, 18% of lung cancers are diagnosed at an early stage and 53% at an advanced stage.<sup>1</sup> The five-year survival for lung cancers diagnosed a stage 1 and stage 2 are 68% and 32% respectively compared to 17% and 3% for those diagnosed at stage 3 and stage 4.<sup>1</sup>

### *Rationale for amendment: Lung cancer in Australia*

- Where possible, amendments have been made to the reporting of statistical information to avoid redundancy of information with the ageing of the resource. Where the inclusion of statistics adds power to the message being portrayed (i.e. lung cancer survival and stage data), the information has been updated to reflect the most recent data available, primarily from the AIHW report *Cancer in Australia, 2019*.<sup>1</sup>
- Statistics relating to the proportion of never-smokers who are diagnosed with lung cancer has been included to reinforce the message that lung cancer is not just a 'smokers' disease' and can occur in non-smokers. This information has been explicitly stated and moved to precede the statistics for the incidence amongst smoking populations. Previously, the Guide only reported on the proportion of lung cancers estimated to be caused by tobacco smoking, expecting the audience to infer the statistics relating to never-smokers diagnosed with lung cancers through deduction. Explicit reporting of this information aims to help with recall and referral of those with suspected lung cancer who may not have risk factors.
- A review published by Cancer Australia in 2012 suggests that health-related stigma is part of the lung cancer experience and that it contributes to psychological distress for patients and impairs quality of life.<sup>37</sup> Information regarding stigma and associated psychosocial distress that is experienced by people affected by lung cancer has been included with the aim to reinforce the need for continued psychosocial support for those affected by lung cancer in Australia. Qualitative studies have reported that lung cancer stigma can delay patient help-seeking for symptoms,<sup>35, 36, 40-42</sup> including two Australian studies.<sup>35, 36</sup>
- The importance of primary care in cancer control has been included to highlight the challenge for lung cancer diagnosis in primary care, as individual primary care health professionals may only diagnose one to two cases of lung cancer per year.<sup>4</sup> This has been followed up with a statement on early diagnosis and recent statistics on stage of diagnosis in Australia. This information is provided to highlight the importance of clinicians to recognise when investigation and referral is required and the significant opportunity for improvement in early diagnosis within Australia.

## 4.2.3 The role of multidisciplinary teams in early diagnosis and patient care

2012 Guide

### The role of multidisciplinary teams in early diagnosis and patient care

#### **Multidisciplinary care is the best practice approach to providing evidence-based cancer care.**

The GP's role is vital in the early and rapid referral of patients with suspected lung cancer to lung cancer multidisciplinary teams (MDTs). Aboriginal Health Workers provide a critical link for Aboriginal and Torres Strait Islander people with cancer in providing information, support and co-ordination to improve health outcomes.

Multidisciplinary care (MDC) is an integrated team-based approach to cancer care where medical and allied health care professionals consider all relevant treatment options and collaboratively develop an individual treatment and care plan for each patient.<sup>43</sup>

Evidence indicates that a team approach to cancer care can improve patient survival and quality of life, improve delivery of best practice care in accord with evidence-based guidelines, improve coordination of care, and facilitate the provision of information and support for patients.<sup>44, 45</sup>

In lung cancer, a small number of available studies have found improved survival of patients<sup>46, 47</sup> who had been diagnosed via an MDT.<sup>48-50</sup> MDC has also been associated with improved patient satisfaction, increased rates of surgical resection, radical radiotherapy, chemotherapy and timeliness of care.<sup>51</sup>

The existence of lung cancer MDTs across Australia provide the mechanism to improve patient care, outcomes and address variations in care.

2020 Guide

#### **Multidisciplinary care (MDC) is the best practice approach to providing evidence-based cancer care.<sup>24</sup>**

All patients with suspected lung cancer should be referred to a specialist with expertise in lung cancer who is affiliated with a multidisciplinary team (MDT).

MDC is an integrated team-based approach to cancer care where medical and allied health care professionals consider all relevant treatment options and collaboratively develop an individual treatment and care plan for each patient. Each MDT member has varying responsibilities, with all playing a role in providing supportive and palliative care.<sup>52</sup> MDC for lung cancer patients is associated with:

- Improved survival<sup>53, 54</sup>, quality of life and reduced hospitalisation at the end of life.<sup>55</sup>
- Reduction in time to treatment after diagnosis and improved patient satisfaction.<sup>51, 53, 56, 57</sup>
- Increased likelihood of patients receiving guideline-adherent care<sup>55, 58-60</sup> and curative treatment.<sup>51, 58, 59, 61</sup>
- More frequent referrals to specialist supportive and palliative care and increased opportunities for clinical trial participation.<sup>10,60</sup>
- Improved cancer treatment planning, documentation of patient preferences and more accurate and complete pre-operative staging.<sup>57, 60, 61</sup>

- Lung Foundation Australia's MDT directory provides useful information about MDTs with expertise in lung cancer, visit <https://lungfoundation.com.au/lung-cancer-mdt/>

*Rationale for amendment: The role of multidisciplinary teams*

The MDT section required amendment as a strengthened evidence base has been identified on multidisciplinary care in relation to lung cancer, since the 2012 Guide.

- The wording of the section as a whole has remained as close to the original language as possible with changes to reflect the changing audience of the resource, i.e. from GPs to all health professionals, and to replicate language used in the *Optimal Care Pathway for people with lung cancer*,<sup>21</sup> with references being updated to reflect this change.
- The recommendation 'All patients with suspected lung cancer should be referred to a specialist with expertise in lung cancer who is affiliated with a multidisciplinary team (MDT)' is included to help prompt a response in the clinician. This recommendation aligns with advice included in the *Optimal Care Pathway for people with lung cancer*.<sup>21</sup> The specialist linked to the MDT may include a respiratory physician, thoracic surgeon or medical oncologist depending on the local setting. However, it should be noted that the referral to a specialist linked with an MDT will be based on the individual recommendations included in the Guide and the signs or symptoms with which the patient is presenting. For example, patients with persistent cough and persistent or unexplained haemoptysis may both have suspected lung cancer, however the current Guide's recommended referral pathway for persistent cough is to urgently refer to a chest X-ray, whilst the recommended referral pathway for persistent or unexplained haemoptysis is urgent referral to a specialist linked with an MDT and concurrent chest CT scan.
- Information pertaining to the roles of the MDT have been included to show that there are varying responsibilities and to emphasise the importance of all clinicians providing supportive and palliative care for patients with lung cancer. Additionally, the information regarding the primary care provider role in the MDT has been removed in line with the broadening of the target audience to all health professionals. The information regarding Aboriginal Health Workers has been removed from this recommendation, however the updated recommendation regarding culturally appropriate information (see recommendation 21 on page 47-48) includes reference to the *Optimal Care Pathway for Aboriginal and Torres Strait Islander people with cancer (2018)*,<sup>25</sup> which notes that the MDT should include an expert in providing culturally appropriate care to Aboriginal and Torres Strait Islander people. The Optimal Care Pathway specifies that this may be an Aboriginal and Torres Strait Islander Health Worker, Health Practitioner or Hospital Liaison Officer.<sup>25</sup>
- The outcomes of MDC have been amended to reflect information contained within Cancer Australia's *Lung Cancer Framework: Principles of best practice lung cancer care (the Lung Cancer Framework)*.<sup>24</sup> The *Lung Cancer Framework* includes international evidence published from 2000 to 2017 regarding the effectiveness of MDC in improving lung cancer care processes and/or outcomes.

## 4.2.4 Symptoms and signs of lung cancer

Table 2 Symptoms and signs: Summary of original and updated recommendations, and method for update

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
<p>Investigate symptoms of lung cancer in patients with the following risks:</p> <p>lifestyle factors:</p> <ul style="list-style-type: none"> <li>• tobacco smoking, former tobacco smoking.</li> </ul> <p>environmental factors:</p> <ul style="list-style-type: none"> <li>• passive smoking</li> <li>• radon exposure</li> <li>• occupational exposure, e.g. previous exposure to asbestos, diesel exhaust</li> <li>• air pollution.</li> </ul> <p>personal factors:</p> <ul style="list-style-type: none"> <li>• age</li> <li>• family history of lung cancer</li> <li>• smoking-related chronic obstructive pulmonary disease</li> <li>• previous lung diseases</li> <li>• history of cancer especially head and neck cancer</li> </ul>	<p>International expert opinion, NZGG 2009</p> <p>Adapted to include risks identified in AIHW 2011 and IARC 2012.</p>	<p>1* Consider possible risk factors when investigating patients with signs or symptoms consistent with lung cancer. Risk factors for lung cancer include:</p> <ul style="list-style-type: none"> <li>• lifestyle factors: <ul style="list-style-type: none"> <li>– Current or former tobacco smoking</li> </ul> </li> <li>• environmental or occupational factors: <ul style="list-style-type: none"> <li>– passive smoking</li> <li>– occupational exposure, e.g. radon (including underground workers in poorly ventilated environments, such as underground miners), asbestos, diesel exhaust, silica</li> <li>– air pollution</li> </ul> </li> <li>• personal factors: <ul style="list-style-type: none"> <li>– age</li> <li>– family history of lung cancer</li> <li>– chronic lung disease, e.g. chronic obstructive pulmonary disease (COPD), pulmonary fibrosis</li> </ul> </li> </ul>	<p>Method for update: Category B</p> <p>Reworded to group environmental or occupational factors together to be consistent with Cancer Australia <i>risk factors for lung cancer</i> report (2014), amendments to personal factors as agreed by consensus by the ERG.</p>

\* Recommendation included in the Guide

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Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
		<ul style="list-style-type: none"> <li>– personal history of cancer e.g. lung cancer, head and neck cancer, bladder cancer</li> </ul>	
<p>2 Urgently refer a patient for a chest X-ray if they have:</p> <ul style="list-style-type: none"> <li>• unexplained haemoptysis</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• any of the following unexplained, persistent symptoms and signs (lasting more than 3 weeks or less than 3 weeks in patients with known risk factors):</li> <li>• new or changed cough</li> <li>• chest and/or shoulder pain</li> <li>• shortness of breath</li> <li>• hoarseness</li> <li>• weight loss/loss of appetite</li> <li>• unresolved chest infection</li> <li>• abnormal chest signs</li> <li>• finger clubbing</li> <li>• cervical and/or supraclavicular lymphadenopathy</li> <li>• features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin)</li> <li>• signs of pleural effusion.</li> </ul>	<p>International expert opinion, NZGG 2009</p> <p>Reworded to include “new or changed” cough, “unresolved chest infection” and “signs of pleural effusion”.</p>	<p>2* Urgently refer a patient for a chest X-ray if they have:</p> <ul style="list-style-type: none"> <li>• any of the following unexplained, persistent symptoms and signs (lasting more than 3 weeks or earlier in patients with known risk factors or with more than one symptom):</li> <li>– new or changed cough</li> <li>– chest and/or shoulder pain</li> <li>– shortness of breath</li> <li>– hoarseness</li> <li>– weight loss/loss of appetite</li> <li>– persistent or recurrent chest infection</li> <li>– fatigue</li> <li>– deep vein thrombosis (DVT)</li> <li>– abnormal chest signs</li> <li>– finger clubbing</li> <li>– cervical and/or supraclavicular lymphadenopathy</li> <li>– features suggestive of lung cancer metastasis (for example, in brain, bone, liver or skin)</li> </ul>	<p>Method for update: Category B</p> <p>Reworded “unresolved chest infection” to “persistent or recurrent chest infection”, and included “fatigue”, “deep vein thrombosis (DVT)” and “thrombocytosis” as these are included in NICE 2015 guidelines.</p> <p>Included earlier referral for patients with more than one symptom as agreed by consensus with the ERG.</p>

\* Recommendation included in the Guide



Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
		<ul style="list-style-type: none"> <li>- signs of pleural effusion</li> <li>- thrombocytosis.</li> </ul>	

\* Recommendation included in the Guide

### *Rationale for amendment: Symptoms and signs*

- The 2012 recommendation regarding risk factors was endorsed from the NZGG 2009 guidelines<sup>12</sup> and included additional risks that were identified in a review by the Australian Institute of Health and Welfare (AIHW)<sup>31</sup> and the identification of diesel engine exhaust as a carcinogenic to humans by International Agency for Research on Cancer (IARC) in June 2012.<sup>62</sup> The recommendation has been updated to be in line with other resources including the *Cancer Australia Risk factors for lung cancer report (2014)*.<sup>26</sup>
- ERG members discussed the importance of considering risk factors along with symptoms and signs that may be consistent with lung cancer. ERG members agreed to remove the section on 'differences in smoking rates may occur by:' as the differences in lung cancer outcomes for these groups have been included in the *Lung cancer in Australia* section.
- Lifestyle factors have been amended from the algorithm in the 2012 2-page Guide to explicitly include former tobacco smoking as the ERG agreed that it was important to be clear that former smokers are still at increased risk. An additional risk factor 'diet low in fruit' was included in the AIHW *Cancer in Australia 2019 report*,<sup>1</sup> however the ERG agreed to not include in the Guide as dietary intake of fruit is of lesser importance in this context.
- Environmental and occupational exposures have been amended in the Guide to be listed together to be consistent with the format of the *Cancer Australia Risk factors for lung cancer report*.<sup>26</sup> Radon exposure is consistently reported as a risk factor for lung cancer, and is listed as the second highest risk factor in the *Cancer Australia Risk factors for lung cancer report*.<sup>26</sup> However, in Australia, this is mainly due to radon exposure in uranium miners (Relative Risk 1.3-3.8) and therefore radon has been removed as a separate bullet point but included with the list of other occupational exposures that can increase risk of lung cancer. A selection of occupational exposure risk factors (radon, asbestos, diesel exhaust, silica) have been included in the Guide. Additional risk factors described in *Cancer Australia Risk factors for lung cancer report*<sup>26</sup> and the AIHW *Cancer in Australia 2019 report*<sup>1</sup> include: arsenic, beryllium, cadmium, chromium, nickel, polycyclic hydrocarbons, iron and steel founding and painting as an occupation. See also Spyratos (2013) for an overview of environmental and occupational exposures, and the importance of taking a detailed occupational history with patients.<sup>63</sup>
- As part of personal factors, 'history of cancer especially head and neck cancer' has been modified to 'personal history of cancer e.g. lung cancer, head and neck cancer, bladder cancer' as a range of cancers can increase the risk of second primary lung cancer.<sup>64, 65</sup> Two previous bullet points 'smoking-related chronic obstructive pulmonary disease' and 'previous lung diseases' have been merged into one. The new wording 'chronic lung disease e.g. chronic obstructive pulmonary disease' is consistent with the *Optimal Care Pathway for people with lung cancer*<sup>21</sup> which lists 'smoking-related chronic obstructive pulmonary disease' and 'chronic lung disease, such as emphysema'. Recent guidelines by Cancer Care Ontario note the following lung diseases have been shown to increase the risk of lung cancer: chronic obstructive pulmonary disease (COPD), asthma and pulmonary fibrosis.<sup>23</sup> The AIHW report *Lung cancer in Australia, 2011*<sup>31</sup> notes that having a disease that damages the lungs may increase the risk of lung cancer; examples include pulmonary tuberculosis, lung fibrosis, chronic bronchitis and emphysema.
- The 2012 recommendations about symptoms and signs were endorsed from the 2009 NZGG guidelines.<sup>12</sup> A targeted evidence review was conducted to identify any recent publications to inform this recommendation update, focusing on combinations

of symptoms and/or risk factors. The recommendation was also informed by the 2015 NICE guidelines.<sup>22</sup>

- The evidence review did not identify any particular combinations of symptoms with other symptoms or risk factors that were highly predictive of lung cancer. Systematic reviews did report that the individual symptoms with the highest diagnostic/predictive value for lung cancer were haemoptysis,<sup>66-68</sup> dyspnoea, cough and chest pain.<sup>66</sup> The 2015 NICE guidelines<sup>22</sup> recommend that people who are aged 40 and over with unexplained haemoptysis be referred using a suspected cancer referral pathway (for an appointment within 2 weeks) for lung cancer. The ERG agreed that unexplained haemoptysis would warrant urgent referral to a specialist linked to a lung cancer multidisciplinary team, while awaiting results of a chest CT scan (see recommendation 12) and therefore was removed from this list of symptoms for urgent referral for a chest X-ray.
- While the evidence review did not identify specific combinations of symptoms that are more indicative of lung cancer, cohort/case control studies indicated that having more than one symptom (or a repeat consultation with the same symptom) tended to increase the probability of cancer<sup>69-72</sup>. Earlier references by Hamilton 2009<sup>73</sup>/2005<sup>74</sup> reported increased positive predictive values (PPVs) for various pairs of lung cancer symptoms (Cancer Prediction in Exeter (CAPER) study including 247 lung cancer cases matched with 1235 controls), see figure 1 below. Therefore, the original recommendation has been modified to recommend that urgent referral for a chest X-ray may be considered earlier if more than one symptom or sign is present.
- The 2015 NICE guidelines<sup>22</sup> recommend various combinations of symptoms and/or risk factors to warrant specialist referral or chest X-ray. The 2015 NICE guidelines identified nine studies regarding positive predictive values of symptoms and signs of lung cancer, most were older publications (2007 or earlier), one study was published in 2011 and two in 2013. Haemoptysis was the only single symptom with a positive predictive value (PPV) above 2%. While other single symptoms had low PPVs, these were slightly higher in smokers. The PPVs for pairs of symptoms were primarily from one older study (CAPER study<sup>74</sup>).
- The Guide recommendation has been amended to include additional symptoms included in the 2015 NICE guidelines: fatigue (also reported in updated CAPER study analyses<sup>69, 70, 73</sup>), deep vein thrombosis and thrombocytosis.<sup>22</sup>
- Fatigue and deep vein thrombosis are both considered non-site-specific symptoms which can indicate lung cancer.<sup>22</sup>
- Thrombocytosis (defined as a platelet count  $>400 \times 10^9/L$ )<sup>75</sup>, especially in the presence of another symptom or sign of lung cancer, is associated with lung cancer.<sup>73, 74</sup> A repeated raised platelet count should also be considered significant and should warrant further investigation for the investigation of lung cancer.<sup>75</sup>
- Unresolved chest infection has been modified to persistent or recurrent chest infection to be consistent with the 2015 NICE guidelines.<sup>22</sup>

Cough	Fatigue	Dyspnoea	Chest pain	Loss of weight	Loss of appetite	Thrombocytosis	Abnormal spirometry	Haemoptysis	
<b>0.40</b> 0.3, 0.5	<b>0.43</b> 0.3, 0.6	<b>0.66</b> 0.5, 0.8	<b>0.82</b> 0.6, 1.1	<b>1.1</b> 0.8, 1.6	<b>0.87</b> 0.6, 1.3	<b>1.6</b> 0.8, 3.1	<b>1.6</b> 0.9, 2.9	<b>2.4</b> 1.4, 4.1	PPV as a single symptom
<b>0.58</b> 0.4, 0.8	<b>0.63</b> 0.5, 0.9	<b>0.79</b> 0.6, 1.0	<b>0.76</b> 0.6, 1.0	<b>1.8</b> 1.1, 2.9	<b>1.6</b> 0.9, 2.7	<b>2.0</b> 1.1, 3.5	<b>1.2</b> 0.6, 2.6	<b>2.0</b> 1.1, 3.5	Cough
	<b>0.57</b> 0.4, 0.9	<b>0.89</b> 0.6, 0.3	<b>0.84</b> 0.5, 1.3	<b>1.0</b> 0.6, 1.7	<b>1.2</b> 0.7, 2.1	<b>1.8</b>	<b>4.0</b>	<b>3.3</b>	Fatigue
		<b>0.88</b>	<b>1.2</b> 0.9, 1.8	<b>2.0</b> 1.2, 3.8	<b>2.0</b> 1.2, 3.8	<b>2.0</b>	<b>2.3</b>	<b>4.9</b>	Dyspnoea
			<b>0.95</b> 0.7, 1.4	<b>1.8</b> 1.0, 3.4	<b>1.8</b> 0.9, 3.9	<b>2.0</b>	<b>1.4</b>	<b>5.0</b>	Chest pain
				<b>1.2</b> 0.7, 2.3	<b>2.3</b> 1.2, 4.4	<b>6.1</b>	<b>1.5</b>	<b>9.2</b>	Loss of weight
					<b>1.7</b>	<b>0.9</b>	<b>2.7</b>	<b>&gt;10</b>	Loss of appetite
							<b>3.6</b>	<b>&gt;10</b>	Thrombocytosis
								<b>&gt;10</b>	Abnormal spirometry
								<b>17</b>	Haemoptysis

**Figure 1 Positive Predictive Values (%) for lung cancer for individual risk markers, and for pairs of risk markers in combination (against a background risk of 0.18%).<sup>73, 74</sup>**

Notes:

(1) The top row (bold) gives the PPV for an individual feature. The cells along the diagonal relate to the PPV when the same feature has been reported twice. Other cells show the PPV when a patient has two different features.

(2) The top figure in each cell is the PPV. It has only been calculated when a minimum of 10 cases had the feature or combination of features. The two other figures are the 95% CIs for the PPV. These have not been calculated when any cell in the 2 x 2 table was below 10.

(3) The yellow shading is when the PPV is above 1%. The amber shading is when the PPV is above 2%. The red shading is for PPVs above 5.0%.<sup>73</sup>

## 4.2.5 Investigations

**Table 3 Investigations: Summary of original and updated recommendations, and method for update**

<b>Recommendation (2012 Guide)</b>	<b>Original evidence base and source (2012)</b>	<b>Recommendation amendment (2020 Guide)</b>	<b>Method for update, additional evidence base and source (2020 Guide)</b>
3 Review previous chest X-rays and other relevant imaging tests in every patient with a pulmonary nodule(s) that is visible on chest X-ray.	Level III-3, ACCP 2007	3* Review previous chest X-rays and other relevant imaging tests in every patient with a pulmonary nodule(s) that is visible on chest X-ray.	Method for update: Category D
4 Refer any patient with risk factors for lung cancer, who has clinical and chest X-ray features of pneumonia for a repeat chest X-ray within 6 weeks to confirm resolution.	International expert opinion, NZGG 2009  Reworded to include "has clinical and chest X-ray features of pneumonia"	4* If chest X-ray shows consolidation consistent with the clinical picture, treat accordingly and repeat chest X-ray within 6 weeks. If persistent consolidation, refer to chest CT scan.	Method for update: Category A  Reworded to be consistent with recommendation as presented in Guide algorithm
5 After urgent referral for chest X-ray, ensure the chest X-ray is completed, reported and reviewed as soon as possible.	International expert opinion, NZGG 2009  Reworded to replace "the chest X-ray should be completed and reported within one week", with "ensure the chest X-ray is completed, reported and reviewed as soon as possible"	5* After urgent referral for chest X-ray, ensure the chest X-ray is completed, reported and reviewed as soon as possible. Test results should be provided to the patient within one week.	Method for update: Category B  Reworded to include "Test results should be provided to the patient within one week." Expert opinion, OCP for lung cancer 2016
6 Perform chest computed tomography (CT) in every patient with a pulmonary nodule(s) that shows change on chest X-ray or if no previous imaging is available.	Level III-3, ACCP 2007  Reworded from "indeterminate single pulmonary nodule" to "a pulmonary nodule(s) that shows change on chest X-ray or if no previous imaging is available"	6* Perform chest CT scan in every patient with a pulmonary nodule(s) that shows change on chest X-ray or if no previous imaging is available.	Method for update: Category A

\* Recommendation included in the Guide

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Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
7 Review previous imaging tests in every patient with a pulmonary nodule(s) that is/are visible on chest CT scan.	Level III-3, ACCP 2007  Reworded from “indeterminate single pulmonary nodule” to “pulmonary nodule(s)”	7* Review previous imaging tests in every patient with a pulmonary nodule(s) that is/are visible on chest CT scan.  Urgently refer to a specialist linked to a lung cancer multidisciplinary team for patients with a pulmonary nodule(s) that shows change on chest CT scan or if no previous imaging is available for review.  If no change is visible and symptoms persist, refer to a respiratory physician (or a specialist with expertise in lung disease).	Method for update: Category A  Reworded to be consistent with recommendation as presented in Guide algorithm, minor amendments made as agreed by consensus by the ERG
8 In the general practice setting sputum cytology is not recommended for the investigation of lung cancer due to its low sensitivity and increased risk of delay.	International expert opinion, NZGG 2009  Reworded to qualify this statement to relate to the general practice setting and include limitations of the test	8 In the general practice setting sputum cytology is not recommended for the investigation of lung cancer due to its low sensitivity and increased risk of delay.	Method for update: Category D  Nil amendments
9 If a chest X-ray is normal and symptoms persist, refer the patient for a chest CT scan.	New recommendation Australian local expert advisory panel consensus statement	9* If a chest X-ray is normal, monitor for persistent symptoms. Advise the patient to return for referral for a chest CT scan if symptoms persist at 6 weeks.	Method for update: Category A  Australian local ERG consensus statement
10 If a chest CT scan is normal and symptoms persist, refer the patient to a respiratory physician (or a designated	New recommendation Australian local expert advisory panel consensus statement	10* If a chest CT scan is normal, monitor for persistent symptoms. If symptoms persist, refer the patient to a respiratory physician (or a specialist with expertise	Method for update: Category D  Reworded to include “monitor for persistent symptoms” to be

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
specialist with expertise in lung disease)		<p>in lung disease).</p> <ul style="list-style-type: none"> <li>i. If chest CT scan findings are abnormal or non-specific, and not suggestive of lung cancer, refer the patient to a respiratory physician (or a specialist with expertise in lung disease).</li> </ul>	consistent with recommendation as presented in the Guide algorithm

\* Recommendation included in the Guide

### *Rationale for amendment: Investigation recommendations*

- *Chest CT scans:* A targeted evidence review was conducted to identify any recent publications regarding the effectiveness of first line investigations (chest X-ray, CT scans or LDCT scans) for patients presenting to primary care with symptoms and signs consistent with lung cancer.

The review identified little evidence regarding the use of LDCT scan for investigating patients with suspected lung cancer. Most of the current research for LDCT scan is in the screening setting. One Danish cluster randomised controlled trial (RCT) investigated the use of direct access to LDCT (combined with a one hour continuing medical education (CME) lung cancer update meeting) in general practice on the time to diagnosis and the stage at diagnosis of lung cancer<sup>76</sup>. The trial included 266 GPs from 119 practices and over the study period 331 lung cancer patients were diagnosed. Overall, the intervention had no statistically significant effect on time to diagnosis or stage at diagnosis in lung cancer patients. However, within the LDCT group, for GPs who attended the lung cancer update meeting, time from first presentation to secondary care referral or decisive diagnosis was reduced.<sup>76</sup> In a cohort within this cluster-RCT, of the patients who underwent LDCT scans (n=648), half the patients needed further diagnostic work-up and 15 patients (2.3%) were diagnosed with non-small cell lung cancer, of which nine were early stage (six stage I).<sup>77</sup>

- *Radiation associated with CT scans:* The ERG discussed that there may be concern regarding referral to chest CT scans due to radiation exposure. Table 4 provides relative radiation exposure from chest X-rays, LDCT scans and conventional chest CT scans. LDCT scans have a lower radiation dose compared to conventional chest CT scans, provide good clinical information and are more sensitive than chest X-ray in the diagnosis of lung cancer.<sup>78</sup> The Royal Australian and New Zealand College of Radiologists (RANZCR) actively encourages medical imaging providers to use the minimum level of radiation during CT scanning consistent with obtaining diagnostic quality images; this is known as the ALARA principle—As Low As Reasonably Achievable.<sup>79</sup> [Radiation risk of medical imaging for adults and children – Health professional information \(2017\)](#) provides further information.<sup>80</sup>



**Table 4 Radiation dose for various sources of radiation**

Source of radiation	Radiation dose (mSv)*
<b>Medical imaging investigations</b>	
Digital chest X-ray (two views)	0.06 <sup>81</sup>
Low-dose chest CT scan	1.0 – 1.4 <sup>82-84</sup>
Conventional chest CT scan	5.0 <sup>81</sup>
<b>Other sources of radiation</b>	
Return flight from Melbourne to London	0.11 <sup>81</sup>
Annual natural background radiation in Australia	1.5 <sup>81</sup>

\* For dosages up to 10mSv there is no direct evidence of human health effects<sup>80</sup>

Note: There was ERG consensus that radiation doses associated with CT scan equipment may be lower in contemporary practice than the doses listed above.

- *Assessment and management of pulmonary nodules:* The 2012 recommendations regarding pulmonary nodules were based on the ACCP guidelines (2007).<sup>16</sup> The ERG agreed to minor amendments to these recommendations to reflect how they were presented in the algorithm in the 2-page Guide. It should be noted that since the publication of the 2012 Guide, specific high-quality guidelines have been published regarding the assessment and management of pulmonary nodules. However, these guidelines did not refer specifically to symptomatic patients and the ERG accepted the original recommendations with minor amendments. Guidelines identified on pulmonary nodules include:
  - the British Thoracic Society guidelines for the investigation and management of pulmonary nodules (2015)<sup>85</sup>
  - the Fleischner Society Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images (2017)<sup>86</sup>
  - the American College of Chest Physicians 2013 guidelines: Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed.<sup>87</sup>
  - In addition, the Cancer Council Australia is currently developing guidelines on the topic 'What is the most effective way to manage small solid, sub-solid and non-solid nodules?'.<sup>88</sup>
- *Referral for and review of chest X-ray:* For the recommendation 'If chest X-ray shows consolidation consistent with the clinical picture, treat accordingly and repeat chest X-ray within 6 weeks', the ERG agreed that the wording should be updated to be consistent with the algorithm in the 2012 2-page Guide.

The recommendation 'After urgent referral for chest X-ray, ensure the chest X-ray is completed, reported and reviewed as soon as possible' has been expanded to be in line with the *Optimal Care Pathway for people with lung cancer*.<sup>21</sup> An additional sentence regarding timeframes for the test results to be provided within one week has been included. These recommended timeframes were based on expert advice from the Lung Cancer Working Group; the multidisciplinary Expert Group who participated in a clinical workshop to develop content for the *Optimal Care Pathway for people with lung cancer*.<sup>21</sup>

- The 2012 Guide included two new consensus based recommendations developed by the EAP. The first was 'if a chest X-ray is normal and symptoms persist, the GP should refer the patient for a chest CT scan' and the second, 'if a chest CT scan is normal and symptoms persist, the GP should refer the patient to a respiratory physician, or a designated specialist with expertise in lung disease'. A targeted evidence review was conducted to identify any recent publications to inform any updates to these recommendations. The evidence review did not identify any papers investigating primary care strategies for how to manage patients with persistent symptoms and a normal chest X-ray or CT scan.
- *Monitoring for persistent symptoms*: The recommendation for monitoring for persistent symptoms following a normal chest X-ray, was updated by consensus agreement. The ERG included that chest CT scan should be performed if symptoms persist at 6 weeks, as 6 weeks was sufficient to allow for resolution of most viral respiratory symptoms. The ERG agreed that it was important to include a timeframe to review persistent symptoms and refer to chest CT scan to avoid delays in further investigating symptoms in case of false-negative results. The recommendation for monitoring for persistent symptoms following a normal chest CT scan has remained consistent with the original recommendation as presented in the 2012 2-page Guide.
- The ERG members agreed that no changes needed to be made to the original recommendation regarding sputum cytology, which was based on international expert opinion from the NZGG 2009 guideline.<sup>12</sup>

## 4.2.6 Referral

**Table 5 Referral: Summary of original and updated recommendations, and method for update**

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
11 Immediately refer a patient to an emergency department if any of the following are present: <ul style="list-style-type: none"> <li>• massive haemoptysis</li> <li>• stridor.</li> </ul>	International expert opinion NICE 2011, with adaptations by the Australian local expert advisory panel consensus  Reworded to recommend immediate referral to emergency department for symptoms of massive haemoptysis and stridor, regardless of smoking status	11* Immediately refer a patient to an emergency department if any of the following are present: <ul style="list-style-type: none"> <li>• massive haemoptysis</li> <li>• stridor.</li> </ul>	Method for update: Category D  Nil amendments
12 Urgently refer a patient to a specialist linked to a lung cancer multidisciplinary team, while awaiting results of a chest CT, if the patient has: <ul style="list-style-type: none"> <li>• persistent haemoptysis and are smokers or former smokers aged 40 years or older or who have other risk factors,</li> <li>• signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure), or</li> <li>• a chest X-ray suggestive of lung cancer (including pleural effusion and slowly</li> </ul>	International expert opinion, NZGG 2009  International expert opinion, NICE 2011  Reworded to include "specialist linked to a lung cancer Multidisciplinary team"	12* Urgently refer (within 2 weeks) a patient to a specialist linked to a lung cancer multidisciplinary team, while awaiting results of a chest CT, if the patient has: <ul style="list-style-type: none"> <li>• persistent or unexplained haemoptysis</li> <li>• signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure), or</li> <li>• imaging findings suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)</li> <li>• high clinical suspicion of lung cancer.</li> </ul>	Method for update: Category A/B  "unexplained haemoptysis" added to be consistent with NICE 2015 guidelines  Reworded to recommend urgent referral for persistent or unexplained haemoptysis, regardless of smoking status, age or other risk factors as agreed by consensus by the ERG  "chest X-ray" reworded to "imaging findings" as agreed by consensus by the ERG

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
resolving consolidation).			"high clinical suspicion of lung cancer" included as agreed by consensus by the ERG
13 Urgently refer a patient to a specialist linked to a lung cancer multidisciplinary team if a chest X-ray or CT scan suggests lung cancer (including pleural effusion and slowly resolving consolidation).	International expert opinion, NICE 2011  Reworded to include "specialist linked to a lung cancer multidisciplinary team"	13* Urgently refer (within 2 weeks) a patient to a specialist linked to a lung cancer multidisciplinary team if imaging suggests lung cancer (including pleural effusion and slowly resolving consolidation).	Method for update: Category A  Minor amendments made to the original recommendation as agreed by consensus by the ERG
14 Urgently refer a patient to a specialist linked to a lung cancer multidisciplinary team, while awaiting results of a chest CT scan, if the patient has a normal chest X-ray, but there is a high suspicion of lung cancer.	International expert opinion, NZGG 2009  Reworded to replace "referral to specialist" with "referral to a specialist linked to a lung cancer multidisciplinary team, while awaiting the results of a chest CT scan"	14* Urgently refer (within 2 weeks) a patient for chest CT scan and concurrently refer to a specialist linked to a lung cancer multidisciplinary team, if the patient has a normal chest X-ray, but there is a high clinical suspicion of lung cancer.	Method for update: Category A  Minor amendments made to the original recommendation as agreed by consensus by the ERG
15 Consider immediate telephone contact with an appropriate specialty service when the patient has a high index of suspicion of lung cancer.	International expert opinion, NZGG 2009  Reworded to include reference to lung cancer	15* Urgently refer (within 2 weeks) to a specialist linked to a lung cancer multidisciplinary team (consider immediate telephone contact) when there is a high index of suspicion of lung cancer.	Method for update: Category A  Minor amendments made to the original recommendation to be consistent with recommendation as presented in the Guide algorithm as agreed by consensus by the ERG
<i>Recommendations to facilitate referral and patient support</i>			
16 Ensure referrals: • are made in a timely manner,	International expert opinion, NZGG 2009	16 Ensure referrals provide relevant and sufficiently detailed	Method for update: Category B

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
<p>and</p> <ul style="list-style-type: none"> <li>provide relevant and sufficiently detailed information to the specialist, including the most appropriate way to contact the patient.</li> </ul>		<p>information to the specialist, including:</p> <ul style="list-style-type: none"> <li>the most appropriate way to contact the patient</li> <li>all relevant clinical information and investigations</li> <li>notification if an interpreter service is required.</li> </ul> <p>Ensure referrals are made in a timely manner; the first specialist appointment should take place within two weeks of referral.*</p>	<p>Amendments informed by OCP for lung cancer 2016 and agreed by consensus by the ERG</p>
<p>17 Ensure that the patient is aware of the timeframes, where available, for:</p> <ul style="list-style-type: none"> <li>receiving an acknowledgment of the referral, or</li> <li>being seen by a specialist or an investigation service.</li> </ul>	<p>International expert opinion, NZGG 2009</p>	<p>17 When a patient presents with signs or symptoms suggestive of lung cancer, provide information that clearly describes:</p> <ul style="list-style-type: none"> <li>why and where they are being referred and how to obtain information about lung cancer</li> </ul>	<p>Method for update: Category B</p> <p>Amendments informed by OCP for lung cancer 2016, and NICE 2015 guidelines and agreed by consensus by the ERG</p>
<p>18 When a patient presents with signs or symptoms suggestive of lung cancer, provide information that clearly describes:</p> <ul style="list-style-type: none"> <li>where the patient is being referred</li> <li>by whom the patient will be seen</li> <li>what a patient can expect from</li> </ul>	<p>International expert opinion, NZGG 2009</p> <p>Reworded to include reference to lung cancer</p>	<ul style="list-style-type: none"> <li>by whom the patient will be seen and who to contact if they have any questions about their appointment</li> <li>what a patient can expect from the specialty service</li> <li>the expected timeframes for appointments and when they will be seen by a specialist or</li> </ul>	

\* Recommendation included in the Guide

<b>Recommendation (2012 Guide)</b>	<b>Original evidence base and source (2012)</b>	<b>Recommendation amendment (2020 Guide)</b>	<b>Method for update, additional evidence base and source (2020 Guide)</b>
the speciality service.		an investigation service	
19 Advise patients to carry their previous imaging results when they attend for a new chest X-ray or chest CT scan.	New recommendation, Australian local EAP consensus statement	18 Advise patients to carry all relevant imaging and results, where possible, when they attend for a chest X-ray or chest CT scan.	Method for update: Category A  Minor amendments made to the original recommendation as agreed by consensus by the ERG
20 Advise patients to stop smoking, and advise the patient why this is important.	Level III-3, NICE 2011  Reworded to remove "as soon as the diagnosis of lung cancer is suspected"	19 All current smokers should be offered smoking cessation advice and support to quit.	Method for update: Category B  Consensus statement, OCP for lung cancer 2016
21 Offer nicotine replacement therapy and other therapies to assist patients to stop smoking.	Level III-3, NICE 2011		
22 Address the patient's need for continuing support while the patient is waiting for a referral appointment(s). Include inviting the patient to contact the GP again if the patient has concerns or further questions before their specialist appointment.	International expert opinion, NZGG 2009	20 Address the patient's need for continuing support while the patient is waiting for a referral appointment(s). Include inviting the patient to contact the GP and GPN again if the patient has concerns or further questions before their specialist appointment.  Assess supportive and palliative care needs and refer to appropriate health professionals or organisations.	Method for update: Category B  Added supportive care statement to be consistent with OCP for lung cancer 2016
23 Where possible, provide culturally-appropriate information and support.	International expert opinion, NZGG 2009	21 Provide information that is appropriate for the person in terms of language, health literacy and	Method for update: Category B  International expert opinion,

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
	Reworded to replace “enquire about a person’s ethnicity to ensure that the person’s health care preferences can be met” with “provide culturally appropriate information and support”	culture, recognising the potential for different cultural meanings associated with the possibility of cancer.	NICE 2015  Reworded “ability” to “health literacy”
		<ul style="list-style-type: none"> <li>• Every patient will have different communication needs, including cultural and language differences. The <i>Lung cancer framework</i> and the <i>Optimal Care Pathway for people with lung cancer</i> provide further information regarding communication and coordination of care strategies.</li> </ul>	Added to be consistent with OCP for lung cancer 2016
		<ul style="list-style-type: none"> <li>• Some Aboriginal and Torres Strait Islander people may have personal or cultural factors that affect the presentation and investigative pathway. Refer to the <i>Optimal Care Pathway for Aboriginal and Torres Strait Islander people with cancer</i> for detailed information.</li> </ul>	Added to be consistent with OCP for Aboriginal and Torres Strait Islander people with cancer 2018
24 Share information between healthcare professionals about: <ul style="list-style-type: none"> <li>• the management plan</li> <li>• what the patient has been told</li> </ul>	Level IV, NICE 2011  Reworded to include “other relevant patient information” and	22 Share information between healthcare professionals about: <ul style="list-style-type: none"> <li>• the management plan</li> <li>• what the patient has been told</li> </ul>	Method for update: Category D  Nil amendments

\* Recommendation included in the Guide

Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
<ul style="list-style-type: none"> <li>• what the patient has understood (where possible)</li> <li>• the involvement of other agencies and healthcare professionals</li> <li>• any advance decision made by the patient with regard to end-of-life care</li> <li>• other relevant patient information</li> </ul>	<p>exclude "any problems the patient has"</p>	<ul style="list-style-type: none"> <li>• what the patient has understood (where possible)</li> <li>• the involvement of other agencies and healthcare professionals</li> <li>• any advance decision made by the patient with regard to end-of-life care</li> <li>• other relevant patient information</li> </ul>	
		<p>23 Ensure that the results of investigations are reviewed and acted upon appropriately, with the healthcare professional who ordered the investigation taking, or explicitly passing on, responsibility for this. Be aware of the possibility of false-negative results for chest X-rays.</p> <p>Consider a review for patients with any symptom that is consistent with an increased risk of lung cancer, but who do not meet the criteria for referral or other investigative action. The review may be:</p> <ul style="list-style-type: none"> <li>• planned within a time frame agreed with the patient or</li> <li>• patient-initiated if new symptoms develop, the</li> </ul>	<p>International expert opinion, NICE 2015</p> <p>Reworded to be lung cancer specific; after chest X-rays removed "and tests for occult blood in faeces"; modified "person(s)" to "patient(s)" and "associated" to "consistent"</p>

\* Recommendation included in the Guide



Recommendation (2012 Guide)	Original evidence base and source (2012)	Recommendation amendment (2020 Guide)	Method for update, additional evidence base and source (2020 Guide)
		patient continues to be concerned or their symptoms recur, persist or worsen.	

\* Recommendation included in the Guide

### *Rationale for amendment: Referral recommendations*

The 2012 recommendations for referral were developed through local expert consensus by adapting the relevant sections in the NZGG 2009 guidelines<sup>12</sup> and the NICE 2011 guidelines.<sup>13</sup> In the update of the Guide, most of the referral recommendations have only had minor amendments made, as agreed by consensus by the ERG. Throughout the recommendations, urgent referral has been clarified to be within 2 weeks.

- *Persistent or unexplained haemoptysis:* The referral recommendation regarding persistent or unexplained haemoptysis has been updated as agreed by ERG consensus, but was also informed by other international guidelines and findings from the targeted evidence review. Systematic reviews have identified that haemoptysis is a symptom reported with the highest diagnostic/predictive value for lung cancer.<sup>66-68</sup> The 2015 NICE guidelines<sup>22</sup> recommend that people who are aged 40 and over with unexplained haemoptysis be referred using a suspected cancer referral pathway (for an appointment within 2 weeks) for lung cancer. The ERG agreed that unexplained haemoptysis would warrant urgent referral to a specialist (within 2 weeks), regardless of age or other risk factors.
- *Incidental findings of lung cancer:* The recommendation to refer a patient who has a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation), has been amended to include imaging findings suggestive of lung cancer. This amendment identifies that other diagnostic imaging, such as coronary computed tomography angiography (CTA) or other CT scans conducted as part of routine investigation of other health conditions, may result in incidental findings suggestive of lung cancer.<sup>89, 90</sup>
- *Facilitating referral and patient support:* Most of the recommendations to facilitate referral and patient support were previously based on international expert opinion from the NZGG 2009 guidelines.<sup>12</sup> These have been updated to provide additional information and align more closely with the *Optimal Care Pathway for people with lung cancer* (2016).<sup>21</sup> The wording for the additional sentences regarding information for the specialist and timeframes for referral were informed by the *Optimal Care Pathway for people with lung cancer*,<sup>21</sup> with further amendments agreed by consensus with the ERG. The 2 week timeframe was based on expert advice from the Lung Cancer Working Group, the multidisciplinary Expert Group who participated in a clinical workshop to develop content for the *Optimal Care Pathway for people with lung cancer*.<sup>21</sup>
- The recommendations regarding patient information provision have been expanded and were informed by the *Optimal Care Pathway for people with lung cancer* (2016),<sup>21</sup> the Scottish Intercollegiate Guidelines Network (SIGN) *Management of lung cancer* guidelines (2014)<sup>91</sup> and the 2015 NICE guidelines.<sup>22</sup>
- *Previous imaging results:* The 2012 recommendation advising patients to carry their previous imaging results has been amended to encompass all relevant imaging and results, to ensure the clinician can assess all relevant information and consider the management and monitoring of radiological findings. The ERG agreed that physical copies of scans are preferred by some clinicians and assist health professionals who may not have the technologies or accessibility to review digitalised versions of scans.

- *Smoking cessation messaging*: The 2012 recommendations regarding smoking cessation and nicotine replacement therapy have been merged and amended to be in line with the *Optimal Care Pathway for patients with lung cancer (2016)*.<sup>21</sup> ERG members considered it was important to avoid the perception that smokers were being blamed for their symptoms and not to detract from the purpose of the primary health care visit from symptom investigation to focus on smoking cessation.
- *Assessing supportive care needs*: The original 2012 recommendation regarding the continuing need for patient support was endorsed from the 2009 NZGG guidelines.<sup>12</sup> This recommendation has been maintained with an additional sentence added to assess patient supportive and palliative care needs. This is consistent with the *Optimal Care Pathway for people with lung cancer*,<sup>21</sup> which notes that assessing supportive and palliative care needs should be applied at every step throughout the lung cancer pathway.
- *Culturally appropriate information and support*: The recommendation regarding culturally appropriate information was updated to be in line with the Australian *Optimal Care Pathways for people with lung cancer*,<sup>21</sup> *Aboriginal and Torres Strait Islander people with cancer*<sup>25</sup> and the 2015 NICE guidelines. The first paragraph is adapted from a recommendation in the 2015 NICE guidelines<sup>22</sup> and is based on expert opinion rather than clinical evidence. This recommendation provides a larger scope than just culturally appropriate information and includes other patient-specific considerations such as health literacy (modified from 'ability' in original 2015 NICE guideline). The recommendation was expanded to include additional information regarding communication/coordination of care and patient support for individual groups such as Aboriginal and Torres Strait Islander persons, and those from culturally and linguistically diverse backgrounds. This amendment is consistent with the *Optimal Care Pathways for people with lung cancer*<sup>21</sup> and for *Aboriginal and Torres Strait Islander people with cancer*<sup>25</sup>, which provides detailed information regarding personal or cultural factors that may affect the presentation and investigative pathway.
- *Sharing information between health professionals*: recommendation about sharing information between health professionals was checked for consistency with the *Cancer Australia Lung cancer Framework (2018)*<sup>24</sup> and the *Optimal Care Pathways for people with lung cancer*<sup>21</sup> and *Aboriginal and Torres Strait Islander people with cancer*.<sup>25</sup> The original recommendation is considered to be in line with these other resources and the ERG agreed to retain the recommendation with no amendments. The *Lung Cancer Framework (2018)*<sup>24</sup> includes the Principle: coordination, communication and continuity of care which means that all relevant health professionals, including general practitioners, provide coordinated delivery of care across the lung cancer continuum of care. The *Optimal Care Pathway for Aboriginal and Torres Strait Islander people with cancer*<sup>25</sup> states that "regular and timely two-way communication between the lead clinician and the person's general or primary practitioner or primary care provider is an essential component of optimal care coordination" and provides some examples of what this may include.
- *Guidance for monitoring patients*: The ERG discussed that an additional recommendation regarding guidance for monitoring patients should be included. This recommendation was informed by International consensus guidelines, as well as a targeted evidence review. The wording for the new recommendation is adapted from the 2015 NICE guidelines<sup>22</sup> and has been modified to be lung cancer specific.

The 2015 NICE recommendation is based on expert opinion as no clinical evidence was identified in the NICE evidence review.

Similarly, the targeted evidence review did not identify any comparative effectiveness studies for the research question: What strategies are effective to assess and follow-up patients who present in primary care with persistent symptoms/signs that either are considered at low-risk of lung cancer or who have had previous normal/negative imaging results? Most of the relevant information identified in the targeted evidence review consisted of small qualitative studies which may not be generalisable to, or representative of, primary care practice in Australia. The evidence review identified there are no standard definitions/practices for what encompasses 'safety netting' for monitoring low-risk symptoms<sup>92</sup>, however the studies identified elements such as planned follow-up visits and communication with patients.<sup>6</sup> Provision of explicit advice to patients regarding when to re-consult with symptoms may reduce uncertainty and encourage patients to re-present to primary care with ongoing, worsening or additional symptoms.<sup>93, 94</sup>

## Appendix A – Expert Reference Group

Professor David Barnes (Co-Chair), Respiratory Physician, Royal Prince Alfred Hospital, NSW

Professor Danielle Mazza (Co-Chair), General Practitioner, Royal Australian College of General Practitioners (RACGP) representative, VIC

Dr Brendan Adler, Radiologist, Royal Australian and New Zealand College of Radiologists (RANZCR) representative, WA

Dr Lisa Briggs, Lung cancer consumer representative, VIC

Associate Professor Phillip Carson, General Surgeon, Royal Australasian College of Surgeons (RACS) representative, NT

Professor Suzanne Chambers AO, Health Psychologist, NSW

Dr Philippa Ell, Radiation Oncologist, Royal Australian and New Zealand College of Radiologists (RANZCR) representative, NSW

Ms Beth Ivimey, Lung Cancer Nurse Coordinator, Cancer Nurses Society of Australia (CNSA) representative, NSW

Ms Carolyn Riordan, Lung cancer consumer representative, NSW

Dr Tanya Schramm, General Practitioner, Australian Indigenous Doctors' Association (AIDA) representative, TAS

Associate Professor Robert Stirling, Respiratory Physician, Royal Australasian College of Physicians (RACP) and Thoracic Society of Australia and New Zealand (TSANZ) representative, VIC

## Appendix B – Targeted evidence review

### Research questions

Three research questions for the targeted systematic evidence reviews were determined in consultation with the ERG:

- 1) What is the effectiveness of first-line investigations for patients presenting to primary care with symptoms and signs consistent with lung cancer?
  - Population/participants: patients presenting to primary care with symptoms and signs consistent with lung cancer
  - Intervention: initial investigations of symptoms (prior to definitive diagnosis) including chest X-ray, CT scan or low-dose CT (LDCT) scan
  - Comparator: comparisons between investigations or usual care
  - Outcomes: Patient outcomes, such as survival, morbidity, stage of disease at diagnosis, time-to-referral/diagnosis/treatment, quality of life and/or psychosocial outcomes; Diagnostic outcomes, such as sensitivity, specificity and/or accuracy
  - Exclusion criteria:
    - asymptomatic people attending lung cancer screening
    - investigations undertaken in secondary care
- 2) What strategies are effective to assess and follow-up patients who present in primary care with persistent symptoms/signs who are either considered at low-risk of lung cancer or who have had previous normal/negative imaging results?
  - Population/participants: patients presenting to primary care with symptoms/signs at low risk of cancer; or patients who have had previous negative imaging results
  - Intervention: any reported strategies used by PCPs to reassess patients with persistent symptoms, and/or follow-up of investigations
  - Comparator: usual care or prior to implementation of strategy
  - Outcomes: Patient outcomes, such as survival, morbidity, stage of disease at diagnosis, time-to-referral/diagnosis/treatment, quality of life and/or psychosocial outcomes; Provider outcomes, such as satisfaction, time factors
- 3) Are there combinations of signs, symptoms and/or risk factors that are more likely to predict lung cancer?
  - Population/participants: patients presenting with signs, symptoms or indications consistent with lung cancer
  - Intervention: initial presentation with combination of signs/symptoms/risk factors and/or algorithms to predict lung cancer
  - Comparator: N/A
  - Outcomes: positive predictive value (PPV), frequency of lung cancer, prognosis/survival

## Literature search

Literature searches were undertaken in February 2019 in electronic databases PubMed and OVID (EMBASE, Medline and PsycINFO). Individual targeted search strategies were performed for each research question. The searches were limited to publication date 2012-2019 and English language.

**Table 6 Search terms for each topic area**

#	Topic area	Search terms
1	Lung cancer	<p><i>MeSH Terms:</i> Lung neoplasms</p> <p><i>Other terms in titles and abstracts:</i> Lung AND (cancer OR cancers OR neoplasm OR neoplasms OR tumour OR tumours OR tumor OR tumors OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas)</p>
2	Signs/symptoms	<p><i>MeSH terms:</i> Signs and symptoms; OR Symptom assessment</p> <p><i>Other terms in titles and abstracts:</i> Sign OR signs OR symptom OR symptoms OR symptomatic OR suspected OR suspicious OR suspect OR suggestive OR "clinically indicated" OR cough OR hemoptysis OR haemoptysis OR breathlessness OR dyspnoea OR dyspnea OR "chest pain"</p>
3	Risk factors	<p><i>MeSH terms:</i> Risk factors</p> <p><i>Other terms in titles and abstracts:</i> "risk factor" OR "risk factors" OR "increased risk" OR "increases risk"</p>
4	Primary care	<p><i>MeSH terms:</i> General Practice; OR Primary Health Care; OR Physicians, Family; OR Physicians, Primary Care; OR General Practitioners; OR Practice Patterns, Physicians'; OR Family Practice</p> <p><i>Other terms in titles and abstracts:</i> "general practice" OR "general practices" OR "general practitioner" OR "general practitioners" OR GP OR GPs OR "family physician" OR "family physicians" OR "family practice" OR "family practices" OR "family practitioner" OR "family practitioners" OR "primary care" OR PCP OR "primary health" OR "community health" OR nurse OR nurses OR "family doctor" OR "family doctors"</p>
5	Investigation/referral/diagnosis	<p><i>MeSH terms:</i> Diagnostic Tests, Routine; OR Referral and consultation; OR Early detection of cancer; OR Early diagnosis</p> <p><i>Other terms in titles and abstracts:</i> Investigate OR investigation OR evaluation OR evaluate OR diagnosis OR diagnose OR assessment OR assess OR present OR presenting OR presentation OR refer OR referral OR "early diagnosis" OR "early detection" OR consult* OR attend* OR help-seeking OR "reason for encounter" OR "missed diagnosis" OR "delay* diagnosis"</p>
6	Diagnostic imaging	<p><i>MeSH terms:</i> Tomography, X-ray Computed; Diagnostic Imaging; X-rays; Radiography</p>

		<p><i>Other terms in titles and abstracts:</i>  “chest X-ray” OR “CXR” OR “CT scan” OR “chest CT” OR  “computed tomography” OR “LDCT” OR “low-dose CT”</p>
7	Previous negative imaging	<p>‘Diagnostic imaging’ terms AND</p> <p><i>Other terms in titles and abstracts:</i>  normal OR negative OR inconclusive</p>
8	Monitoring	<p><i>MeSH terms:</i>  “Watchful waiting”;</p> <p><i>Other terms in titles and abstracts:</i>  "safety netting" OR observation OR "active monitoring" OR "active surveillance" OR ((monitor* OR surveillance) AND ("persistent symptoms" OR "symptoms persist")) OR repeat* consult* OR "ongoing symptoms"</p>
9	Risk prediction	<p><i>MeSH terms:</i>  “Risk assessment” or “predictive value of tests” or “sensitivity and specificity”</p> <p><i>Other terms in titles and abstracts:</i>  predictive OR PPV OR PPVs OR “likelihood ratio” OR “likelihood ratios” OR “relative risk” OR “relative risks” OR “hazard ratio” OR “hazard ratios” OR “odds ratio” OR “odds ratios” OR “risk prediction” OR “risk assessment”</p>
10	Low risk	<p><i>Other terms in titles and abstracts:</i>  “low risk” or non-alarm or non-specific</p>
11	Ongoing symptoms	<p>‘signs/symptoms’ terms AND</p> <p><i>Other terms in titles and abstracts:</i>  Ongoing or unresolved or persistent</p>
12	Cancer	<p><i>MeSH Terms:</i>  Neoplasms</p> <p><i>Other terms in titles and abstracts:</i>  cancer OR cancers OR neoplasm OR neoplasms OR tumour OR tumours OR tumor OR tumors OR carcinoma OR carcinomas OR adenocarcinoma OR adenocarcinomas</p>
13	Metastases	<p><i>MeSH Terms:</i>  Metastases*; OR metastasis*; OR recurrence  *OVID uses Neoplasm metastasis/</p> <p><i>Other terms in titles and abstracts:</i>  Metastases OR metastasis OR recurrence</p>



**Table 7 Search strategies for each research question**

Research question	Targeted search strategy	Citations identified*
1	<p>lung cancer terms (#1) AND symptoms terms (#2) AND diagnostic imaging terms (#6) AND investigation/referral/diagnosis terms (#5)</p> <ul style="list-style-type: none"> <li>• NOT metastases terms (#13)</li> <li>• AND (first OR first-line OR initial OR direct OR fast-track OR fast OR rapid OR immediate OR urgent)[Title/Abstract]</li> <li>• limited by publication date (2012 onwards)</li> </ul> <p>OR</p> <p>lung cancer terms (#1) AND symptoms terms (#2) AND diagnostic imaging terms (#6) AND primary care terms (#4), limited by publication date (2012 onwards)</p>	677
2 <sup>^</sup>	<p>cancer terms (#12) AND symptoms terms (#2) AND primary care terms (#4) AND monitoring terms (#8)</p> <p>OR</p> <p>cancer terms (#12) AND symptoms terms (#2) AND primary care terms (#4) AND ongoing symptoms terms (#11)</p> <p>OR</p> <p>cancer terms (#12) AND symptoms terms (#2) AND primary care terms (#4) AND low-risk terms (#10)</p> <p>OR</p> <p>cancer terms (#12) AND symptoms terms (#2) AND primary care terms (#4) AND negative diagnostic imaging terms (#7)</p> <ul style="list-style-type: none"> <li>• Limited by publication date (2012 onwards)</li> </ul>	554
3	<p>Lung cancer terms (#1) AND (symptoms terms (#2) OR risk factors terms (#3)) AND risk prediction terms (#9) AND investigation/referral/diagnosis terms (#5)</p> <ul style="list-style-type: none"> <li>• NOT metastases terms (#13)</li> <li>• limit publication date 2012-2019</li> </ul> <p>OR</p> <p>Lung cancer terms (#1) AND (symptoms terms (#2) OR risk factors terms (#3)) AND risk prediction terms (#9) AND primary care terms (#4), limit publication date 2012-2019</p>	2726

\*PubMed and OVID (Medline, EMBASE, PsycInfo) databases combined

<sup>^</sup>Broad cancer terms were used for this research question to identify primary care strategies that may not be cancer type specific

## Results

### Research question 1

#### What is the effectiveness of first-line investigations for patients presenting to primary care with symptoms and signs consistent with lung cancer?

Only six studies were identified as relevant for research question 1:

- One cluster-randomised controlled trial (RCT), and a nested cohort within this RCT, investigated direct low-dose CT (LDCT) for suspected lung cancer in primary care.<sup>76, 77</sup>
- One feasibility RCT investigated chest X-ray for selected high-risk patients that did not meet the previous NICE 2005 guidance<sup>95</sup> for 2-week referral.<sup>96</sup>
- One quasi-RCT and one cohort investigated performing CT following referral by GP but before detailed specialist review.<sup>97, 98</sup>
- One cohort study reported likelihood ratios for cancer following X-ray and supplemental CT scan for investigating patients with non-specific serious symptoms.<sup>72</sup>

#### Research question 1 summary

Limited relevant studies were identified reporting the effectiveness of chest X-ray, CT or LDCT for investigating patients with signs or symptoms consistent with lung cancer.

One Danish cluster-RCT investigated the use of direct access LDCT (combined with a continuing medical education (CME) lung cancer meeting) for GPs investigating patients that have signs or symptoms suspicious for lung cancer, but not red flag symptoms.<sup>76</sup> The trial included 266 GPs from 119 practices and over the study period 331 lung cancer patients were diagnosed. While overall the intervention had no statistically significant effect on time to diagnosis or stage at diagnosis in lung cancer patients within the intervention group, for those who attended the one hour lung cancer update meeting, reduced time from first presentation to secondary care referral or decisive diagnosis were observed.<sup>76</sup> In a cohort within this cluster-RCT, of the patients who underwent LDCT scans (n=648), half the patients needed further diagnostic work-up and 15 patients (2.3%) were diagnosed with non-small cell lung cancer, of which nine were early stage (six stage I).<sup>77</sup>

A feasibility RCT demonstrated that a trial of immediate chest X-ray for patients >60 years with a smoking history and respiratory symptoms of any duration is acceptable, this may be investigated in a fully powered phase III RCT in the future.<sup>96</sup>

Performing CT scans prior to specialist appointments may reduce specialist appointment time and provide specialists with valuable information at consultation.<sup>97, 98</sup>

## Research question 2

### What strategies are effective to assess and follow-up patients who present in primary care with persistent symptoms/signs who are either considered at low-risk of lung cancer\* or who have had previous normal/negative imaging results?

Nine relevant studies were identified which provide descriptions of various primary care strategies and the implications of these on patient outcomes:

- Three studies reported information on monitoring ongoing/low-risk symptoms.<sup>6, 92, 99</sup>
- Two cohort studies reported on various investigations for serious but non-specific symptoms.<sup>100, 101</sup> In addition, a qualitative study including some information regarding investigating non-specific symptoms for lung cancer.<sup>102</sup>
- Two small UK qualitative articles describe patient perspectives of their diagnosis of lung cancer.<sup>93, 94</sup>
- One international survey reported quantitative and qualitative data on the responsibilities for follow-up of patients undergoing diagnostic investigations in primary care.<sup>103</sup>

#### Research question 2 summary

No comparative effectiveness studies were identified regarding primary care strategies for monitoring ongoing/low-risk symptoms. Most of the relevant information was reported by small qualitative studies which may not be generalisable to or representative of primary care practice in Australia.

There are no standard definitions/practices for what encompasses 'safety netting' for monitoring low-risk symptoms.<sup>92</sup> Elements that were discussed include planned follow-up visits and communication with patients.<sup>6</sup> International variation appears to exist regarding responsibilities for follow-up of patients undergoing diagnostic investigations in primary care.<sup>103</sup>

Provision of explicit advice to patients regarding when to re-consult with symptoms may reduce uncertainty and encourage patients to re-present to primary care with ongoing, worsening or additional symptoms.<sup>93, 94</sup>

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\* Articles on cancer in general were also included

## Research question 3

### Are there combinations of signs, symptoms and/or risk factors that are more likely to predict lung cancer?

Five systematic reviews and nine primary studies were identified as relevant for research question 3:

- Four systematic reviews summarise the diagnostic/predictive value of various lung cancer symptoms<sup>66-68, 104</sup>
  - These systematic reviews include many of the same primary studies, some of which were also identified in the evidence review. To avoid duplication, the most recent systematic review was presented in most detail.<sup>66</sup>
- Six primary studies (three cohorts,<sup>71, 72, 105</sup> two case-controls<sup>69, 70, 106, 107</sup> and one cross-sectional study<sup>108</sup>) include relevant information regarding combinations of symptoms, including one article identified in the research question 2 literature search but considered to have some relevant information for research question 3.<sup>108</sup>
- Two primary studies include relevant information regarding combinations of symptoms and risk factors.<sup>109, 110</sup>
- One systematic review<sup>111</sup> and one primary study<sup>112</sup> reported on risk prediction tools for symptomatic patients presenting in primary care.

#### Research question 3 summary

A recent systematic review reported that individual symptoms with the greatest diagnostic value for lung cancer were haemoptysis, dyspnoea, cough and chest pain.<sup>66</sup> The authors reported that the positive predictive value of diagnostic symptoms depends on an individual's prior risk of lung cancer (based on age, sex, smoking status and intensity), as well as their presenting symptom pattern.<sup>66</sup>

While specific combinations of symptoms that are more indicative of lung cancer were not identified, cohort/case-control studies indicated that having more than one symptom (or a repeat consultation with the same symptom) tended to increase the probability of cancer.<sup>69-72</sup> An older study which provides positive predictive values for individual and pairs of symptoms is still regularly referenced in more recent articles.<sup>73</sup>

While a number of risk prediction tools have been identified for assessing patients with symptoms suspicious for lung cancer, there is insufficient evidence for the recommendation of the use of any particular one.<sup>111</sup>

## Abbreviations

ACCP	American College of Chest Physicians
AGREE II	Appraisal of Guidelines for Research & Evaluation II
AIDA	Australian Indigenous Doctors' Association
AIHW	Australian Institute of Health and Welfare
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews
CAPER	Cancer Prediction in Exeter
CNSA	Cancer Nurses Society of Australia
CT	Computed tomography
EAP	Expert Advisory Panel
ERG	Expert Reference Group
GP	General practitioner
GPN	General practice nurse
LDCT	Low-dose computed tomography
MDT	Multidisciplinary team
NICE	National Institute of Health and Clinical Excellence
NZGG	New Zealand Guidelines Group
OCP	Optimal Care Pathway
PPV	Positive predictive value
RCT	Randomised controlled trial
RACGP	Royal Australian College of General Practitioners

RACS

Royal Australasian College of Surgeons

RANZCR

Royal Australian and New Zealand College of Radiologists

## References for Investigating symptoms of lung cancer: a guide for all health professionals

The reference list below is specifically for the resource *Investigating Symptoms of Lung Cancer: a guide for all health professionals*, which is provided on pages 6-7. This resource can also be downloaded from [www.canceraustralia.gov.au](http://www.canceraustralia.gov.au).

1. Australian Institute of Health and Welfare & Cancer Australia 2011. Lung cancer in Australia: an overview. Cancer series no. 64. Cat. no. CAN 58. Canberra: AIHW.
2. Australian Institute of Health and Welfare 2018. Cancer in Aboriginal & Torres Strait Islander people of Australia. Accessed October 2019; <https://www.aihw.gov.au/reports/cancer/cancer-in-indigenoustralian/contents/table-of-contents>
3. Australian Institute of Health and Welfare 2019. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW.
4. Crane M, Scott N, O'Hara BJ, et al. Knowledge of the signs and symptoms and risk factors of lung cancer in Australia: mixed methods study. *BMC Public Health*. 2016;16(1):508.
5. Scott N, Crane M, Lafontaine M, et al. Stigma as a barrier to diagnosis of lung cancer: patient and general practitioner perspectives. *Prim Health Care Res Dev*. 2015;16(6):618-22.
6. Chambers SK, Dunn J, Occhipinti S, et al. A systematic review of the impact of stigma and nihilism on lung cancer outcomes. *BMC Cancer*. 2012;12(1):184.
7. Smith SM, Campbell NC, MacLeod U, et al. Factors contributing to the time taken to consult with symptoms of lung cancer: a cross-sectional study. *Thorax*. 2009;64(6):523-31.
8. Cancer Australia 2019. National Cancer Control Indicators (NCCI). Relative survival by stage at diagnosis (lung cancer). Accessed October 2019; <https://ncci.canceraustralia.gov.au/outcomes/relative-survivalrate/relative-survival-stage-diagnosis-lung-cancer>
9. Emery JD. The challenges of early diagnosis of cancer in general practice. *Med J Aust*. 2015;203(10):391-3.
10. Purdie S, Creighton N, White KM, et al. Pathways to diagnosis of nonsmall cell lung cancer: a descriptive cohort study. *NPJ Prim Care Respir Med*. 2019;29(1):2.
11. Cancer Australia 2019. National cancer control indicators (NCCI). Relative survival by stage at diagnosis (lung cancer) Accessed October 2019; <https://ncci.canceraustralia.gov.au/diagnosis/cancer-incidence/cancer-incidence>
12. Australian Institute of Health and Welfare 2019. Cancer data in Australia. Cat. no. CAN 122. Canberra: AIHW. Accessed October 2019; <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia>
13. Toyoda Y, Nakayama T, Kusunoki Y, et al. Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography. *Br J Cancer*. 2008;98(10):1602-7.
14. Cancer Australia 2018. Lung Cancer Framework: Principles for Best Practice Lung Cancer Care in Australia, Cancer Australia, Surry Hills, NSW.
15. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011; 365(5):395-409.
16. Bradley S, Abraham S, Grice A, et al. Sensitivity of chest X-ray for lung cancer: systematic review. *Br J Gen Pract*. 2018; 68(suppl 1):bjgp18X696905.
17. Stapley S, Sharp D and Hamilton W. Negative chest X-rays in primary care patients with lung cancer. *Br J Gen Pract*. 2006; 56(529):570-3.

## References for the *Evidence report for Investigating symptoms of lung cancer: a guide for all health professionals*

1. Australian Institute of Health and Welfare. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Accessed: <https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019/contents/table-of-contents>
2. Cancer Australia. National Cancer Control Indicators. Relative survival by stage at diagnosis (lung cancer). Accessed: <https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/relative-survival-stage-diagnosis-lung-cancer>
3. Cassim S, Chepulis L, Keenan R, et al. Patient and carer perceived barriers to early presentation and diagnosis of lung cancer: a systematic review. *BMC cancer*. 2019;19(1):25.
4. Weller DP, Peake MD and Field JK. Presentation of lung cancer in primary care. *NPJ primary care respiratory medicine*. 2019;29(1):21.
5. Bradley SH, Kennedy MPT and Neal RD. Recognising Lung Cancer in Primary Care. *Advances in therapy*. 2019;36(1):19-30.
6. Mitchell ED, Rubin G and Macleod U. Understanding diagnosis of lung cancer in primary care: qualitative synthesis of significant event audit reports. *The British Journal of General Practice*. 2013;63(606):e37-46.
7. Smith SM, Campbell NC, MacLeod U, et al. Factors contributing to the time taken to consult with symptoms of lung cancer: a cross-sectional study. *Thorax*. 2009;64(6):523-31.
8. Cancer Australia and The Royal Australian College of General Practitioners. Investigating symptoms of lung cancer: a guide for GPs. Australian Government, Cancer Australia, 2012.
9. Cancer Australia. Evidence relevant to the guide for the investigation of symptoms of lung cancer. Cancer Australia, Surry Hills, NSW, 2012.
10. Collaboration A. Guideline adaptation: A resource toolkit 2009. Accessed: [www.g-i-n.net](http://www.g-i-n.net)
11. AGREE Next Steps Consortium. The AGREE II Instrument [Electronic version]. Accessed: <http://www.agreetrust.org>
12. New Zealand Guidelines Group. Suspected cancer in primary care: Guidelines for investigation, referral and reducing ethnic disparities. New Zealand Guidelines Group, Wellington, 2009.
13. NICE. The diagnosis and treatment of lung cancer (update). National Collaborating Centre for Cancer, Wales, 2011.
14. Kvale PA. Chronic cough due to lung tumors: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(1 Suppl):147S-53S.
15. Alberts WM and American College of Chest Physicians. Introduction: Diagnosis and management of lung cancer: ACCP evidence-based clinical practice guidelines (2nd Edition). *Chest*. 2007;132(3 Suppl):20S-2S.
16. Gould MK, Fletcher J, Lannettoni MD, et al. Evaluation of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):108S-30S.
17. McCrory DC, Lewis SZ, Heitzer J, et al. Methodology for lung cancer evidence review and guideline development: ACCP evidence-based clinical practice guidelines (2nd Edition). *Chest*. 2007;132(3 Suppl):23S-8S.



18. Rivera MP, Mehta AC and American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):131S-48S.
19. Spiro SG, Gould MK, Colice GL and American College of Chest Physicians. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):149S-60S.
20. Wahidi MM, Govert JA, Goudar RK, et al. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):94S-107S.
21. Department of Health and Human Services – Victoria. Optimal care pathway for people with lung cancer. Accessed: <https://www.cancer.org.au/health-professionals/optimal-cancer-care-pathways.html>
22. NICE. Suspected cancer: recognition and referral. National Institute for Health and Care Excellence, 2015.
23. Del Giudice ME, Young S, Vella E, et al. Referral of suspected lung cancer by family physicians and other primary care providers. 2011 Aug 29 [ENDORSED 2019 Jan]. Program in Evidence-based Care Evidence-Based Series No.: 24-2 Version 2 ENDORSED. Cancer Care Ontario, Toronto (ON), 2019.
24. Cancer Australia. Lung Cancer Framework. Principles for Best Practice Lung Cancer Care in Australia. Cancer Australia, Surry Hills: NSW, 2018.
25. Cancer Australia. Optimal care pathway for Aboriginal and Torres Strait Islander people with cancer. Accessed: [www.cancer.org.au/content/ocp/Optimal\\_care\\_pathways\\_ATSI\\_Report\\_August\\_2018.PDF](http://www.cancer.org.au/content/ocp/Optimal_care_pathways_ATSI_Report_August_2018.PDF)
26. Cancer Australia. Risk factors for lung cancer: an overview of the evidence. Cancer Australia, Surry Hills, NSW, 2014.
27. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj*. 2017;358:j4008.
28. Critical Appraisal Skills Programme (CASP) UK. CASP Checklists. Accessed: <http://www.casp-uk.net/casp-tools-checklists>
29. Pluye P, Robert E, Cargo M, et al. Proposal: A mixed methods appraisal tool for systematic mixed studies reviews. Accessed: <http://mixedmethodsappraisaltoolpublic.pbworks.com>
30. Downes MJ, Brennan ML, Williams HC and Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ open*. 2016;6(12):e011458.
31. Australian Institute of Health and Welfare and Cancer Australia. Lung cancer in Australia: an overview. Cancer series no. 64. Cat. no. CAN 58. AIHW, Canberra, 2011.
32. Australian Institute of Health and Welfare. Cancer survival and prevalence in Australia: period estimated from 1982 to 2010. Cat. no. CAN 58. AIHW, Canberra, 2012.
33. Hippisley-Cox J and Coupland C. Identifying patients with suspected lung cancer in primary care: derivation and validation of an algorithm. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2011;61(592):e715-23.
34. Australian Institute of Health and Welfare. Cancer in Aboriginal & Torres Strait Islander people of Australia. Accessed: [www.aihw.gov.au/reports/cancer/cancer-in-indigenous-australians/contents/cancer-type/lung-cancer-c33-c34](http://www.aihw.gov.au/reports/cancer/cancer-in-indigenous-australians/contents/cancer-type/lung-cancer-c33-c34)
35. Crane M, Scott N, O'Hara BJ, et al. Knowledge of the signs and symptoms and risk factors of lung cancer in Australia: mixed methods study. *BMC public health*. 2016;16:508.
36. Scott N, Crane M, Lafontaine M, et al. Stigma as a barrier to diagnosis of lung cancer: patient and general practitioner perspectives. *Primary health care research & development*. 2015;16(6):618-22.
37. Chambers SK, Dunn J, Occhipinti S, et al. A systematic review of the impact of stigma and nihilism on lung cancer outcomes. *BMC cancer*. 2012;12:184.

38. Emery JD. The challenges of early diagnosis of cancer in general practice. *The Medical journal of Australia*. 2015;203(10):391-3.
39. Purdie S, Creighton N, White KM, et al. Pathways to diagnosis of non-small cell lung cancer: a descriptive cohort study. *NPJ Prim Care Respir M*. 2019;29(1):2.
40. Wagland R, Brindle L, Ewings S, et al. Promoting Help-Seeking in Response to Symptoms amongst Primary Care Patients at High Risk of Lung Cancer: A Mixed Method Study. *PLoS one*. 2016;11(11):e0165677.
41. Tod AM, Craven J and Allmark P. Diagnostic delay in lung cancer: a qualitative study. *Journal of advanced nursing*. 2008;61(3):336-43.
42. Carter-Harris L. Lung cancer stigma as a barrier to medical help-seeking behavior: Practice implications. *Journal of the American Association of Nurse Practitioners*. 2015;27(5):240-5.
43. National Breast Cancer Centre. *Multidisciplinary Care in Australia: a National Demonstration Project in Breast Cancer*. NBCC, Camperdown, 2003.
44. Wilcoxon H, Luxford K, Saunders C, et al. Multidisciplinary cancer care in Australia: a national audit highlights gaps in care and medico-legal risk for clinicians. *Asia-Pacific journal of clinical oncology*. 2011;7(1):34-40.
45. Saini KS, Taylor C, Ramirez AJ, et al. Role of the multidisciplinary team in breast cancer management: results from a large international survey involving 39 countries. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2012;23(4):853-9.
46. Price A, Kerr G, Gregor G, et al. The impact of multidisciplinary teams and site specialisation on the use of radiotherapy in elderly people with non-small cell lung cancer (NSCLC). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2002;64(Suppl 1):S80 (Abstract 237).
47. Forrest LM, McMillan DC, McArdle CS and Dunlop DJ. An evaluation of the impact of a multidisciplinary team, in a single centre, on treatment and survival in patients with inoperable non-small-cell lung cancer. *British journal of cancer*. 2005;93(9):977-8.
48. Murray PV, O'Brien ME, Sayer R, et al. The pathway study: results of a pilot feasibility study in patients suspected of having lung carcinoma investigated in a conventional chest clinic setting compared to a centralised two-stop pathway. *Lung cancer*. 2003;42(3):283-90.
49. Martin-Ucar AE, Waller DA, Atkins JL, et al. The beneficial effects of specialist thoracic surgery on the resection rate for non-small-cell lung cancer. *Lung cancer*. 2004;46(2):227-32.
50. Dillman RO and Chico SD. Cancer patient survival improvement is correlated with the opening of a community cancer center: comparisons with intramural and extramural benchmarks. *Journal of oncology practice*. 2005;1(3):84-92.
51. Coory M, Gkolia P, Yang IA, et al. Systematic review of multidisciplinary teams in the management of lung cancer. *Lung cancer*. 2008;60(1):14-21.
52. Olver I, Keefe D, Herrstedt J, et al. Supportive care in cancer—a MASCC perspective. *Supportive Care in Cancer*. 2020;
53. Osarogiagbon RU, Phelps G, McFarlane J and Bankole O. Causes and consequences of deviation from multidisciplinary care in thoracic oncology. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2011;6(3):510-6.
54. Stone E, Rankin N, Kerr S, et al. Does presentation at multidisciplinary team meetings improve lung cancer survival? Findings from a consecutive cohort study. *Lung cancer*. 2018;124:199-204.
55. Taplin SH, Weaver S, Salas E, et al. Reviewing cancer care team effectiveness. *Journal of oncology practice*. 2015;11(3):239-46.
56. Freeman RK, Van Woerkom JM, Vyverberg A and Ascoti AJ. The effect of a multidisciplinary thoracic malignancy conference on the treatment of patients with lung cancer. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2010;38(1):1-5.

57. Prades J, Remue E, van Hoof E and Borrás JM. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. *Health policy*. 2015;119(4):464-74.
58. Boxer MM, Vinod SK, Shafiq J and Duggan KJ. Do multidisciplinary team meetings make a difference in the management of lung cancer? *Cancer*. 2011;117(22):5112-20.
59. Onukwugha E, Petrelli NJ, Castro KM, et al. ReCAP: Impact of Multidisciplinary Care on Processes of Cancer Care: A Multi-Institutional Study. *Journal of oncology practice*. 2016;12(2):155-6; e7-68.
60. Freeman RK, Ascioti AJ, Dake M and Mahidhara RS. The Effects of a Multidisciplinary Care Conference on the Quality and Cost of Care for Lung Cancer Patients. *The Annals of thoracic surgery*. 2015;100(5):1834-8; discussion 8.
61. Pillay B, Wootten AC, Crowe H, et al. The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: A systematic review of the literature. *Cancer treatment reviews*. 2016;42:56-72.
62. International Agency for Research on Cancer. Press release no. 213: IARC—diesel exhaust carcinogenic. IARC, Lyon, 2012.
63. Spyrtos D, Zarogoulidis P, Porpodis K, et al. Occupational exposure and lung cancer. *J Thorac Dis*. 2013;5 Suppl 4(Suppl 4):S440-S5.
64. Wu GX, Nelson RA, Kim JY and Raz DJ. Non-Small Cell Lung Cancer as a Second Primary Among Patients With Previous Malignancy: Who Is at Risk? *Clinical lung cancer*. 2017;18(5):543-50.e3.
65. Donin N, Filson C, Drakaki A, et al. Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. *Cancer*. 2016;122(19):3075-86.
66. Okoli GN, Kostopoulou O and Delaney BC. Is symptom-based diagnosis of lung cancer possible? A systematic review and meta-analysis of symptomatic lung cancer prior to diagnosis for comparison with real-time data from routine general practice. *PloS one*. 2018;13(11):e0207686.
67. Shim J, Brindle L, Simon M and George S. A systematic review of symptomatic diagnosis of lung cancer. *Family practice*. 2014;31(2):137-48.
68. Huggenberger IK and Andersen JS. Predictive value of the official cancer alarm symptoms in general practice—a systematic review. *Danish Medical Journal*. 2015;62(5)
69. Ades AE, Biswas M, Welton NJ and Hamilton W. Symptom lead time distribution in lung cancer: natural history and prospects for early diagnosis. *International journal of epidemiology*. 2014;43(6):1865-73.
70. Biswas M, Ades AE and 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.
71. Dregan A, Moller H, Charlton J and Gulliford MC. Are alarm symptoms predictive of cancer survival?: population-based cohort study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2013;63(617):e807-12.
72. Naeser E, Fredberg U, Moller H and Vedsted P. Clinical characteristics and risk of serious disease in patients referred to a diagnostic centre: A cohort study. *Cancer epidemiology*. 2017;50(Pt A):158-65.
73. Hamilton W. The CAPER studies: five case-control studies aimed at identifying and quantifying the risk of cancer in symptomatic primary care patients. *British journal of cancer*. 2009;101 Suppl 2:S80-6.
74. Hamilton W, Peters TJ, Round A and Sharp D. What are the clinical features of lung cancer before the diagnosis is made? A population based case-control study. *Thorax*. 2005;60(12):1059-65.
75. Bailey SE, Ukoumunne OC, Shephard EA and 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. *The British Journal of General Practice*. 2017;67(659):e405-e13.

76. Guldbrandt LM, Fenger-Gron M, Rasmussen TR, et al. The effect of direct access to CT scan in early lung cancer detection: an unblinded, cluster-randomised trial. *BMC cancer*. 2015;15:934.
77. Guldbrandt LM, Rasmussen TR, Rasmussen F and Vedsted P. Implementing direct access to low-dose computed tomography in general practice--method, adaption and outcome. *PLoS one*. 2014;9(11):e112162.
78. Toyoda Y, Nakayama T, Kusunoki Y, et al. Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography. *British Journal of Cancer*. 2008;98(10):1602-7.
79. The Royal Australian and New Zealand College of Radiologists (RANZCR). Computed Tomography and Radiation Risks. Position statement. Accessed: <https://www.ranzcr.com/college/document-library/fcr-position-statement-ct-and-radiation-risks>
80. The Royal Australian and New Zealand College of Radiologists (RANZCR). Radiation Risk of Medical Imaging for Adults and Children. Accessed: <https://www.insideradiology.com.au/radiation-risk-hp/>
81. Australian Radiation Protection and Nuclear Safety Agency. Fact Sheet - Ionising Radiation and Health. Accessed: <https://www.arpansa.gov.au/understanding-radiation/radiation-sources/more-radiation-sources/ionising-radiation-and-health>
82. Rampinelli C, De Marco P, Origgi D, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. *Bmj*. 2017;356:j347.
83. Cohen SL, Wang JJ, Chan N, et al. Lung Cancer Screening CT: Sex-Specific Conversion Factors to Estimate Effective Radiation Dose From Dose-Length Product. *Chest*. 2019;156(6):1214-22.
84. Demb J, Chu P, Yu S, et al. Analysis of Computed Tomography Radiation Doses Used for Lung Cancer Screening Scans. *JAMA internal medicine*. 2019;179(12):1650-57.
85. Callister ME, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax*. 2015;70 Suppl 2:ii1-ii54.
86. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. *Radiology*. 2017;284(1):228-43.
87. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e93S-e120S.
88. Cancer Council Australia. Clinical practice guidelines for the prevention and diagnosis of lung cancer. Accessed: [https://wiki.cancer.org.au/australia/Guidelines:Lung\\_cancer/Prevention\\_and\\_diagnosis?\\_ga=2.181609639.1269369823.1526011486-942572395.1517912083](https://wiki.cancer.org.au/australia/Guidelines:Lung_cancer/Prevention_and_diagnosis?_ga=2.181609639.1269369823.1526011486-942572395.1517912083)
89. Zanon M, Pacini GS, de Souza VVS, et al. Early detection of lung cancer using ultra-low-dose computed tomography in coronary CT angiography scans among patients with suspected coronary heart disease. *Lung cancer*. 2017;114:1-5.
90. Kim TJ, Han DH, Jin KN and Won Lee K. Lung cancer detected at cardiac CT: prevalence, clinicoradiologic features, and importance of full-field-of-view images. *Radiology*. 2010;255(2):369-76.
91. SIGN. SIGN 137. Management of lung cancer. A national clinical guideline. Healthcare Improvement Scotland, 2014.
92. Evans J, Ziebland S, MacArtney JI, et al. GPs' understanding and practice of safety netting for potential cancer presentations: a qualitative study in primary care. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2018;68(672):e505-e11.
93. Birt L, Hall N, Emery J, et al. Responding to symptoms suggestive of lung cancer: A qualitative interview study. *BMJ Open Respir Res*. 2014;1(1):e000067.

94. Brindle L, Pope C, Corner J, et al. Eliciting symptoms interpreted as normal by patients with early-stage lung cancer: could GP elicitation of normalised symptoms reduce delay in diagnosis? Cross-sectional interview study. *BMJ open*. 2012;2:e001977.
95. NICE. Referral Guidelines for Suspected Cancer. National Institute for Health and Care Excellence, 2005.
96. Neal RD, Barham A, Bongard E, et al. Immediate chest X-ray for patients at risk of lung cancer presenting in primary care: randomised controlled feasibility trial. *British journal of cancer*. 2017;116(3):293-302.
97. Guldbrandt LM, Fenger-Gron M, Folkersen BH, et al. Reduced specialist time with direct computed tomography for suspected lung cancer in primary care. *Danish medical journal*. 2013;60(12):A4738.
98. Raj V, Gupta S, Sivashanmugam T, et al. The Role of Multi Detector Computed Tomographic Imaging Prior to Clinic Consultation in Patients Suspected to Have Lung Cancer. *World journal of oncology*. 2012;3(3):113-8.
99. Hirst Y and Lim AW. Acceptability of text messages for safety netting patients with low-risk cancer symptoms: A qualitative study. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2018;68(670):e333-e41.
100. Guldbrandt LM, Fenger-Gron M, Rasmussen TR, et al. The role of general practice in routes to diagnosis of lung cancer in Denmark: a population-based study of general practice involvement, diagnostic activity and diagnostic intervals. *BMC health services research*. 2015;15:21.
101. Naeser E, Moller H, Fredberg U, et al. Routine blood tests and probability of cancer in patients referred with non-specific serious symptoms: a cohort study. *BMC cancer*. 2017;17(1):817.
102. Green T, Martins T, Hamilton W, et al. Exploring GPs' experiences of using diagnostic tools for cancer: a qualitative study in primary care. *Family practice*. 2015;32(1):101-5.
103. Nicholson BD, Goyder CR, Bankhead CR, et al. Responsibility for follow-up during the diagnostic process in primary care: A secondary analysis of International Cancer Benchmarking Partnership data. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2018;68(670):e323-e32.
104. Nicholson BD, Hamilton W, O'Sullivan J, et al. Weight loss as a predictor of cancer in primary care: A systematic review and meta-analysis. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2018;68(670):e311-e22.
105. Athey VL, Walters SJ and Rogers TK. Symptoms at lung cancer diagnosis are associated with major differences in prognosis. *Thorax*. 2018;73(12):1177-81.
106. Ewing M, Naredi P, Nemes S, et al. Increased consultation frequency in primary care, a risk marker for cancer: a case-control study. *Scandinavian journal of primary health care*. 2016;34(2):205-12.
107. Ewing M, Naredi P, Zhang C, et al. Clinical features of patients with non- metastatic lung cancer in primary care: A case-control study. *BJGP Open*. 2018;2(1):bjgpopen18X101397.
108. Ingeman ML, Christensen MB, Bro F, et al. 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.
109. Abbasowa L and Madsen PH. Lung cancer in younger patients. *Danish medical journal*. 2016;63(7)
110. Toori KU, Nomani AZ, Winson M and ur Rehman M. Is there light at the end of the tunnel; symptoms and chest x-ray help identify patients at high risk of lung cancer. *RMJ*. 2015;40(1):14-7.
111. Schmidt-Hansen M, Berendse S, Hamilton W and Baldwin DR. Lung cancer in symptomatic patients presenting in primary care: a systematic review of risk prediction tools. *The British Journal of General Practice*. 2017;67(659):e396-e404.
112. Markaki M, Tsamardinos I, Langhammer A, et al. A Validated Clinical Risk Prediction Model for Lung Cancer in Smokers of All Ages and Exposure Types: A HUNT Study. *EBioMedicine*. 2018;31:36-46.

