Evidence-Based Series 24-2

Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers


A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: August 29, 2011

An assessment conducted in January 2017 deferred the review of Evidence-based Series (EBS) 24-2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 24-2 is comprised of 3 sections and is available on the CCO Website on the PEBC Primary Care Web page at: https://www.cancercare.on.ca/toolbox/qualityguidelines/clin-program/primarycare/

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

For further information about this series, please contact:

Dr. Lisa Del Giudice, Family Physician
Sunnybrook Family Practice Unit, Room A112
2075 Bayview Ave, Toronto, M4N 3M5
Phone: 416-480-4939   Fax: 416-480-6038   Email: Lisa.DelGiudice@sunnybrook.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822   Fax: 905-526-6775   E-mail: ccopgi@mcmaster.ca


Evidence-Based Series 24-2: Section 1

Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers: Guideline Recommendations


A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: August 29, 2011

QUESTIONS

Overall Question
In patients presenting to primary care services with signs and/or symptoms of lung cancer, what should the referral process include?

The following questions are the factors considered in answering the overall question:

1. What signs, symptoms and other clinical features are predictive of lung cancer?
2. What is the diagnostic accuracy of investigations for lung cancer?
3. What major, known risk factors are predictive of lung cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

TARGET POPULATION
Patients presenting in primary care settings comprise the target population. This guideline does not provide recommendations for patients in a screening program.

INTENDED USERS
This guideline is targeted to family physicians (FPs), general practitioners, emergency room physicians, other primary care providers (PCPs) (nurse practitioners, registered nurses, and physician assistants), respirologists, thoracic surgeons, and radiologists. For the purposes of this document, we have referred to FPs, general practitioners, emergency room physicians, and other PCPs as ‘FPs and other PCPs. The guidelines are also intended for policymakers to help ensure that resources are in place so that target wait times are achieved. They are
intended to coincide with the introduction of lung cancer Diagnostic Assessment Programs (DAPs) in Ontario. DAPs provide a single point of referral, coordination of care using a clinical navigator, fast tracking of diagnostic tests and a multidisciplinary team approach. They are an Ontario-wide strategic priority designed to improve patient access and outcomes, and are outlined in the Ontario Cancer Plan since 2005-2011 and 2011-2014 (1).

RECOMMENDATIONS

The following recommendations were adapted from the New Zealand Guidelines Group (NZGG) guideline Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities and the National Institute for Health and Clinical Excellence (NICE 2005), Referral guidelines for suspected cancer (2,3). The recommendations below reflect the integration of the NZGG 2009 and NICE 2005 recommendations, an updated systematic review of the research evidence since the NZGG 2009 and the NICE 2005 guidelines, and consensus by the PEBC Lung Cancer Referral Working Group (see Section 2: Appendix 1) (2,3).

Special consideration for these recommendations:

<table>
<thead>
<tr>
<th>Factors that Increase the Risk of Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following factors have been shown to increase the risk of lung cancer and will be referred to in the recommendations below:</td>
</tr>
<tr>
<td>- Current or previous smoker or second-hand exposure to tobacco smoke</td>
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<tr>
<td>- History of chronic obstructive pulmonary disease</td>
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<tr>
<td>- Previous exposure to asbestos or other known carcinogens (e.g., radon, chromium, nickel)</td>
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<tr>
<td>- Occupational exposure to dust or microscopic particles (e.g., wood dust, silica)</td>
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<tr>
<td>- Personal or family history of cancer (especially lung, head and neck cancer)</td>
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<tr>
<td>- Silicosis, tuberculosis</td>
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<table>
<thead>
<tr>
<th>Indications for Referral to the Emergency Department</th>
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<tbody>
<tr>
<td>A person should be referred to the Emergency Department for the following:</td>
</tr>
<tr>
<td>- Signs of superior vena cava obstruction</td>
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<tr>
<td>- Stridor</td>
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<tr>
<td>- Massive hemoptysis</td>
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<tr>
<td>- New neurological signs suggestive of brain metastases or cord compression</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Indications for Chest X-ray</th>
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<tr>
<td>A person should have a chest X-ray within two working days if they present with any of the following:</td>
</tr>
<tr>
<td>- Hemoptysis</td>
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<tr>
<td>- New finger clubbing</td>
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<tr>
<td>- Suspicious lymphadenopathy</td>
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<tr>
<td>- Dysphagia</td>
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<tr>
<td>- Features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung</td>
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<tr>
<td>- Features suggestive of paraneoplastic syndromes</td>
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<tr>
<td>OR</td>
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<tr>
<td>any of the following unexplained signs or symptoms lasting more than three weeks (patients with known risk factors may be considered sooner):</td>
</tr>
<tr>
<td>- Cough</td>
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<tr>
<td>- Weight loss/loss of appetite</td>
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</table>
Patients with underlying chronic respiratory problems should have a chest X-ray within three weeks if they have unexplained changes in existing symptoms.

The requisition for a chest X-ray should include the presenting history, including signs and symptoms suspicious of lung cancer and whether risk factors exist.

Chest X-rays should be completed, reviewed, and reported by the radiologist, and the report read by the FP or other PCPs within one week of being ordered. If the chest x-ray is suspicious for lung cancer, an alternate mechanism of informing the FP or other PCPs of the suspicion should be done - (e.g., telephone call, flagging)

### Indications for Chest CT scan

A person should have a chest CT scan within two weeks if they have any of the following:
- An abnormal chest X-ray that reports suspicion of lung cancer
- A normal chest X-ray, but there is a high suspicion of lung cancer, based on clinical judgement

The ordering physician (i.e., FP or other PCPs, specialist, radiologist, or clinicians in the DAP) will depend on locally available resources and processes for expedited CT scans.

### Sputum Cytology

Sputum cytology is not recommended for the investigation of suspected lung cancer.

### Follow-up to diagnostic investigations

A person who has consolidation or unexplained pleural effusion on an initial chest X-ray should be treated and have a chest X-ray repeated within six weeks to confirm complete resolution.

### Indications for Referral to a Specialist (Respirologist or Thoracic Surgeon) or DAP

Patients should be referred and expect a consultation to a specialist or where locally available to a DAP within one to two weeks if they have any of the following:
- Persistent hemoptysis
- A chest X-ray suggestive or suspicious of lung cancer including:
  - A nodule or mass
  - Multiple pulmonary nodules
  - Non-resolving pleural effusion
  - Mediastinal or contralateral hilar adenopathy
  - Interstitial infiltrates
  - Slowly or non-resolving pneumonia or consolidation
  - Fibroapical disease suggesting possible tuberculosis
  - Unexplained elevated diaphragm
- A normal chest X-ray, but there is a high suspicion of lung cancer, based on clinical judgement

If promptly accessible, a chest CT scan can be simultaneously ordered with the referral while awaiting the specialist’s consultation. This will depend on locally available resources. If the CT scan is entirely negative, then further referral to a specialist can be cancelled.
To expedite the diagnosis and avoid duplication of investigations, at a minimum, the following information should be provided to the specialist:

- History of the patient, including all risk factors and signs or symptoms suspicious of lung cancer
- All efforts should be made to provide all pre-existing imaging results, including chest X-rays and CT scans (films and digital images should be available at the time of consultation)
- All relevant other medical conditions and medications taken by patient
- All recent blood work

### Recommendations to Reduce Diagnostic Delay

There should be appropriate educational tools developed and disseminated that highlight the signs and symptoms of lung cancer for FPs and other PCPs and for patients.

FPs and other PCPs should have a high index of suspicion with a low threshold for investigation of suspected lung cancer in ordering chest x-rays and referral to lung cancer specialists or the DAP. Decision support tools should be readily available to assist FPs and other PCPs.

FPs and other PCPs should include as much information as possible in their referral letters and should ask patients to help retrieve electronic copies of their imaging tests to bring to specialist appointments.

Counselling of patients should occur to address common fears and concerns.

Public health and other health agencies should work with local community leaders to address challenges, such as lower levels of education or demographic discrepancies in communities with high rates of lung cancer or known delays in lung cancer diagnosis.
Lung Cancer Guideline Recommendations

Does the patient have any of the following signs/symptoms?

- Persistent haemoptysis
- Stridor
- Massive haemoptysis (>600ml of blood in 24 hours or cup full (250ml) at one sitting)
- New neurological signs suggestive of brain metastases or cord compression

**Unexplained** changes in existing symptoms in patients with underlying chronic respiratory problems

- Haemoptysis
- New finger clubbing
- Suspicious lymphadenopathy
- Dysphagia
- Features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung
- Features suggestive of paraneoplastic syndromes
- OR any of the following unexplained signs or symptoms lasting more than 3 weeks (patients with known risk factors* may be considered sooner):
  - Cough
  - Weight loss/loss of appetite
  - Shortness of breath
  - Chest and/or shoulder pain
  - Abnormal chest signs
  - Hoarseness

**Performed within 3 weeks**

Chest X-ray

**Read within 1 week**

- Normal
  - High suspicion of Lung Cancer
    - Referred and seen within 1-2 weeks
    - Specialist Referral and CT Scan
      - Referred and seen within 1-2 weeks
      - Referral and managed

- Abnormal
  - A chest x-ray suggestive or suspicious of lung cancer including:
    - A nodule or mass
    - Multiple pulmonary nodules
    - Non-resolving pleural effusion
    - Mediastinal or contralateral hilar adenopathy
    - Interstitial infiltrates
    - Slowly or non-resolving pneumonia or consolidation
    - Fibrosapical disease suggesting possible tuberculosis
    - Unexplained elevated diaphragm

- Consolidation or unexplained pleural effusion
  - Repeat Chest X-ray within 6 weeks to confirm resolution

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*Risk factors: Current or previous smoker or second-hand exposure to tobacco smoke, history of chronic obstructive pulmonary disease, previous exposure to asbestos or other known carcinogens, occupational exposure to dust or microscopic particles, personal or family history of cancer (especially lung, head and neck cancer), silicosis, tuberculosis.
KEY EVIDENCE

- Many of these recommendations were adapted or endorsed from the NZGG 2009 or NICE 2005 recommendations (2,3). Signs and symptoms listed in the NZGG 2009 or NICE 2005 recommendations were derived from their systematic reviews, which mainly included case-series studies (2,3). The development of the recommendations in this guideline can be found in Section 3 of this report.

- There was no evidence found on wait times and their effects on patient outcomes. One study found that wait times to referral for specialist consultation for patients with signs or symptoms suspicious for lung cancer can be reduced from 20 days to six days with the implementation of a DAP (4). For this guideline, the wait times for diagnostic investigations and referral developed by the Lung Cancer Referral Working Group were chosen because they considered them to be achievable targets in the Ontario health care system, especially with the introduction of DAPs across the province.

- The list of risk factors was broadened to include all risk factors summarized by NZGG 2009 based on the review by NICE 2005 (2,3).

Indications for Referral to Emergency Department

- This recommendation was adapted from the NICE 2005 guidelines for immediate referral. New neurological signs suggestive of brain metastases or cord compression were included based on common practice in Ontario and massive hemoptysis was included based on the Time-to-Treat Program (4).

Indications for Chest X-ray

- This recommendation was adapted from the NZGG 2009 guidelines for urgent referral for a chest X-ray (3). Based on expert opinion, it was felt that, for new finger clubbing, features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung, and suspicious lymphadenopathy, the three-week time frame was not required for referral for a chest X-ray. The Working Group chose to include dysphagia as an indicator for a chest X-ray, because it was reported in the NICE 2005 review as a symptom of lung cancer and was found to be a major clinical symptom among lung cancer patients in a tertiary care setting (2,5). Furthermore, paraneoplastic syndromes were included as indications for chest X-ray based on the review by Spiro et al (2007) that reported that paraneoplastic syndromes may occur in 10% of patients with lung cancer (6).

- For patients with underlying chronic respiratory problems, the Working Group chose to adapt the recommendation from NICE 2005 (2).

Indications for CT Scan

- There was little evidence to inform these recommendations; therefore, the Working Group decided to develop their own recommendations based on experiences within their own practices.

Sputum Cytology

- The updated literature search found high specificity but variable sensitivity of sputum cytology in detecting lung cancer (7-11). Therefore, this recommendation was endorsed from the NZGG 2009 referral guidelines (3).
Follow-up to Diagnostic Investigations

- The recommendation for follow-up to consolidation on a chest X-ray was adapted from the NZGG 2009 referral guideline, which was based on the experience of their guideline development team (3). The Working Group chose to modify the NZGG’s 2009 recommendation by including all patients rather than specifying only patients with risk factors for lung cancer. In addition to consolidation, the Working Group also included unexplained pleural effusion based on their experience in their practices.

Indications for Referral to a Specialist (Respirologist or Thoracic Surgeon) or the DAP

- These recommendations were adapted from the NZGG 2009 and NICE 2005 referral guidelines, which were based on expert opinion (2,3). Additional abnormal chest X-ray results were included from the Time-to-Treat Program (4). Unexplained elevated diaphragm was included based on the suggestion of an expert panel member.

Recommendations to Reduce Diagnostic Delay

- There is evidence to suggest that the following may delay the diagnosis of lung cancer (2,3,6,12,13):
  - Patient-Related Delay:
    - patient’s lack of appreciation regarding the association of symptoms with lung cancer
    - fear of cancer diagnosis
  - Family Physician related delay:
    - not recognizing signs and symptoms suggestive of lung cancer
    - co-morbidity of conditions increased delay
    - multiple consecutive investigations in primary care
    - over-reliance on chest X-ray results to diagnose lung cancer
    - imaging follow-up failure
    - initial referral to a non-respiratory physician

Algorithm

- The process used to develop this algorithm can be found in Section 3.

FUTURE RESEARCH

Further studies could be designed to investigate the diagnostic performance of signs, symptoms, or tests for lung cancer in the primary care setting. In addition, studies are needed to determine which educational initiatives would be best at decreasing practitioner- or patient-related delay.

GLOSSARY

Diagnostic Assessment Programs
Diagnostic Assessment Programs, emerging across the province, provide a single point of referral, coordination of care using a clerical navigator, fast tracking of diagnostic tests and a multidisciplinary team approach, thereby improving the quality of care and the patient experience. They are an Ontario-wide strategic priority designed to improve patient access and outcomes and outlined in the Ontario Cancer Plan since 2005-2011 and 2011-2014 (1).

Abnormal Chest Signs
e.g., crackles or wheezes
Abnormal Chest X-ray that Reports Suspicion of Lung Cancer
  e.g., nodule(s), infiltrates, non-resolving consolidation or effusion despite treatment

Features Suggestive of Metastatic Disease
  Family physicians can refer to the American College of Chest Physicians (ACCP) Clinical Practice Guidelines for features of a standardized evaluation for systematic metastases (available at: http://chestjournal.chestpubs.org/content/132/3_suppl/149S.full.pdf)(6)

Massive Hemoptysis
  >600 mL of blood in 24 hours or one cup full of blood (250 mL) at one sitting

Features Suggestive of Paraneoplastic Syndromes
  Family physicians can refer to the ACCP Clinical Practice Guidelines for a list of paraneoplastic syndromes associated with lung cancer (available at: http://chestjournal.chestpubs.org/content/132/3_suppl/149S.full.pdf)(6)

Signs of Superior Vena Cava Obstruction
  Swelling of the face and or neck with fixed elevation of jugular venous pressure

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Contact Information
  For further information about this report, please contact:

  Dr. Lisa Del Giudice, Family Physician, Sunnybrook Family Practice Unit, Room A112
  2075 Bayview Ave, Toronto, M4N 3M5
  Phone: 416-480-4939  Fax: 416-480-6038  Email: Lisa.DelGiudice@sunnybrook.ca

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RECOMMENDATIONS - page 8
REFERENCES

1. Cancercare.on.ca [Internet]. Toronto (ON): Cancer Care Ontario (CCO); 2011 [cited 2010 Aug 3].
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QUESTIONS

Overall Question

In patients presenting to primary care services with signs and/or symptoms of lung cancer, what should the referral process include?

The following questions are the factors considered in answering the overall question:

1. What signs, symptoms and other clinical features are predictive of lung cancer?
2. What is the diagnostic accuracy of investigations for lung cancer?
3. What major, known risk factors are predictive of lung cancer?
4. Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

INTRODUCTION

Lung cancer is the most common cause of cancer death in Ontario for both men (26%) and women (22%) (1). Tobacco use is the primary cause of lung cancer, accounting for an estimated 86% of cases (1). The chance of surviving lung cancer in Ontario is low, with a five-year survival rate of 15% for both men and women combined (1). Lung cancers are frequently diagnosed at a late stage, and the prognosis is very poor (1). While some presenting symptoms might be vague and imprecise, delays in diagnosis might be avoided when patients with a history suggesting an increased risk of lung cancer and suspicious signs and symptoms receive a timely chest X-ray and, where warranted, are referred to a specialist or a Diagnostic Assessment Program (DAP) for further investigation. To date, there are no Ontario guidelines for FPs and other PCPs to assist them in identifying and initiating the management of these
patients. Because of a need for guidance regarding referral for suspected lung cancer, the CCO’s Provincial Primary Care and Cancer Network (PPCCN) in collaboration with the Program in Evidence-based Care (PEBC) has developed this guideline for patients who present with signs and symptoms that might be indicative of lung cancer. The New Zealand Guidelines Group (NZGG) 2009 guideline, Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities and the National Institute for Health and Clinical Excellence (NICE) 2005 guideline, Referral guidelines for suspected cancer in adults and children were chosen as a baseline documents for the development of this systematic review (2,3). The aim of this guideline is to assist primary care physicians to recognize features that should raise their suspicion of lung cancer and ultimately lead to more timely and appropriate referrals of these patients.

METHODS
The evidence-based series (EBS) guidelines developed by Cancer Care Ontario’s PEBC use the methods of the Practice Guidelines Development Cycle (4). A priori the Lung Cancer Referral Working Group chose the NZGG 2009 and NICE 2005 documents as a foundation because they were considered to be of high quality, comprehensive, recent in publication, and relevant to this topic (2,3). The Working Group updated the literature searches of the NZGG 2009 or NICE 2005 systematic reviews to determine if any new evidence would change the NZGG 2009 or NICE 2005 recommendations (2,3).

Evidence was selected and reviewed by nine members of the PEBC Lung Cancer Referral Expert Panel and one methodologist (Appendix 1). If the new evidence did not substantially change the recommendations of NZGG 2009 or NICE 2005, then the Working Group would adapt the NZGG 2009 and NICE 2005 recommendations as well as any recommendations from evidence-based guidelines found during the updated literature search or the environmental scan (2,3).

This updated evidentiary base and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy
In order to determine if there were other higher quality guidelines compared to NICE 2005 or NZGG 2009, or guidelines with more recent systematic reviews, or what other agencies were recommending, a targeted environmental scan of international guideline developers and key organizations was conducted (March 5-8, 2010) for documents about primary care referral for suspected lung cancer (2,3). A listing of the organizations that were examined is given in Appendix 2.

Following this search of other guidelines, the Lung Cancer Referral Working Group considered the NICE 2005 and NZGG 2009 guidelines to be of the highest quality and updated their literature search strategies (2,3). The search strategies from NZGG 2009 and NICE 2005 were kindly provided to us for this systematic review (2,3). NZGG 2009 performed systematic reviews for questions concerning the diagnostic accuracy of signs, symptoms, and diagnostic tests and for the clinical questions investigating factors associated with delay in referral (3). For these clinical questions, an updated search since the NZGG 2009 publication of MEDLINE (Ovid, August 2007 - February Week 3 2010) and EMBASE (Ovid, 2007 - 2010 week 07) was performed using the NZGG 2009 literature search strategy (3). For the clinical question investigating risk factors for lung cancer, NZGG 2009 did not perform a systematic review (3). Therefore, an updated search, since the NICE 2005 publication, of MEDLINE (Ovid, June 2004-February Week 3 2010) and EMBASE (Ovid, 2004 - 2010 week 08) using the NICE 2005 search
strategies for systematic reviews for lung cancer was performed (2,3). A second literature search update of all strategies for literature available to June 27, 2011 was performed. The search strategies can be found in Appendix 3.

**Study Selection Criteria**
Guidelines were included if they addressed at least one of our research questions, were not cited in the NZGG 2009 or NICE 2005 guidelines, and included recommendations not found or different from those in either the NICE 2005 or NZGG 2009 guidelines (2,3).

For the clinical question about the predictive characteristics of signs or symptoms, all prospective or retrospective case series or cohort or case control studies of symptom recognition/identification for lung cancer were included. Studies conducted in the secondary care setting that provided predictive information about signs/symptoms for suspected lung cancer were included when limited evidence was available from the primary care setting. Screening studies were excluded because they include asymptomatic patients. This report focuses on patients presenting to primary care with signs or symptoms of lung cancer.

All diagnostic studies in which symptomatic primary care patients underwent one or more investigations including complete blood count, chest X-ray, spirometry, sputum cytology and CT scan were sought. If limited evidence was available from the primary care setting, studies conducted in secondary care settings were included if they provided diagnostic information for suspected lung cancer for the specified investigations. Screening studies were excluded.

For the clinical questions concerning risk factors and delay in referral, a search for practice guidelines, systematic reviews (with meta-analyses), and systematic reviews (without meta-analyses) was performed. If these articles did not definitively answer the particular clinical question, then searches for randomized phase III trials and randomized phase II trials followed by prospective or retrospective case series or cohort or case-control studies were performed. If information from systematic reviews definitively answered the question(s), then articles from the time of publication of the systematic review and onwards were retrieved.

Publications in a language other than English were not eligible because of lack of funding for translation. Non-systematic reviews, abstracts, case studies, letters, editorials, and commentaries were excluded.

**Synthesizing the Evidence**
There was considerable heterogeneity between studies; therefore, data were not pooled.

**Quality Appraisal of Evidence-Based Guidelines**
The Appraisal of Guidelines Research and Evaluation (AGREE II) tool was used by three independent methodologists to evaluate the quality of included evidence-based guidelines, or the AGREE II scores were taken from the Standards and Guidelines Evidence Inventory of Cancer Guidelines developed by the Canadian Partnership Against Cancer if available (5,6). Only clinical practice guidelines in which the objective of the guideline was specifically described and the document included a review of the evidence were evaluated using the AGREE II tool (5,6). Systematic reviews and meta-analyses were assessed for quality using the ‘assessment of multiple systematic reviews’ or ‘AMSTAR’ tool (7).

**Guideline Selection for Adaptation**
Guidelines appropriate for adaptation were selected in a two-step screening process. First, two physicians evaluated each guideline using two questions modified from the AGREE II
instrument: Would you use this guideline? and Were the recommendations based on evidence or expert opinion (5,6)? As a second level of screening, the quality of the remaining guidelines was assessed with the AGREE II instrument (5,6). These guidelines are described in Section 2, below. The process of adapting the recommendations is described in Section 3.

RESULTS
Literature Search Results
Of 7719 articles identified in the updated literature search, 168 were deemed relevant for a full article review. Of these, 16 articles not included in the NZGG 2009 systematic review met the inclusion criteria and were retained (3,8-23). In addition to the NICE 2005 and NZGG 2009 guidelines (2,3), six guidelines were found during the environmental scan (24-29). The American College of Chest Physicians (ACCP) published a series of evidence-based clinical practice guidelines for the management of patients with lung cancer. Four of these guidelines were included because they addressed at least one of the research questions (24-27). The other two guidelines were developed by SIGN and Australia (28,29). In the second updated literature search, one systematic review and two studies were included (30-32). Table 2 provides a summary of included articles for each research question.

Table 2 Summary of included articles for each research question.

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Guideline</th>
<th>Systematic review</th>
<th>Prospective studies</th>
<th>Retrospective studies</th>
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<tbody>
<tr>
<td>Signs / symptoms</td>
<td>5*</td>
<td>1</td>
<td>1</td>
<td>8**</td>
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<tr>
<td>Tests</td>
<td>7*</td>
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<tr>
<td>Delay</td>
<td>4*</td>
<td>3</td>
<td>1</td>
<td>6**</td>
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</table>

*Some guidelines were relevant for more than one research question.
**Three articles addressed both the research question about signs or symptoms and the research question about the factors associated with delayed referral.

Study Design and Quality
Research Questions for Signs/Symptoms, Tests, and Risk Factors
Guidelines and Reviews
The NZGG 2009 guideline was based on the NICE 2005 guideline (2,3) and provided updated evidence since the NICE guideline for research questions about signs and symptoms as well as for diagnostic tests. The authors did not do a systematic review for the research question about risk factors, and their recommendations were essentially endorsed from the NICE recommendations with minor word changing.

NICE performed systematic reviews for these research questions, but the link of the evidence to the recommendations was not always clear (2). For example, it is unclear why certain risk factors for lung cancer were included in their recommendations and others were not. Presumably, the included risk factors are more established in the literature, but this is not specifically mentioned. They note that the literature is lacking to adequately address these research questions, especially within the context of primary care.

There were six guidelines, in addition to the NZGG 2009 and NICE 2005 guidelines, found during the environmental scan that addressed at least one of our research questions, were not cited in the NZGG or NICE guidelines (2,3) and included recommendations not found or different from those in either the NICE or NZGG guideline (24-29). The four guidelines developed by the ACCP that addressed at least one of the research questions did not provide lists or details of the included studies and did not assess the quality of the included studies.
although each of the recommendations was followed by a grading of the supporting evidence (24-27). Kvale 2006 was published in the first edition of the ACCP clinical practice guidelines (25). Although MEDLINE was searched, only two terms were listed: “cough” and “lung neoplasms.” Rivera and Mehta 2007, Spiro 2007, and Gould 2007 were published in the second addition of the ACCP clinical practice guidelines (24,26,27). Rivera and Mehta, and Gould searched more than one database and included their research questions as well as their inclusion and exclusion criteria (24,26). The search terms in MEDLINE and the inclusion and exclusion criteria were not outlined in the Spiro article (27).

SIGN 2005 included evidence summaries from their systematic review before each of their recommendations, and they included a grade of the strength of the evidence for each recommendation (29). They provided their search strategies for MEDLINE, but their inclusion and exclusion criteria were not clearly defined. This guideline addressed the management of patients with lung cancer and was not solely focused on the referral process; as such, whether the included studies were performed in the primary care setting was not a priority.

The Australian guidelines also covered a broad spectrum of care for patients with lung cancer from prevention and diagnosis to management (28). Therefore, the focus was not on the referral process, and studies were not selected on the basis of the primary care setting. They did not include their search strategy or their inclusion or exclusion criteria. They provided the strength of the level of evidence to support their recommendations, as well as the citations for each recommendation.

One systematic review by Stapley et al 2010 was included in the updated literature search since the NZGG search (30). Table 3 shows how this systematic review scored on each of the 11 AMSTAR items. This systematic review scored well, with eight of the 11 items meeting the AMSTAR criteria. The authors did not include all excluded studies and did not assess the likelihood of publication bias. Although a conflict of interest statement was included for the authors of the systematic review, conflict of interest statements were not acknowledged for the included studies.

Table 3. Evaluation of included publications using AMSTAR.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was an ‘a priori’ design provided?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2. Was there duplicate study selection and data extraction?</td>
<td>Can’t answer</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>3. Was a comprehensive literature search performed?</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>5. Was a list of studies (included and excluded) provided?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>6. Were the characteristics of the included studies provided?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>7. Was the scientific quality of the included studies assessed and documented?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>8. Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>9. Were the methods used to combine the findings of the studies appropriate?</td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
</tr>
</tbody>
</table>
10. Was the likelihood of publication bias assessed?  
- Hanna et al. 2005 (12)  
- Olson et al. 2009 (17)  
- Shapley et al. 2010 (30)  
- Singh et al. 2007 (19)  

11. Was the conflict of interest stated?  
- Hanna et al. 2005 (12)  
- Olson et al. 2009 (17)  
- Shapley et al. 2010 (30)  
- Singh et al. 2007 (19)  

TOTAL AMSTAR POINTS  
- 1  
- 5  
- 8  
- 3  

**Abbreviations:** N, no; NA, not applicable; Y, yes.

**Primary Studies**

Of the 11 primary studies published since the NZGG search that addressed the first three research questions, nine had retrospective designs (Table 4)(8-11,13,14,16,21,22,31,32). None of these studies were performed in a primary care setting, and only two articles included patients with and without lung cancer and were blinded to the diagnostic results (11,13). The Working Group decided these primary studies would not significantly change the recommendations found in the eight evidence-based guidelines that provided recommendations for the first three research questions (2,3,24-29). Therefore, the Working Group decided to adapt the recommendations from these existing guidelines for use in Ontario.

**Table 4: Study characteristics of included articles not included in the NZGG 2009 search.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Country</th>
<th>No. of Patients</th>
<th>No. of Patients with Lung Cancer (%)</th>
<th>Setting</th>
<th>Investigations Used</th>
<th>Consecutive Patients</th>
<th>Blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ak et al 2007 (8)</td>
<td>Retrospective</td>
<td>Turkey</td>
<td>1340</td>
<td>1340</td>
<td>Secondary care</td>
<td>X-ray; Histopathologically confirmed</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Beatty et al 2009 (9)</td>
<td>Retrospective</td>
<td>New Zealand</td>
<td>159</td>
<td>159</td>
<td>Secondary care</td>
<td>NR</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Chandra et al 2009 (10)</td>
<td>Retrospective</td>
<td>India</td>
<td>165</td>
<td>165</td>
<td>Tertiary care</td>
<td>Cytologically or histologically confirmed</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Choi et al 2008 (11)</td>
<td>Retrospective</td>
<td>Korea</td>
<td>955; 352 histologically confirmed</td>
<td>127 (36%)</td>
<td>Secondary setting</td>
<td>ThinPrep sputum test versus conventional preparation; 352 histologically confirmed</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Kemp et al 2007 (13)</td>
<td>Prospective</td>
<td>Canada</td>
<td>1123 with medical history or clinical symptoms suspicious of lung cancer</td>
<td>370 (33%)</td>
<td>Secondary care, Sponsored by Perceptronix Medical Inc.</td>
<td>LungSign sputum test versus conventional cytological or minimum of 3 mths follow-up</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Koumarianou et al 2009 (14)</td>
<td>Retrospective</td>
<td>Greece</td>
<td>1906</td>
<td>1906 with non-small cell lung</td>
<td>Cancer registry - mainly</td>
<td>Histologically or cytologically confirmed</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Author</td>
<td>Study</td>
<td>Country</td>
<td>No. of Patients</td>
<td>No. of Patients with Lung Cancer (%)</td>
<td>Setting</td>
<td>Investigations Used</td>
<td>Consecutive Patients</td>
<td>Blinded</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------------</td>
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<td>--------------------------------------------------------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Lo et al 2007 (15)</td>
<td>Program implementation and assessment</td>
<td>Canada</td>
<td>52</td>
<td>52</td>
<td>Primary and secondary care</td>
<td>X-ray</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lovgren et al 2008 (16)</td>
<td>Retrospective</td>
<td>Sweden</td>
<td>314</td>
<td>314</td>
<td>Secondary care</td>
<td>Cytology results available for 291</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rolke et al 2007 (18)</td>
<td>Retrospective</td>
<td>Norway</td>
<td>479</td>
<td>479</td>
<td>Secondary care</td>
<td>43T Histologically confirmed</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Smith et al 2009 (20)</td>
<td>Retrospective</td>
<td>UK</td>
<td>360</td>
<td>360</td>
<td>Secondary care</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thammakumpee et al 2007 (21)</td>
<td>Retrospective</td>
<td>Thailand</td>
<td>116</td>
<td>116 with small-cell lung cancer</td>
<td>Secondary care</td>
<td>X-ray; Histologically and/or cytologically confirmed</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Thomas et al 2008 (22)</td>
<td>Retrospective</td>
<td>India</td>
<td>25</td>
<td>25 with pulmonary carcinoid tumours</td>
<td>Tertiary care</td>
<td>Bronchoscopy; all had biopsy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Uzun et al 2010 (31)</td>
<td>Prospective</td>
<td>Turkey</td>
<td>178</td>
<td>51 (29%)</td>
<td>Tertiary care</td>
<td>All X-ray, some bronchoscopy and/or CT scan; final diagnosis based on consensus</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yaman et al 2009 (32)</td>
<td>Retrospective</td>
<td>Turkey</td>
<td>109</td>
<td>109</td>
<td>Secondary care</td>
<td>Histopathologically confirmed</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Yilmaz et al 2008 (23)</td>
<td>Retrospective</td>
<td>Turkey</td>
<td>138</td>
<td>138 with non-small cell lung carcinoma</td>
<td>Secondary care</td>
<td>CT/PET; thoracotomy</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; mths, months; NR, not reported; PET, positron emission tomography.

**Research Question about Delay in Referral**

For the research question associated with delay, additional factors affecting delay beyond those mentioned in the NICE and NZGG guidelines were found in the SIGN guideline, the ACCP guideline by Spiro et al, three systematic reviews, and seven primary studies (Table 4)(2,3,10,12,15-20,23,27,29,32). Table 3 shows how the included systematic reviews scored on each of the 11 AMSTAR items. The overall scores were low for all the systematic reviews. Two of the systematic reviews did not include the characteristics of the included studies, nor did they assess the quality of the included studies (12,19). The one systematic review that did include characteristics and assessments of included studies searched only one electronic database (17).

**Guideline Selection for Adaptation**

Based on the two physicians’ answers in the first level of screening, the recommendations from Spiro et al were felt to be too general (27). These recommendations were excluded when developing the recommendations for Ontario. The quality of the remaining guidelines from NICE, NZGG, the Australian National Health and Medical Research Council, the Scottish Intercollegiate Guidelines Network (SIGN) and the ACCP (includes Kvale,
Rivera and Mehta, and Gould et al) was assessed with the AGREE II instrument (Table 5)\(^{(2,3,24-26,28,29)}\).

### Table 5. Results of AGREE II Tool quality rating of evidence-based guidelines.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>AGREE II Domain Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Scope and Purpose (%)</td>
</tr>
<tr>
<td>NICE 2005(2)</td>
<td>97.2</td>
</tr>
<tr>
<td>NZGG 2009 (3)</td>
<td>74.1</td>
</tr>
<tr>
<td>Australian 2004 (28)</td>
<td>80.6</td>
</tr>
<tr>
<td>SIGN 2005 (29)</td>
<td>61.1</td>
</tr>
<tr>
<td>ACCP (Kvale 2006)(25)</td>
<td>50.0</td>
</tr>
<tr>
<td>ACCP (Rivera and Mehta 2007)(26)</td>
<td>72.2</td>
</tr>
<tr>
<td>ACCP (Gould et al 2007)(24)</td>
<td>46.3</td>
</tr>
</tbody>
</table>

Abbreviations: ACCP, American College of Chest Physicians; NICE, National Institute for Health and Clinical Excellence; NZGG, New Zealand Guidelines Group; SIGN, Scottish Intercollegiate Guidelines Network.

The applicability and editorial independence were generally low and showed scores below 50% for five and four of the guidelines, respectively. Gould et al had a score of less than 50% for scope and purpose, and Kvale had scores below 50% for stakeholder involvement and rigour of development \(^{(24,25)}\). The Working Group decided the Kvale recommendations should be excluded when formulating the recommendations for Ontario because four of six of their domain scores were below 50% \(^{(25)}\). The recommendations for consideration can be found in Appendix 4.

### Outcomes

**What signs, symptoms and other clinical features are predictive of lung cancer?**

### Evidence from NICE 2005 and NZGG 2009

The systematic review conducted by NICE included three guidelines, only one of which provided a table of common signs and symptoms based on evidence from case series \(^{(2)}\). These were not described in detail. The NICE systematic review of studies performed in secondary care settings also found one systematic review by Liedekerken et al \(^{(1997)}\) that yielded little evidence to link prolonged cough with lung cancer \(^{(33)}\). Nine additional studies were included in the NICE systematic review. Data from only two of the nine studies were collected from primary care records. Based on the results of the NICE systematic review, common signs and symptoms included cough (persistent or unexplained), chest and/or shoulder pain, dyspnea, hemoptysis, and weight loss (unexplained). Other signs and symptoms included finger clubbing, dysphagia, fever, hoarseness, pneumonia, superior vena cava obstruction, weakness, wheezing and stridor, and enlarged lymph nodes. Furthermore, patients may present with signs and/or symptoms of metastases.
The NZGG updated literature search from NICE included a case-control study by Hamilton et al (2005) and a case-series study by Jones et al (2007) that were not described (34,35). Jones et al evaluated the association between hemoptysis and respiratory tract neoplasms, which included lung cancer but other respiratory tract cancers as well (35). This paper would have been excluded from our systematic review. Hamilton et al reported on a case-control study (n=247) and found loss of appetite, hemoptysis, dyspnea, loss of weight, fatigue, chest pain, second attendance with cough, and finger clubbing were independently associated with lung cancer (34).

Evidence from Newly Identified Reviews

In addition to the NICE and NZGG reports, three guidelines, developed by the ACCP, and one systematic review provided evidence to address this question (24,25,27,30). Kvale focused on the management of cough associated with lung tumours (25), and reported that a cough is found in greater than 65% of patients diagnosed with lung cancer and that dyspnea often accompanies the cough associated with lung cancer. Spiro et al conducted a systematic review and found the initial symptoms and signs of lung cancer, in order of most to least frequent, included cough, weight loss, dyspnea, chest pain, hemoptysis, bone pain, clubbing, fever, weakness, superior vena cava obstruction, dysphagia, and wheezing and stridor (27). They also provided information on the symptoms, signs, and laboratory tests that could be used in a standardized evaluation for systematic metastases, as well as a list of the paraneoplastic syndromes associated with lung cancer. They report that paraneoplastic syndromes may occur in 10% of patients with lung cancer. Gould et al performed a systematic review on the diagnosis and management of patients with pulmonary nodules (24). They did not distinguish between screen-detected nodules and nodules that were detected incidentally. In terms of follow-up of patients with pulmonary nodules, they found no evidence to suggest that extending the follow-up beyond two years would detect more malignant nodules or improve patient outcomes.

Shapley et al 2010 included studies that had a PPV of 5% or more for any sign or symptom as well as studies with PPVs less than of 5% for the same sign or symptom (30). The two articles included for lung cancer were already referenced in the NZGG guideline (34,35).

Evidence from Newly Identified Primary Studies

One prospective study and eight retrospective studies, beyond those mentioned by NICE or NZGG, of patients with lung cancer provided predictive information about the signs or symptoms for lung cancer (8-10,14,16,21,22,31,32). A prospective study by Uzun et al (2010), included consecutive patients with hemoptysis at a tertiary referral hospital (31). Thirty-two percent of patients with mild hemoptysis, 38% with moderate hemoptysis, 24% with severe hemoptysis and 13% with massive hemoptysis were diagnosed with lung cancer.

Ak et al (2007) compared symptom and sign presentation between young (<50 yrs, n=179) and older (≥50 yrs, n=1161) patients in a secondary care setting (8). Using multivariate analysis, exposure to occupational risk factors was a risk factor in the younger group, while in the older group, smoking was a risk factor. Chest pain was more common in younger patients, while cough and dyspnea were more common in older patients.

Beatty et al (2009) performed a retrospective review of 159 cases of primary lung cancer seen in an emergency department in Australia (9). Of those patients that were referred by their general practitioner (n=66), 47% presented with respiratory symptoms, 38% presented with hemoptysis, and 31% presented with no hemoptysis. Symptom duration varied from less than one week (35%, n=16) to greater than two months (33%, n=8).

Chandra et al (2009) reviewed 165 patients with lung cancer in a tertiary care setting (10). Major clinical features at the time of diagnosis of lung cancer included coughing (75.2%),
shortness of breath (66.9%), weight loss (63.7%), chest pain (63.1%), hemoptysis (33.1%), hoarseness of voice (29.3%), excessive weakness/fatigue (26.8%), clubbing (22.9%), dysphagia (9.3%), and superior vena cava syndrome (8.0%).

Koumarianou et al (2009) reviewed the medical records of patients with non-small cell lung cancer (PS 0-3) (14). Most patients had been enrolled in phase II/III studies of cytotoxic chemotherapy combinations. They compared the symptom characteristics of 417 patients aged 70 years or more (elderly), 1374 patients aged 45-70 and 115 patients aged 45 years or less (young). The most commonly reported symptoms were hemoptysis, cough, and weight loss. Elderly patients presented with more symptoms such as pain, dyspnea, cough, and fatigue compared to younger patients.

Lovgren et al (2008) reviewed 314 patients diagnosed with primary lung cancer at a university hospital (16). Five of the most commonly reported first symptoms were cough, dyspnea, weight loss, fatigue, and thoracic pain. Four of the most common symptoms triggering health care system appointments included cough, dyspnea, and thoracic pain for men and women, and as a fourth symptom, neurological symptoms for women and haemoptysis for men.

Thammakumpee et al (2007) reviewed the symptoms of patients with small-cell lung cancer in Thailand in a secondary care setting (21). The symptoms and signs, in order of frequency, included cough, weight loss, dyspnea, chest pain, hemoptysis, hoarseness, superior vena cava syndrome, neurological syndrome, syndrome of inappropriate antidiuretic hormone, Cushing’s syndrome, and massive hemoptysis.

Thomas et al (2008) reviewed the signs and symptoms of patients with pulmonary carcinoid tumours in India in a tertiary care setting (22). Only 25 patients were included in this study. Presenting symptoms or signs included hemoptysis, cough, breathlessness, chest pain, fever, and superior vena cava syndrome.

Yaman et al (2009) reviewed records of lung cancer patients at a speciality clinic (32). The percentage of first symptoms related to lung cancer grouped into five categories was 32% for cough, 21% for dyspnea, 11% for hemoptysis, 20% for chest pain and 16% for other first symptoms.

What is the diagnostic accuracy of investigations for lung cancer?

Evidence from NICE 2005 and NZGG 2009

The systematic review conducted by NICE included one systematic review with meta-analyses comparing the diagnostic accuracy of cytology, bronchoscopy, transthoracic needle aspirate, or biopsy (2). As well, three primary studies were included: two about chest radiography and one about blood work. Based on the studies reviewed, NICE concluded that a chest X-ray is the principal diagnostic investigation for lung cancer in primary care, that false-negative chest X-ray results do occur, and that sputum cytology is not a discriminatory investigation in symptomatic patients.

NZGG (2009) included complete blood count, chest X-ray, spirometry, and sputum cytology as investigations in their updated systematic review since NICE 2005 (3). In addition to NICE, they included one systematic review and two primary studies (34,36,37). Hamilton and Sharp (2004) suggested referral, despite a negative chest X-ray, should occur only if there is persistent hemoptysis and not for other symptoms, because the evidence is strongest only for persistent hemoptysis (36). For other symptoms negative for a chest X-ray, diagnoses other than lung cancer might be more likely and should be considered. They also emphasized that the experience of the doctor and the patient is an important factor in diagnostic assessment. However, in a more recent publication, they found that up to a quarter of lung cancer patients had negative chest X-rays taken in primary care for a variety of symptoms...
This suggests that physicians should not over-rely on negative chest X-rays if there is a suspicion of lung cancer.

Using multivariate analysis, Hamilton et al (2005) found that an abnormal spirometric test and thrombocytosis were associated with lung cancer, each with a PPV of 1.6% (34). Abnormal spirometric results remained significantly associated with lung cancer even after the exclusion of data in the last 180 days before diagnosis. They suggested that spirometric testing be performed in patients with dyspnea and no clear diagnosis. As well, thrombocytosis in symptomatic patients should raise a physician's suspicion of lung cancer.

Evidence from Newly Identified Reviews

Five guidelines in addition to the NICE and NZGG guidelines and that included systematic reviews provided information on the diagnostic accuracy of investigations for lung cancer (25-29). SIGN included one study that found that only 2% of 345 lung cancer patients presented with a normal chest X-ray (29). For CT scans, four studies were included, although none of them were in the primary care setting. SIGN found that CT scans have a good sensitivity (89%-100%) but low specificity (56%-63%) in differentiating malignant from benign solitary pulmonary nodules, which may be improved with serial scans. For sputum cytology, three studies showed a wide variation in sensitivity (10%-97%) in the diagnosis of lung cancer that was dependent on the techniques of sample collection. SIGN suggested sputum cytology should be reserved for cases with large central lesions where bronchoscopy or other diagnostic tests are contraindicated.

The ACCP guideline by Kvale included a systematic review and found that chest radiographs negative for lung cancer may show positive results with bronchoscopy or CT imaging (25). From their systematic review based on two primary studies, Spiro et al reported symptoms, signs, and laboratory tests that would be useful in screening patients for metastatic disease (27). Another ACCP guideline by Rivera and Mehta found a pooled sensitivity of 0.66 and pooled specificity of 0.99 based on 17 studies for sputum cytology (26). They found that sensitivity was highly variable across studies, and there was no clear explanation for this.

The guideline developed by the Australian National Health and Medical Research Council in 2004 included five articles about sputum cytology (28). They found that sensitivity increased with the number of samples obtained (50% with one sample to 90% with three or more samples) with centrally placed squamous cell carcinomas and lowest with peripheral tumours or centrally placed small cell carcinomas, and with the use of induced ultrasonic nebulised sputum or optimal processing. In an editorial (38), they reported a specificity of 97.9%

Evidence from Newly Identified Primary Studies

Only two studies were found in addition to the studies reported by NICE and NZGG (11,13). Kemp et al prospectively collected sputum samples from patients suspected of having lung cancer based on medical history or symptoms. Smears were assessed by conventional cytology (reference standard) or by using an automated technique (LungSign test) (13). LungSign showed a sensitivity of 40% and a specificity of 91%.

Choi et al retrospectively compared the diagnostic accuracy of sputum samples from a hospital using conventional preparation (CP) versus a ThinPrep method (TP) (11). The diagnosis of lung cancer was confirmed histologically. The sensitivity of TP and CP were 50.4% and 30.6%, respectively. The specificity was 99.1% with TP and 100.0% with CP.
What major, known risk factors are predictive of lung cancer?

Evidence from NICE 2005

The systematic review by NICE included four secondary studies and concluded that people with the following risk factors were at higher risk of developing lung cancer: current or previous tobacco smoking, smoking-related chronic obstructive pulmonary disease (COPD), previous exposure to asbestos, or a previous history of cancer (especially head and neck cancer) (2). Other risk factors from the NICE systematic review and listed in the NZGG guideline included occupational exposure to dust or microscopic particles (e.g., wood dust, silica); a history of COPD, silicosis, or tuberculosis; a family history of cancer; or exposure to known carcinogens (e.g., radon, chromium, nickel) (2,3).

Evidence from Newly Identified Reviews

Two guidelines that included systematic reviews provided information addressing this question (25,29). The SIGN guideline included one prospective study that found 22% of patients diagnosed with lung cancer had coexistent COPD (29). The ACCP guideline by Kvale suggested the risk factors for lung cancer included tobacco smoking; passive cigarette smoke exposure; asbestos, radon, and selected other carcinogen exposure; COPD; and a family history of lung cancer (25).

Which factors are associated with delayed referral? Which factors influence delay by patient and which delay by provider? Does a delay in the time to consultation affect patient outcome?

Evidence from NICE 2005 and NZGG 2009

The systematic review conducted by the NZGG included seven primary studies about delay (3). The authors found that patients experiencing non-specific symptoms common in the primary care setting (e.g., cough, pain) were associated with patient delay. In addition, people with multiple medical problems or multiple consecutive investigations in primary care were associated with practitioner delay.

The NICE systematic review included two primary studies and reported that delay can occur when patients fail to recognize the significance of a symptom(s) such as a prolonged cough (2). Also, presentation with non-respiratory symptoms such as shoulder pain can increase the delay in diagnosis.

Evidence from Newly Identified Reviews

There were five systematic reviews, two of which included guidelines, in our updated literature search from NZGG that investigated the factors associated with delay (12,17,19,27,29). SIGN included two primary cohort studies (29). One study found no association between delayed referral and the stage of lung cancer, and another study found shorter delays were associated with poorer prognosis.

In addition to the factors affecting delay mentioned in the NZGG and NICE guidelines, Spiro et al suggested primary care physicians may fail to recognize the signs or symptoms of lung cancer in their patients (27). This may be due to the infrequent experience of seeing lung cancer patients in practice, as well as attributing the often common and non-specific symptoms to benign diseases.

Olsson et al (2009) performed a systematic review of timeliness of care for lung cancer patients (n=53 studies) (17). The median time from primary care referral to specialist ranged from 13 to 33 days across four studies. Factors associated with less timely care included
atypical symptoms, co-morbid conditions, requirement for multiple diagnostic tests, and initial referral to a non-respiratory physician.

The Singh et al (2007) systematic review of diagnostic errors in cancer found that the factors associated with increased patient-mediated delay included the refusal of closer examination and patient beliefs about their health changes (19). Practitioner-mediated factors that increased delay included not recognizing symptoms, an insufficient or ineffective work-up (e.g., performing numerous other procedures before biopsy), over-reliance on chest X-rays to diagnose lung cancer, and imaging (X-ray and CT scan) follow-up failure.

Hanna et al (2005) performed a systematic review of all cancers, assessing the two-week referral rule developed in the United Kingdom (12). They included two audits for lung cancer and found a high rate of adherence to the two-week referral guideline. They suggested that this may be attributed to the ability of referring clinicians to make a diagnosis on the basis of an abnormal chest radiograph.

Evidence from Newly Identified Primary Studies

Since the literature review conducted by the NZGG, only one prospective study was included (15). Lo et al (2007) implemented a Time to Treat Program in Ontario, Canada to reduce wait times (15). They developed a referral form to be completed by referring physicians and used a clerical facilitator to fast-track patients through a diagnostic pathway algorithm. The median wait time from suspicion of lung cancer to referral for specialist consultation decreased from 20 days to 6 days.

Our updated literature search since the NZGG guideline includes six retrospective studies that examined factors influencing delay (10,16,18,20,23,32). Chandra et al (2009) retrospectively reviewed patients with lung cancer in a tertiary care setting (10). They found that delay between the onset of symptoms to a confirmed diagnosis had no correlation with the presence of cough, shortness of breath, chest pain, hemoptysis, or hoarseness of voice. Delay in diagnosis was significantly higher in patients who had received antitubercular treatment initially (mean difference, 65.5 days; 95% confidence interval [CI] of difference, 24.5 to 106.6, p=0.002).

Lovgren et al (2008) reviewed 314 patients diagnosed with primary lung cancer at a university hospital (16). The presence of a lump and or resistance recorded in the medical records shortened the delay from first symptom reported to first visit at a health care system. Hemoptysis and appetite loss decreased the delay from first visit at a health care system to referral to a specialist.

Rolke et al (2007) prospectively recruited patients with primary lung cancer in Norway and retrospectively asked patients about symptom and referral history (18). Having an X-ray or CT scan of the chest prior to specialist referral did not affect delay from the general practitioner to the final diagnosis. Multivariate logistic analysis showed that the diagnosis of advanced tumour stage (odds ratio [OR], 0.49; 95% CI, 0.27 to 0.90) or poor performance status (OR, 0.48; 95% CI, 0.28 to 0.80) reduced referral delay.

Smith et al (2009) recruited consecutive patients with lung cancer and retrospectively asked about initial symptoms (20). Multiple linear regression analysis revealed independent factors associated with increased time before consulting such as living alone, a history of COPD, and longer pack-years of smoking. Hemoptysis, new onset of shortness of breath, cough, loss of appetite, history of chest infection, and renal failure were associated with earlier consulting.

Yaman et al (2009) reviewed lung cancer patients at a secondary care setting and found there was no relationship between age, gender, TNM classification, ECOG performance status, presence of endobronchial lesions, radiological localization of the lesion, family history of lung cancer and the intervals from first symptoms to admission or diagnosis (32).
Also, there was no significant relationship between symptom type and the interval to admission to a specialist.

Yilmaz et al (2008) retrospectively collected delay history from all patients with primary lung cancer (23). The time from the onset of symptoms to the first visit to a physician or from first visit to physician to admission to hospital did not correlate with pathologic tumour stage.

**DISCUSSION**

Due to the paucity of evidence for lung cancer in the primary care setting, definitive conclusions could not be derived for the diagnostic accuracy of signs, symptoms, diagnostic tests, or risk factors associated with lung cancer. The Working Group agreed with the signs and symptoms of lung cancer listed in the NICE and NZGG guidelines, which are superior vena cava obstruction, stridor, hemoptysis, finger clubbing, enlarged lymph nodes, cough (persistent or unexplained), weight loss (unexplained), dyspnea, chest and/or shoulder pain, hoarseness, and an abnormal chest X-ray (2,3). Furthermore, patients might present with metastases. In addition, the Working Group chose to include dysphagia as a symptom of lung cancer because it was reported as a symptom for lung cancer in the NICE review and was found to be a major clinical symptom among lung cancer patients in a tertiary care setting (2,10). Furthermore, paraneoplastic syndromes were included by the Working Group, based on the review by Spiro et al that reported that paraneoplastic syndromes may occur in 10% of patients with lung cancer (27). Our literature review did not provide evidence for additional risk factors associated with lung cancer beyond those listed in the NICE or NZGG guidelines (2,3). In addition, no evidence was found to challenge the list of risk factors by suggesting that any item should be removed. Therefore, the Working Group agreed that the risk factors for lung cancer include current or previous smoking, COPD, previous exposure to asbestos, and a history of cancer (especially head and neck cancer). Other risk factors may include occupational exposure to dust or microscopic particles (e.g., wood dust, silica); past medical history of COPD, silicosis or tuberculosis; family history of cancer; exposure to known carcinogens (e.g., radon, chromium, nickel); and passive exposure to tobacco smoke.

The NICE and NZGG guidelines recommend ordering chest X-rays but urge physicians to refer if a chest X-ray is negative but there is still a high suspicion of lung cancer (2,3). This is because false negatives can occur with chest X-rays. In the updated search, two systematic reviews also report the high likelihood of false-negative results with chest X-rays (25,29).

NICE and NZGG do not report studies on the diagnostic accuracy of CT scans (2,3). As well, in the updated search there were few studies assessing the diagnostic accuracy of CT scans; therefore, no conclusions could be drawn (29).

NICE and NZGG do not recommend sputum cytology (2,3). The evidence from our updated systematic review suggests that, although the specificity is high, the sensitivity is highly variable (11,13,26,28,29).

Based on the interpretation of the evidence for diagnostic tests, the opinion of the Working Group is that chest X-rays should be ordered as a preliminary investigation for signs or symptoms of lung cancer. However, if a physician has a suspicion of lung cancer with a negative chest X-ray, a referral should be made. In addition, because sputum cytology shows variable sensitivity, the Working Group does not recommend sputum cytology as a primary investigation test for lung cancer.

The patient-related or family physician-related factors that may delay referral or the diagnosis of lung cancer found in the updated literature search since NZGG 2009 included a fear of a diagnosis of cancer, not recognizing the signs and symptoms suggestive of lung cancer, over-reliance on chest X-ray results to diagnose lung cancer, imaging follow-up failure, or initial referral to a non-respiratory physician (17,19,27).
Section 3 describes the adaptation of the identified guidelines and the development of recommendations from the evidence identified above.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the Lung Cancer Referral Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. Suzie Joanisse received a grant from CCO to develop a program to increase breast, colorectal, and cervical screening in Aboriginal communities. Ranjan Sur owns a business by the name of R and M Sur Medicine Professional Corporation and received a research and development grant of $250,000 to develop the BrachyVision™ planning system for lung cancer brachytherapy. All other authors declared no conflicts of interest.

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Contact Information

For further information about this report, please contact:

Dr. Lisa Del Giudice, Family Physician
Sunnybrook Family Practice Unit, Room A112
2075 Bayview Ave, Toronto, M4N 3M5
Phone: 416-480-4939 Fax: 416-480-6038 Email: Lisa.DelGiudice@sunnybrook.ca

For information about the PEB and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEB office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

EVIDENTIARY BASE - page 15
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<table>
<thead>
<tr>
<th>Lung Cancer Referral Working Group</th>
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<tbody>
<tr>
<td><strong>Co-Chair:</strong></td>
<td><strong>Co-Chair:</strong></td>
</tr>
<tr>
<td>Sheila-Mae Young MD CCFP FCFP</td>
<td>Lisa Del Giudice MD CCFP FCFP</td>
</tr>
<tr>
<td>Regional Primary Care Lead,</td>
<td>Primary Care Practitioner</td>
</tr>
<tr>
<td>Cancer Care Ontario, Central East, ON</td>
<td>Sunnybrook Family Practice Unit, Toronto, ON</td>
</tr>
<tr>
<td>Cheryl Levitt MBBCh CCFP FCFP</td>
<td>Marla Ash MD CCFP FCFP</td>
</tr>
<tr>
<td>Provincial Primary Care Lead</td>
<td>Regional Primary Care Lead,</td>
</tr>
<tr>
<td>Cancer Care Ontario, Toronto, ON</td>
<td>Cancer Care Ontario, Central, ON</td>
</tr>
<tr>
<td>Praveen Bansal MD CCFP FCFP</td>
<td>Andrew Robinson MD</td>
</tr>
<tr>
<td>Regional Primary Care Lead,</td>
<td>Medical Oncologist</td>
</tr>
<tr>
<td>Cancer Care Ontario, Central West and Mississauga Halton, ON</td>
<td>Sudbury Regional Hospital, Sudbury, ON</td>
</tr>
<tr>
<td>Roland Skrastins MD</td>
<td>Yee Ung MD</td>
</tr>
<tr>
<td>Respiriologist</td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td>Toronto East General Hospital, Toronto, ON</td>
<td>Odette Cancer Centre, Toronto, ON</td>
</tr>
<tr>
<td>Robert Zeldin MD</td>
<td>Emily Vella PhD</td>
</tr>
<tr>
<td>Thoracic Surgeon</td>
<td>Research Coordinator</td>
</tr>
<tr>
<td>Toronto East General Hospital, Toronto, ON</td>
<td>Program in Evidence-based Care, Cancer Care Ontario, Hamilton, ON</td>
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<thead>
<tr>
<th>Lung Cancer Referral Expert Panel</th>
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<tbody>
<tr>
<td>Koop Alkema</td>
<td>Hugh Langley</td>
</tr>
<tr>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
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<tr>
<td>Rob Annis</td>
<td>Millie Litt</td>
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<tr>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
</tr>
<tr>
<td>Carole Beals</td>
<td>Doina Lupea</td>
</tr>
<tr>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
<td>Program Manager Primary Care Cancer Care Ontario</td>
</tr>
<tr>
<td>Andrea Bezik (conflict of interest not received)</td>
<td>Richard Malthaner</td>
</tr>
<tr>
<td>Lung Disease Site Group, CCO</td>
<td>Lung Disease Site Group, CCO</td>
</tr>
<tr>
<td>Princess Margaret Hospital, Toronto, ON</td>
<td>London Health Sciences Centre</td>
</tr>
<tr>
<td>Sandy Buchman</td>
<td>Donna Mazik</td>
</tr>
<tr>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
<td>Lung Disease Site Group, CCO Program Director, Thoracic Surgery Ottawa Hospital, ON</td>
</tr>
<tr>
<td>Lynn Chappell</td>
<td>Laura McDonald</td>
</tr>
<tr>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
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<tr>
<td>John Day</td>
<td>Heather McLean</td>
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<tr>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
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<tr>
<td>Lee Donohue</td>
<td>Alison McMullen</td>
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<tr>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
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<tr>
<td>Bill Evans</td>
<td>Michael Mills</td>
</tr>
<tr>
<td>Lung Disease Site Group, CCO</td>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
</tr>
<tr>
<td>Juravinski Cancer Centre, Hamilton, ON</td>
<td>Regional Primary Care Lead, ON</td>
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<tr>
<td>Conrad Falkson</td>
<td>Kim Mundy</td>
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<table>
<thead>
<tr>
<th>Name</th>
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<th>Institution</th>
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<tbody>
<tr>
<td>Lung Disease Site Group, CCO</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
<td></td>
</tr>
<tr>
<td>Cancer Centre of Southeastern Ontario, Kingston General Hospital</td>
<td></td>
<td>EVIDENTIARY BASE - page 20</td>
</tr>
<tr>
<td>Mark Gaskin</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
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<tr>
<td>Danusia Gzik</td>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
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<tr>
<td>Julia Niblett</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
<td></td>
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<tr>
<td>Amanda Hey</td>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
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<tr>
<td>Danusia Gzik</td>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
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<tr>
<td>Rosanne Pegler</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
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<tr>
<td>Suzie Joanisse</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
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<tr>
<td>Janice Owen</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
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<tr>
<td>Sara Kaune</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
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<tr>
<td>Carol Rand</td>
<td>Provincial Primary Care and Cancer Network Regional Administrative Lead, ON</td>
<td></td>
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<tr>
<td>Jaro Kotalik</td>
<td>Provincial Primary Care and Cancer Network Regional Primary Care Lead, ON</td>
<td></td>
</tr>
<tr>
<td>Julian Dobranowski</td>
<td>Professor, Departments of Oncology and Medicine</td>
<td>McMaster University, Hamilton, ON</td>
</tr>
<tr>
<td>Lung Disease Site Group, CCO</td>
<td></td>
<td>EVIDENTIARY BASE - page 20</td>
</tr>
<tr>
<td>Associate Clinical Professor of Diagnostic Imaging</td>
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</tr>
<tr>
<td>McMaster University, Faculty of Health Sciences</td>
<td></td>
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<tr>
<td>Anthony D'Urzo</td>
<td></td>
<td>EVIDENTIARY BASE - page 20</td>
</tr>
<tr>
<td>Associate Professor, Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, ON</td>
<td></td>
<td>EVIDENTIARY BASE - page 20</td>
</tr>
<tr>
<td>Associate Professor, Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, ON</td>
<td></td>
<td>EVIDENTIARY BASE - page 20</td>
</tr>
<tr>
<td>Jeff Sisler</td>
<td>Director, Primary Care Oncology Program, CancerCare Manitoba</td>
<td>EVIDENTIARY BASE - page 20</td>
</tr>
<tr>
<td>Associate Professor, Departments of Family Medicine and Internal Medicine, University of Manitoba</td>
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Appendix 2. List of sites searched for the environmental scan.

CMA Infobase
The Physicians Query Database (National Cancer Institute)
National Guideline Clearing House
NICE (UK) - NICE Guidance
SIGN (UK) - SIGN Guidelines
ASCO (US) - ASCO Guidelines
NCCN (US) - NCCN home (consensus-based)
National Health and Medical Research Council (Aus) - Cancer Guidelines
New Zealand Guidelines Group - Guidelines

Canadian provincial cancer agencies:
BC Cancer Agency - Cancer management guidelines
Alberta Cancer Board - Treatment Guidelines
Saskatchewan Cancer Agency - Follow-up Guidelines
Cancer Care Manitoba - CCM Home
Cancer Care Nova Scotia - Guidelines

National cancer agencies:
NZ Cancer Control Trust
The Cancer Council Australia
National Cancer Control Initiative (AUS)
NHS (UK)

Organizations:
American College of Chest Physicians
Ontario Lung Association
American Thoracic Society - American Journal of Respiratory and Critical Care Medicine
Canadian Cancer Society
Appendix 3. Literature search strategies.

MEDLINE signs/symptoms
Database: Ovid MEDLINE(R) <1996 to February Week 3 2010> Search Strategy:

1  exp "Sensitivity and Specificity"/ (257178)
2  false negative reactions/ or false positive reactions/ (13346)
3  (sensitivity or specificity or accuracy).ab,ti. (474608)
4  diagnosis.ab,ti. (675617)
5  predictive value$.ab,ti. (33435)
6  reference value$.ab,ti. (5372)
7  ROC.ab,ti. (9736)
8  (likelihood adj ratio$1).ab,ti. (4454)
9  monitoring.tw. (135450)
10  (false adj (negative$1 or positive$1)).ab,ti. (24320)
11  (randomized controlled trial or controlled clinical trial).pt. (219134)
12  double-blind method/ or single-blind method/ (69713)
13  practice guideline.pt. (11637)
14  consensus development conference$.pt. (5176)
15  review.pt. (969050)
16  review.ab. (341939)
17  (meta-analysis or metaanalysis).ab. (16867)
18  meta-analysis.pt. (20815)
19  meta-analysis.ti. (10338)
20  (cohort adj study$).ab,ti. (38966)
21  exp cohort studies/ (483039)
22  (single blind$3 or double blind$3 or triple blind$3).ab,ti. (55099)
23  or/1-22 (2632308)
24  letter.pt. (365247)
25  comment.pt. (309637)
26  editorial.pt. (170311)
27  or/24-26 (593853)
28  23 not 27 (2562958)
29  exp Respiratory Tract Neoplasms/ (78859)
30  Adenocarcinoma, Bronchiolo-Alveolar/ (795)
31  ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis$)).tw. (55903)
32  or/29-31 (91728)
33  Cough/ (4973)
34  cough$.tw. (15116)
35  Dyspnea/ (6701)
36  dyspnea.tw. (14924)
37  short$. of breath.tw. (2272)
38  breathless$.tw. (1496)
39  Hemoptysis/ (1683)
40  (hemoptysis or haemoptysis).tw. (3018)
41  (blood$ adj2 (sputum or spit or spittle or phlegm$)).ab,ti. (728)
42  Hoarseness/ (682)
43  hoarse$.tw. (1769)
44  chest pain/ or shoulder pain/ (6935)
45  ((chest or shoulder) adj3 pain$).tw. (13387)
46  Respiratory Sounds/ (3464)
47  wheeze$.tw. (4956)
exp body weight changes/ (26256)
(weight adj1 (loss or gain or chang$)).tw. (41740)
Flushing/ (454)
((face or facial) adj flushing).tw. (212)
Diarrhea/ (12803)
(diarrhea or diarrhoea).tw. (28506)
(Bronchitis/ or exp Pneumonia/) and Recurrence/ (531)
((bronchitis or pneumonia) adj recur$).tw. (34)
"signs and symptoms"/ (37)
or/33-56 (137375)
28 and 32 and 57 (3064)
limit 58 to (english language and humans) (2171)
(200708: or 200709: or 20071: or 2008: or 2009: or 2010:).ed. (1755524)
59 and 60 (541)

EMBASE signs/symptoms
Database: EMBASE <1996 to 2010 Week 07>
Search Strategy:
--------------------------------------------------------------------------------
1 "sensitivity and specificity"/ (61132)
2 false negative result/ or false positive result/ (5935)
3 (sensitivity or specificity or accura$).ab,ti. (447155)
4 diagnos$ .ab,ti. (659380)
5 predictive value$.ab,ti. (32781)
6 reference value$.ab,ti. (5298)
7 ROC.ab,ti. (9233)
8 (likelihood adj ratio$1).ab,ti. (4206)
9 monitoring.tw. (132831)
10 (false adj (negative$1 or positive$1)).ab,ti. (23173)
11 double blind procedure/ or single blind procedure/ or triple blind procedure/ (64369)
12 exp controlled clinical trial/ (165121)
13 double blind procedure/ or single blind procedure/ or triple blind procedure/ (64369)
14 exp practice guideline/ (157434)
15 review.pt. (778874)
16 review.ab. (333674)
17 (meta-analysis or metaanalysis).ab. (16147)
18 Meta Analysis/ (33871)
19 meta-analysis.ti. (10280)
20 (cohort adj stud$).ab,ti. (37996)
21 cohort analysis/ (57607)
22 (single blind$3 or double blind$3 or triple blind$3).ab,ti. (56827)
23 or/1-22 (2157039)
24 letter.pt. (332953)
25 editorial.pt. (198989)
26 or/24-25 (531942)
27 23 not 26 (2107753)
28 exp Respiratory Tract Cancer/ (85473)
29 exp Respiratory Tract Tumor/ (101057)
30 ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw. (56184)
31 or/28-30 (108291)
32 coughing/ or irritative coughing/ (23756)
33 cough$.tw. (15124)
Dyspnea/ (33899)
dyspn$.tw. (14828)
short$ of breath.tw. (2271)
breathless$.tw. (1504)
Hemoptysis/ (5035)
(hemoptysis or haemoptysis).tw. (3053)
(blood$ adj2 (sputum or spit or spittle or phlegm)).ab,ti. (641)
Hoarseness/ (3141)
hoarse$.tw. (1854)
exp Pain/ and (chest or shoulder$).tw. (15220)
((chest or shoulder) adj3 pain$).tw. (13510)
Wheezing/ (6922)
weight change/ or weight gain/ or weight reduction/ (62763)
(weight adj1 (loss or gain or chang$)).tw. (39434)
Flushing/ and (face or facial).tw. (297)
((face or facial) adj flushing).tw. (211)
Diarrhea/ (64316)
(diarhoea or diarrhoea).tw. (26749)
(bronchitis/ or exp Pneumonia/) and Recurrent Disease/ (1108)
(bronchitis or pneumonia) adj recur$.tw. (33)
clinical feature/ or symptom/ (394982)
or/32-54 (578271)
and/27,31,55 (10014)
limit 56 to (human and english language) (8244)
(2007: or 2008: or 2009: or 2010:).ew. (1960406)
57 and 58 (3315)

MEDLINE tests
Database: Ovid MEDLINE(R) <1996 to February Week 3 2010> Search Strategy:
1 Primary health care/ (26352)
2 Family physician/ (7730)
3 ((family or general) adj practitioner$).mp. (17461)
4 gp.mp. (14578)
5 family physician$.mp. (5085)
6 family doctor$.mp. (1844)
7 Family practice/ (28175)
8 ((family or general) adj practice$).mp. (36399)
9 primary care.mp. (35644)
10 primary health care.mp. (29333)
11 or/1-10 (98625)
12 meta-analysis/ (20815)
13 "review literature"/ (969050)
14 meta-analy$.mp. (36194)
15 metaanal$.mp. (972)
16 (systematic$ adj (review$ or overview$)).mp. (20607)
17 meta-analysis.pt. (20815)
18 review.pt. (969050)
19 review.ti. (89020)
20 or/12-19 (1012339)
21 "case reports [publication type]"/ (0)
22 letter.pt. (365247)
23 historical article.pt. (93482)
24 comment.pt. (309637)
25 editorial.pt. (170311)
(ROC adj (analys$ or area or auc or characteristic$ or curve$)).tw. (8197)
family doctor$.mp. (1461)
general practice/ (17822)
((family or general) adj practice$).mp. (23858)
primary care.mp. (32364)
primary health care.mp. (10931)
or/1-11 (108582)
Meta Analysis/ (33871)
"systematic review"/ (30835)
(meta-analy$ or metaanaly$).mp. (45121)
(systematic adj (review$ or overview$)).mp. (39408)
review.pt. (778874)
review.ti. (86948)
or/13-18 (848084)
letter.pt. (332953)
editorial.pt. (198989)
or/20-21 (531942)
19 not 22 (841566)
"sensitivity and specificity"/ (61132)
sensitivity.tw. (216861)
specificity.tw. (133140)
exp "prediction and forecasting"/ (289820)
predictive value$.tw. (32781)
predictive value$ of test$.tw. (74)
roc curve/ (2417)
(ROC adj (analy$ or area or auc or characteristic$ or curve$)).tw. (7784)
exp diagnostic error/ (23207)
(false adj (positive or negative)).tw. (19932)
diagnostic accuracy/ (118607)
accuracy.tw. (90057)
reference value/ (11181)
reference value$.tw. (5298)
likelihood ratio$.tw. (4223)
((pre-test or pretest) adj probability).tw. (718)
post-test probability.tw. (182)
differential diagnosis/ (88178)
or/24-41 (801318)
exp thorax radiography/ (49040)
(chest adj X-ray$).mp. (7096)
cxr.mp. (592)
sputum cytodiagnosis/ (726)
(sputum adj cytolog$).mp. (312)
(cytolog$ adj sputum).mp. (38)
spirometry/ (8754)
spirometry.mp. (9472)
exp computer assisted tomography/ (238414)
(ct adj scan$).mp. (27280)
exp blood cell count/ (65723)
(CBC or FBC).mp. (998)
thrombocytosis.mp. or THROMBOCYTOSIS/ (2185)
c-reactive protein.mp. or C Reactive Protein/ (33758)
erthrocyte sedimentation rate/ (9503)
erthrocyte sedimentation rate.mp. (10136)
or/43-58 (371380)
exp Respiratory Tract Tumor/ (101057)
42 and 59 and 60 (6257)
MEDLINE risk factors
Database: Ovid MEDLINE(R) <1996 to February Week 3 2010> Search Strategy:
------------------------------------------------------------------------
1 meta-Analysis as topic/ (7854)
2 meta analysis.pt. (20815)
3 (meta analy$ or metaanaly$).tw. (24735)
4 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summa$ or mathematical summa$ or quantitative synthes$ or quantitative overview).tw. (21090)
5 (systematic adj (review$ or overview$)).tw. (19541)
6 (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw. (25295)
7 or/1-6 (58753)
8 (cochrane or embase or psychlit or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab. (19163)
9 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab. (12995)
10 (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab. (18337)
11 (study adj selection).ab. (4140)
12 10 or 11 (19500)
13 review.pt. (969050)
14 12 and 13 (12893)
15 7 or 8 or 9 or 14 (73671)
16 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (772629)
17 15 not 16 (69887)
18 limit 17 to (english language and humans) (60155)
19 exp Respiratory Tract Neoplasms/ (78859)
20 Adenocarcinoma, Bronchiolo-Alveolar/ (795)
21 (((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis$)).tw. (55903)
22 exp Lung Neoplasms/ (62936)
23 exp Bronchial Neoplasms/ (19941)
24 exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/ (23676)
25 exp Carcinoma, Non-Small-Cell Lung/ or exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/ (23676)
26 or/19-25 (92832)
27 18 and 26 (1098)
28 (200406: or 200407: or 200408: or 200409: or 20041: or 2005: or 2006: or 2007: or 2008: or 2009: or 2010:).ed. (3719911)
29 27 and 28 (675)

EMBASE risk factors
Database: EMBASE <1996 to 2010 Week 08>
Search Strategy:
------------------------------------------------------------------------
1 exp Meta Analysis/ or exp "Systematic Review"/ (49212)
2 (meta analy$ or metaanaly$).tw. (24549)
(systematic review$ or pooled analy$ or statistical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview).tw. (20607)

exp "Review"/ or review.pt. (782579)

(systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab. (68816)

(study adj selection).ab. (5220)

5 and (6 or 7) (23763)

or/1-4,8 (77888)

(cochrane or embase or psychlit or psyclit or psychinfo or psyctinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab. (14532)

11 (reference list$ or bibliograph$ or hand-search$. or relevant journals or manual search$).ab. (10146)

9 or 10 or 11 (85530)

(editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/ (912302)

12 not 13 (77569)

limit 14 to (human and english language) (62319)

exp Respiratory Tract Cancer/ (85763)

exp Respiratory Tract Tumor/ (101409)

((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw. (56365)

exp lung tumor/ (82442)

exp bronchus tumor/ (1962)

exp lung carcinoma/ (40823)

exp lung non small cell cancer/ (22789)

exp small cell carcinoma/ (1628)

or/16-23 (109737)

15 and 24 (1966)


27 25 and 26 (1412)

MEDLINE delay
Database: Ovid MEDLINE(R) <1996 to February Week 3 2010> Search Strategy:

(lung adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$)).mp. (72095)

exp respiratory tract neoplasms/ (78859)

1 or 2 (89545)

(delay$ adj3 practitioner$).mp. (32)

(delay$ adj3 diagnos$).mp. (7680)

diagnos$. delay$.mp. (851)

diagnos$. early.mp. (1283)

early diagnosis/. (5519)

early$ detection.mp. (17519)

early$ presentation.mp. (370)

early$ symptom$.mp. (1070)

exp health behavior/ (48048)

exp attitude to health/ (156459)

(delay$ adj3 patient$).mp. (5360)

or/4-15 (221476)

"referral and consultation"/ (22446)

referral$.mp. (48091)
EMBASE delay
Database: EMBASE <1996 to 2010 Week 07>
Search Strategy:

1. exp Lung Cancer/di [Diagnosis] (16047)
2. exp lung cancer/ (78320)
3. (lung adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$)).tw. (49515)
4. or/1-3 (85222)
5. Cancer diagnosis/ (43817)
6. early diagnosis/ (34719)
7. earl$ diagnosis.tw. (21124)
8. diagnos$ earl$.tw. (1569)
9. Delayed Diagnosis/ (1531)
10. (delay$ adj3 diagnos$).tw. (7691)
11. diagnos$ delay$.tw. (861)
12. (delay$ adj3 practitioner$).tw. (22)
13. exp Patient attitude/ (100071)
14. Attitude to health/ or Attitude to illness/ (4401)
15. earl$ detection.tw. (16186)
16. detect$ earl$.tw. (3013)
17. earl$ presentation.tw. (359)
18. earl$ symptom$.tw. (1060)
19. or/5-18 (207084)
20. patient referral/ (26907)
21. referral$.tw. (30325)
22. earl$ referral$.tw. (697)
23. late$ referral$.tw. (260)
24. or/20-23 (46360)
25. Time factors/ (53844)
26. exp disease course/ (796755)
27. clinical practice/ (86307)
28. or/20-27 (953739)
29. 4 and 19 and 28 (3330)
30. limit 29 to (human and english language) (2810)
32. 30 and 31 (1138)
Appendix 4. Recommendations to adapt from existing guidelines.

Appendix 4 Table 1. Recommendations from existing guidelines.

<table>
<thead>
<tr>
<th>NZGG 2009¹</th>
<th>NICE 2005²</th>
<th>SIGN 2005³</th>
<th>Australian 2004⁴</th>
<th>ACCP 2007⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Recommendations</strong></td>
<td>A patient who presents with symptoms suggestive of lung cancer should be referred to a team specialising in the management of lung cancer, depending on local arrangements. (D)</td>
<td></td>
<td>All individuals with suspected lung cancer should be referred to a specialist with expertise in the management of lung disease for an opinion. (IV)</td>
<td></td>
</tr>
<tr>
<td><strong>When to Order a Chest X-ray</strong></td>
<td>An urgent referral for a chest X-ray should be made when a patient presents with (D): • haemoptysis, or • any of the following unexplained persistent (that is, lasting more than 3 weeks) symptoms and signs: - chest and/or shoulder pain - dyspnea - weight loss - chest signs - hoarseness - finger clubbing - cervical and/or supraclavicular lymphadenopathy - cough with or without any of the above - features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin).</td>
<td>Patients should be referred urgently for a chest X-ray if they have experienced unexplained or persistent haemoptysis. (D) Patients should be referred for a chest X-ray if any of the following symptoms persist for more than three weeks without an obvious cause (D): • cough • chest/shoulder pain • dyspnea • weight loss • chest signs • hoarseness • finger clubbing • Features suggestive of metastases from lung cancer (e.g., brain, bone, liver or skin) • Persistent cervical/supraclavicular lymphadenopathy A chest X-ray should be</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EVIDENTIARY BASE - page 30
<table>
<thead>
<tr>
<th>NZGG 2009(^1)</th>
<th>NICE 2005(^2)</th>
<th>SIGN 2005(^3)</th>
<th>Australian 2004(^4)</th>
<th>ACCP 2007(^5)</th>
</tr>
</thead>
</table>
| metastasis from a lung cancer (e.g., in brain, bone, liver or skin)  
\(^1\)Current or ex-smokers, smoking-related chronic obstructive pulmonary disease, previous exposure to asbestos, history of cancer (especially head and neck cancer) | A report should be made back to the referring primary healthcare professional within 5 days of referral. Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems should prompt an urgent referral for chest X-ray. (D) In individuals with a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms, lung cancer should be considered and a chest X-ray arranged. If this indicates a pleural effusion, pleural mass or any suspicious lung pathology, an urgent referral should be made. (C) | performed on all patients being investigated for the possibility of lung cancer (D). | | |

When to Order CT Scans

- Contrast enhanced CT scanning of the chest and abdomen is recommended in all patients with suspected lung cancer, regardless of chest X-ray results. (D)
- A tissue diagnosis should not be inferred from CT appearances alone. (D)
- CT scanning should be performed prior to further
<table>
<thead>
<tr>
<th>NZGG 2009&lt;sup&gt;1&lt;/sup&gt;</th>
<th>NICE 2005&lt;sup&gt;2&lt;/sup&gt;</th>
<th>SIGN 2005&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Australian 2004&lt;sup&gt;4&lt;/sup&gt;</th>
<th>ACCP 2007&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>diagnostic investigations, including bronchoscopy, and the results used to guide the investigation that is most likely to provide both a diagnosis and stage the disease to the highest level. (D)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**When to Order Sputum Cytology**

| Sputum cytology is not recommended for the investigation of lung cancer (√) | Sputum cytology should only be used in patients with large central lesions, where bronchoscopy or other diagnostic tests are deemed unsafe. (D) | Sputum cytology is recommended to help establish a positive diagnosis of lung cancer in individuals with a central pulmonary mass. (III) | In patients suspected of having lung cancer, who present with a central lesion with or without radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or transthoracic needle aspiration might pose a higher risk, sputum cytology is recommended as an acceptable method of establishing the diagnosis. However, the sensitivity of sputum cytology varies by the location of the lung cancer. It is recommended that further testing be performed with a nondiagnostic sputum cytology test if the suspicion of lung cancer remains. (1C) (Rivera and Mehta 2007) |

**What to Do After Receiving Results of X-ray**

<p>| A person should be referred urgently to a specialist if they have a normal chest X-ray, but there is a high suspicion of lung cancer (C) | If the chest X-ray is normal, but there is a high suspicion of lung cancer, patients should be offered an urgent referral. (D) | Even with a normal chest X-ray, patients who have experienced unexplained, non-specific symptoms, e.g., fatigue potentially attributable to lung cancer, | In every patient with an SPN, we recommend that clinicians estimate the pretest probability of malignancy either qualitatively by using their clinical judgment or |</p>
<table>
<thead>
<tr>
<th>NZGG 2009¹</th>
<th>NICE 2005²</th>
<th>SIGN 2005³</th>
<th>Australian 2004⁴</th>
<th>ACCP 2007⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>A person with risk factors* for lung cancer who has consolidation on an initial chest X-ray should have a repeat chest X-ray within 6 weeks to confirm resolution (✓) *Current or ex-smokers, smoking-related chronic obstructive pulmonary disease, previous exposure to asbestos, history of cancer (especially head and neck cancer)</td>
<td>for more than six weeks should be referred urgently to a respiratory physician. (D) Quantitatively by using a validated model. (1C) (Gould et al 2007) In a patient with an SPN that is stable on imaging tests for at least 2 years, we suggest that no additional diagnostic evaluation be performed, except for patients with pure ground-glass opacities on CT, for whom a longer duration of annual follow-up should be considered. (2C) (Gould et al 2007)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patients with Risk Factors**

Patients in the following categories have a higher risk of developing lung cancer (C):
- are current or ex-smokers
- have smoking-related chronic obstructive pulmonary disease (COPD)
- have been exposed to asbestos
- have a previous history of cancer (especially head and neck).

An urgent referral for a chest X-ray or to a team specialising in the management of lung cancer should be made as for other patients but may be considered sooner, for

A chest X-ray should be performed in patients with COPD who develop new symptoms (especially weight loss) that might be attributable to lung cancer. (✓)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>example if symptoms or signs have lasted for less than 3 weeks.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**When to Urgently/Immediately Refer**

A person should be referred urgently to a specialist if they have (C):  
- persistent haemoptysis and are smokers or ex-smokers aged 40 years or older  
- a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)

An urgent referral should be made for any of the following (D):  
- persistent haemoptysis in smokers or ex-smokers who are aged 40 years and older  
- a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation).

Immediate referral should be considered for the following (C):  
- signs of superior vena caval obstruction  
  - (swelling of the face and/or neck with fixed elevation of jugular venous pressure)  
  - stridor

Patients should be referred urgently to a chest physician if they have any of the following (D):  
- Persistent hemoptysis in smokers or ex-smokers over 40 years of age  
- A chest X-ray suggestive or suspicious of lung cancer (including pleural effusion and slowly resolving consolidation)

Signs of superior vena caval obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)  
- Stridor (emergency referral)

**Referral Process**

The smoking status of all patients should be recorded and regularly updated in the practice notes (√)

Patients should be offered tailored, clear and accurate information, including an indication of the expected time scale of the referral process (√). Verbal and written communication between
<table>
<thead>
<tr>
<th>NZGG 2009¹</th>
<th>NICE 2005²</th>
<th>SIGN 2005³</th>
<th>Australian 2004⁴</th>
<th>ACCP 2007⁵</th>
</tr>
</thead>
</table>
|健康新聞 Professionals should include information regarding what the patient has been told about their diagnosis, investigation, treatment and prognosis (✓). Clinicians should consider using different approaches for conveying information depending upon patients’ preferences (✓) e.g.:  
• Verbal (from different healthcare professionals)  
• Written (high quality information sheets and leaflets)  
• Details of appropriate websites  
• Recorded audio tapes of the consultation and discussion. |

<table>
<thead>
<tr>
<th>Timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>After urgent referral for chest X-ray, the chest X-ray should be completed and reported within one week (✓)</td>
</tr>
<tr>
<td>Patients referred to a respiratory physician should be seen promptly, ideally within two weeks (✓)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACCP, American College of Chest Physicians; NICE, National Institute for Health and Clinical Excellence; NZGG, New Zealand Guidelines Group; SIGN, Scottish Intercollegiate Guidelines Network.

¹ See Table 2 (below) for Grading explanations
² See Table 3 (below) for Grading and Evidence explanations
³ See Table 4 (below) for Grading and Evidence explanations
⁴ See Table 5 (below) for Evidence explanations
⁵ See Table 6 (below) for Grading of the Evidence and Recommendations
Appendix 4 Table 2. Grading of NZGG 2009 recommendations.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>The recommendation is supported by good evidence (based on a number of studies that are valid, consistent, applicable and clinically relevant)</td>
<td>A</td>
</tr>
<tr>
<td>The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence)</td>
<td>B</td>
</tr>
<tr>
<td>The recommendation is supported by international expert opinion</td>
<td>C</td>
</tr>
</tbody>
</table>

Grades indicate the strength of the supporting evidence rather than the importance of the evidence.

<table>
<thead>
<tr>
<th>Good Practice Points</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Where no evidence is available, best practice recommendations are made based on the experience of the Guideline Development Team, or feedback from consultation within New Zealand</td>
<td>✓</td>
</tr>
</tbody>
</table>
Appendix 4 Table 3. Details of levels of evidence and grading of NICE 2005 recommendations

Levels of evidence

<table>
<thead>
<tr>
<th>Hierarchy of evidence</th>
<th>Systematic review or meta-analysis of randomised controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Systematic review or meta-analysis of randomised controlled trial</td>
</tr>
<tr>
<td>Ib</td>
<td>At least one randomised controlled trial</td>
</tr>
<tr>
<td>IIA</td>
<td>At least one well-designed controlled study without randomization</td>
</tr>
<tr>
<td>IIB</td>
<td>At least one well-designed quasi-experimental study, such as a cohort study</td>
</tr>
<tr>
<td>III</td>
<td>Well-designed non-experimental descriptive studies, case-control studies, and case series</td>
</tr>
<tr>
<td>IV</td>
<td>Expert committee reports, opinions and/or clinical experience of respected authorities</td>
</tr>
<tr>
<td>NICE</td>
<td>NICE guidelines or Health Technology Appraisal programme</td>
</tr>
</tbody>
</table>

Grades of recommendation

<table>
<thead>
<tr>
<th>Grading of recommendations</th>
<th>Based directly on level I evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Based directly on level I evidence</td>
</tr>
<tr>
<td>B</td>
<td>Based directly on level II evidence or extrapolated from level I evidence</td>
</tr>
<tr>
<td>C</td>
<td>Based directly on level III evidence or extrapolated from level I or level II evidence</td>
</tr>
<tr>
<td>D</td>
<td>Based directly on level IV evidence or extrapolated from level I, level II, or level III evidence</td>
</tr>
<tr>
<td>A NICE</td>
<td>Recommendation taken from NICE guideline or Technology Appraisal</td>
</tr>
<tr>
<td>GPP</td>
<td>Good practice point based on the clinical experience of the GDG</td>
</tr>
</tbody>
</table>

Levels of evidence for studies of the accuracy of diagnostic tests for NICE 2005

<table>
<thead>
<tr>
<th>Levels of evidence/Type of evidence</th>
<th>Systematic review (with homogeneity)† of level-1 studies‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Systematic review (with homogeneity)† of level-1 studies‡</td>
</tr>
<tr>
<td>Ib</td>
<td>Level-1 studies‡</td>
</tr>
<tr>
<td>II</td>
<td>Level-2 studies§</td>
</tr>
<tr>
<td></td>
<td>Systematic reviews of level-2 studies</td>
</tr>
<tr>
<td>III</td>
<td>Level-3 studies§</td>
</tr>
<tr>
<td></td>
<td>Systematic reviews of level-3 studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research or ‘first principles.’</td>
</tr>
</tbody>
</table>
Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

Level-1 studies are studies that use a blind comparison of the test with a validation reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

Level-2 studies are studies that have only one of the following: narrow population (the sample does not reflect the population to whom the test would apply), use a poor reference standard (defined as that where a ‘test’ is included in the ‘reference’, or where the ‘testing’ affects the ‘reference’), the comparison between the test and reference standard is not blind or case-control studies.

Level-3 studies are studies that have at least two or three of the features listed above.

Classification of recommendations for studies of the accuracy of diagnostic tests

<table>
<thead>
<tr>
<th>Class Level of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (DS)</td>
<td>Studies with level of evidence Ia or Ib</td>
</tr>
<tr>
<td>B (DS)</td>
<td>Studies with level of evidence II</td>
</tr>
<tr>
<td>C (DS)</td>
<td>Studies with level of evidence III</td>
</tr>
<tr>
<td>D (DS)</td>
<td>Based on studies with level of evidence IV</td>
</tr>
</tbody>
</table>

(DS - diagnostic studies).
Appendix 4 Table 4. Details of levels of evidence and grading of SIGN 2005 recommendations.

### Levels of Evidence For SIGN

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High-quality systematic reviews of case-control or cohort studies; High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g., case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

### Grades of Recommendations for SIGN

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review of RCTs, or RCT rates as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rates as 1++ or 1+</td>
</tr>
<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rates as 2++</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
</tr>
<tr>
<td>✓</td>
<td>Recommended best practice based on the clinical experience of the guideline development group</td>
</tr>
</tbody>
</table>
Appendix 4 Table 5. Designation of levels of evidence for the Australian 2004 Guideline.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from a systematic review of all relevant randomized controlled trials.</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one properly designed randomized controlled trial.</td>
</tr>
<tr>
<td>III-1</td>
<td>Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).</td>
</tr>
<tr>
<td>III-2</td>
<td>Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group.</td>
</tr>
<tr>
<td>III-3</td>
<td>Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from case series, either post-test or pre-test and post-test.</td>
</tr>
</tbody>
</table>

(In effect we listed all level III - as III regardless of category.)

These levels of evidence ratings have been adapted from: US Preventive Services Task Force., Guide to clinical preventive services: an assessment of the effectiveness of 169 interventions. M Fisher, Editor. Baltimore, Maryland: Williams and Williams, Baltimore; 1989.

Appendix 4 Table 6. Grading of the Evidence and Recommendations for ACCP Guidelines.

**Quality of Evidence Scale**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies*</td>
</tr>
<tr>
<td>Moderate</td>
<td>RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies*</td>
</tr>
<tr>
<td>Low or very low</td>
<td>Observational studies or case series</td>
</tr>
</tbody>
</table>

*Although the determination of magnitude of the effect based on observational studies is often a matter of judgment, we offer the following suggested rule to assist this decision: a large effect would be a relative risk > 2 (risk ratio < 0.5) [which would justify moving from weak to moderate], and a very large effect is a relative risk > 5 (risk ratio < 0.2) [which would justify moving from weak to strong]. There is some theoretical justification in the statistical literature for these thresholds (the magnitude of effect that is unlikely or very unlikely to be due to residual confounding after adjusted analysis). However, once the decision is made, authors should be explicit in justifying their decisions.

**Relationship of Strength of the Supporting Evidence to the Balance to Risks and Burdens**

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Balance of benefits to Risks and Burdens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benefits outweigh risks/burdens</td>
</tr>
<tr>
<td>High</td>
<td>1A</td>
</tr>
<tr>
<td>Moderate</td>
<td>1B</td>
</tr>
<tr>
<td>Low or very low</td>
<td>1C</td>
</tr>
</tbody>
</table>
Appendix 4. References.


Evidence-Based Series 24-2: Section 3

Referral of Suspected Lung Cancer by Family Physicians and Other Primary Care Providers: EBS Development Methods and External Review Process


A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: August 29, 2011

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.
The Evidence-Based Series
Each EBS is comprised of three sections:

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

- **Section 3: EBS Development Methods and External Review Process.** Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

**DEVELOPMENT OF THIS EVIDENCE-BASED SERIES**

**Development and Internal Review**
This EBS was developed by the Provincial Primary Care and Cancer Network of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on primary care referral for suspected lung cancer, developed through review of an updated evidentiary base since the National Institute for Health and Clinical Excellence (NICE) 2005 and New Zealand Guidelines Group (NZGG) 2009 guidelines, an adaptation of existing guidelines, consensus of the Lung Cancer Referral Working Group, and input from external review participants in Ontario (3,4).

**Development of the Recommendations**


The Working Group held a teleconference to develop the recommendations through informal consensus. Each of the recommendations in Appendix 4 was discussed taking into consideration any evidence found in the systematic review. The recommendations were written and approved by all members during the meeting. The following content details the results of how the recommendations were generated.

The recommended wait times from the guidelines were all based on consensus. Therefore, all recommended wait times in this document were based on the expert opinion of this Working Group to be feasible in Ontario.

The Working Group felt the general recommendations from NICE 2005 and Australia 2005 were too general and needed to specifically mention the Diagnostic Assessment Programs (3,5). These recommendations could be covered in other recommendations.

For the indications for referral to the emergency department, the Working Group adapted the recommendation from the NICE guidelines for immediate referral (3). The
Working group chose to add massive hemoptysis based on common practice in Ontario as well as the Time-to-Treat Program (9).

For indications for chest X-ray, the working group choose to use the wording from the recommendation from the NZGG guidelines for urgent referral for a chest X-ray (4). Based on expert opinion, the position was that, for unexplained finger clubbing, features suggestive of metastasis from a lung cancer (e.g., brain, bone, liver, skin), and suspicious lymphadenopathy, the three-week time frame was not required for referral for a chest X-ray. The Working Group chose to include dysphagia as an indicator for a chest X-ray because it was reported in the NICE review as a symptom of lung cancer and was found to be a major clinical symptom among lung cancer patients in a tertiary care setting (3,10). Furthermore, paraneoplastic syndromes were included as indications for chest X-ray based on the review by Spiro et al (2007) that reported that paraneoplastic syndromes may occur in 10% of patients with lung cancer (11).

For patients with underlying chronic respiratory problems, the Working Group chose to adapt the recommendation from NICE (3). In addition, the list of risk factors was broadened to include all risk factors summarized by the NZGG, based on the review by NICE (4).

The recommendations for the indications for a CT scan were based on expert opinion. SIGN does provide some recommendations, but the evidence is weak (8). Therefore, the Working Group developed their own recommendations.

The recommendations varied between guidelines as to whether sputum cytology should be performed (4,5,7,8). The updated literature search found high specificity but variable sensitivity of sputum cytology in detecting lung cancer (5,7,8,12,13). Therefore, the Working Group endorsed the recommendation from the NZGG referral guidelines (4).

The recommendation for follow-up to consolidation on a chest X-ray was adapted from the NZGG referral guideline, which was based on the experience of their guideline development team (4). The Working Group chose to modify the NZGG recommendation by including all patients rather than specifying only patients with risk factors for lung cancer. In addition to consolidation, the Working Group also included unexplained pleural effusion based on their experience in their practices.

A recommendation for follow-up of solitary pulmonary nodules on imaging tests, adapted from the American College of Chest Physicians’ Clinical Practice Guidelines for pulmonary nodules (6), was initially included. However, after internal review, the Working Group chose to remove this recommendation because patients with a solitary pulmonary nodule, independent of size, would be referred to a specialist.

The indications for referral to a specialist were adapted from the NZGG and NICE referral guidelines, which were based on expert opinion (3,4). Additional abnormal chest X-ray results were included from the Time-to-Treat Program (9). An unexplained elevated diaphragm was included based on the suggestion of an Expert Panel member. As well, information that should be provided to the specialist was taken from the Time-to-Treat Program (9).

The recommendations to reduce diagnostic delay were taken from evidence found in the NZGG and NICE guidelines, as well as from the updated literature search (11,14,15).

Development of One-Page Algorithms

One-page algorithms were developed to provide a quick reference guide for PCPs and/or educational material for patients. Currently, CCO does not have a general template for algorithm design that can be used for representing guideline information. Therefore, a search for algorithm designs from the following well-recognized, international guideline developers commonly used by the PEBC was conducted.
The search indicated that a variety of designs were being used to disseminate guideline information. From this list, the most commonly used designs were the Condensed Summary, the Flow Chart, and the Sectioned List. Consequently, these were used as models for representing the information. A questionnaire using Survey Monkey\(^1\) (http://www.surveymonkey.com/) was developed and sent to the Expert Panel members for their feedback. Specifically, the questionnaire was used to assess which algorithm style was preferred by Expert Panel members, how it would be utilized (i.e., to make professional decisions or for patient education), and whether any modifications needed to be made to any of the layouts. The data from this survey is shown in Table 1.

Table 1. Responses to five items on the expert panel algorithm questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Reviewer Ratings (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flow Chart</td>
</tr>
<tr>
<td>1. Rank the two best algorithm styles in order of preference</td>
<td>1,1,1,1,2,2,2</td>
</tr>
<tr>
<td>2. If you prefer the Flow Chart algorithm style, which paper layout would you use? (Check one)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Horizontal</td>
</tr>
<tr>
<td></td>
<td>16.7%</td>
</tr>
<tr>
<td></td>
<td>Strongly Disagree</td>
</tr>
<tr>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>3. I would make use of this algorithm layout in my professional decisions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flow Chart</td>
</tr>
<tr>
<td></td>
<td>0</td>
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<td></td>
<td>0</td>
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<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>4. I would make use of this algorithm layout for patient education.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flow Chart</td>
</tr>
<tr>
<td></td>
<td>1</td>
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<td></td>
<td>1</td>
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<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5. Do you prefer to use another algorithm style that is not represented here?</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

Based on the results of the algorithm survey, the Expert Panel preferred the horizontal flow chart design. This design was used to create the algorithm in Section 1.

**Lung Cancer Referral Expert Panel Review**

Key issues raised by the guideline Expert Panel and the Working Group responses (immediately below) included the following:

- I believe FPs want “just in time delivery” of information. So when they get a chest x-ray report that suggests the presence of lung cancer, they might want to have an electronic decision support tool that tells them what set of tests need to be done and how to make a referral to an appropriate specialist for further workup.

The recommendation, “Decision-support tools should be readily available to assist FPs and other PCPs.” was added under the recommendations to reduce diagnostic delay.

- I wonder if there should be a comment about possibly using high dose steroids if time to diagnosis might be delayed? That is if there is a long distance to an ER in a remote area for example or a delay in getting appropriate investigations or specialist care.
  - The Working Group felt this was beyond the scope of this document.

- Some of the recommendations lack clarity on points that could lead to overuse or underuse of referral. E.g. ‘suspicious lymphadenopathy’…could this be defined? I believe NICE 2005 uses cervical and supraclavicular. Some definition of ‘suspicious’ as it relates to known lymph drainage patterns would be helpful.
  - The Working Group chose not to qualify lymphadenopathy, believing that all patients with lymphadenopathy should receive a chest X-ray.

- Features suggestive of metastatic lung cancer (e.g., in brain, bone, liver or skin): numerous patients present with metastatic disease before the primary is known; the presence of metastatic disease should lead to a chest x-ray as lung cancer commonly presents first with evidence of metastasis.
  - The recommendation was changed to “features suggestive of metastatic lung cancer that metastasize elsewhere and cancer that metastasized to the lung.”

- A more specific definition for ‘chest signs’ is needed
  - We have inserted hyperlinks to provide examples, references or explanations of conditions/signs/symptoms.

- All smokers cough, so it is the onset of a new cough or the change in a cough and it has to last for some period of time, as suggested 3 weeks
  - The Working Group decided against including the word ‘new’ because we have the word ‘unexplained’ in the recommendation.

- ...But what are the guidelines criteria for ‘high suspicion’ in this guideline? Is it haemoptysis? Is it weight loss/ loss of appetite? A big difference. It may be worthwhile to state ‘in consultation with the radiologist’ in this section.
  - The Working Group chose not to include ‘in consultation with the radiologist’ because FPs and other PCPs that have a high suspicion of lung cancer would be inclined to consult with the radiologist.

- Is a CT scan always necessary after a highly suspicious CXR, or can some patients go directly to the surgeon?
  - The Working Group agreed that patients should always have a chest computerized tomography (CT) scan after a suspicious chest X-ray; however, the ordering physician will depend on locally available resources.

- Indications for chest CT scan: should include the patient with symptoms of pneumonia whose chest x-ray fails to clear after a two-week course of antibiotic therapy
  - Non-resolving consolidation or effusion despite treatment was included as an example of an abnormal chest X-ray that raises suspicion of lung cancer.

- I suspect that if a work up was done for suspected lung cancer and was negative, yet no cytology was done, the physician may (inappropriately) be faulted and be subjected to a College or malpractice complaint.
  - The Working Group chose not to change their recommendation for sputum cytology based on the opinion of the respirologist, Dr. R. Skrastins.

- Sputum cytology: it is still a useful test for centrally arising tumours, particularly if squamous in histology.
  - The Working Group chose not to change their recommendation for sputum cytology based on the opinion of the respirologist, Dr. R. Skrastins.
• I think physicians might interpret that only individuals with risk factors for lung cancer should have a follow up chest X-ray. I would opt for a statement that is more general—that a person with consolidation should have a follow up chest X-ray.
  o The Working Group removed ‘risk factors for lung cancer’ from the recommendation under follow-up to diagnostic investigations.
• Six weeks is too long an interval. Chest x-ray should be repeated after a 2 week course of antibiotics.
  o The Working Group decided not to change this recommendation, based on their own clinical experiences.
• I don’t see why you have differentiated between ‘non-peripheral mass or nodule in smoker’, ‘peripheral nodule or mass in smoker’ and ‘nodule or mass in non-smoker’. Why not simply say ‘mass or nodule’.
  o The Working Group reworded the recommendation to “a nodule or mass.”
• With pertinent information with referral, many facilities are able to retrieve the previous images by picture archiving and communication systems (PACS), so even including the phrase (with accompanying films and/or electronic copies or stating where previous images were done).
  o The recommendation was changed to “All efforts should be made for pre-existing imaging results including chest X-rays and CT scans (films and digital images should be available at the time of consultation).”
• Some suggested rewording: Family physicians and other primary care providers should include all relevant information regarding risk factors, presentation, diagnostic test results and co-morbidities in their referral letters and should ask patients to help retrieve electronic copies of their imaging tests to bring to specialist appointments and/or provide the consultant/DAP with the site of where previous images were taken to facilitate PACS retrieval.
  o To reflect that co-morbidities should be included in the referral letter, the recommendation was changed to “All relevant other medical conditions and medications taken by patient.”
• Mention if early diagnosis will affect outcome.
  o The Working Group felt they could not speak to this issue due to the lack of evidence.
• Define delay.
  o The Working Group felt this was not necessary since studies measure different intervals between the onset of symptoms and a definitive diagnosis.
• What is appropriate education? Who will do it?
  o This recommendation was changed to “There should be appropriate educational tools developed and disseminated that highlight the signs and symptoms of lung cancer for FPs and other PCPs and for patients.”
• I’m not sure what ‘low threshold of suspicion’ means. Does this mean they should refer lots, or refer sceptically? I’m not sure everyone will interpret this phrase the same way.
  o Reworded the recommendation to “FPs and other PCPs should have a high index of suspicion with a low threshold for investigation of suspected lung cancer in ordering chest X-rays and referral to lung cancer specialists or the DAP.”
• I think it important to give a footnote to the timelines to state these are ‘based on expert opinion. Clinical judgement and access to resources need also to be considered.’
  o The Working Group chose not to make this change. Physicians can refer to the full guideline if they want more information.
METHODS & REVIEW

- Add elevated diaphragm to the box that lists descriptors of a chest x-ray that may be suggestive or suspicious of lung cancer.
  - The Working Group decided to add ‘elevated diaphragm’ to the list of descriptors of a chest X-ray that may be suggestive or suspicious of lung cancer.

PEBC Director’s Review

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the Director of the PEBC, Dr. Melissa Brouwers, with expertise in methodological issues. The key issues raised by the Director and the Working Group responses (italicized) were the following:

- The questions do not lend themselves to actionable recommendations for the most part. The answers to the questions would be statements of facts. Also, the role of primary care here – except in being the intended audience - is a bit unclear.
  - The questions have been reworded to address these issues.
- More detail is needed for the rationale behind wait times and the nature of studies that were included in the NICE 2005 guideline.
  - More detail is provided to address these concerns.
- Explain under the methods section that the NICE 2005 and NZGG 2009 guidelines were chosen a priori and the reasons why. Also, explain why an environmental scan of guidelines was performed.
  - These concerns were explained more thoroughly in the document.
- The discussion should include statements about what the working group believed were the most appropriate signs, symptoms and diagnostic tests for lung cancer.
  - These were included in the discussion.
- More detail is needed about how the consensus was achieved when developing the recommendations.
  - This section was expanded.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC’s Director, the Lung Cancer Referral Working Group circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Lung Cancer Referral Working Group.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review May 19, 2011)

QUESTIONS

Overall question:
In patients presenting to primary care services with signs and/or symptoms of lung cancer, what should the referral process include?

The following questions are the factors considered in answering the overall question:
What signs, symptoms and other clinical features are predictive of lung cancer? What is the diagnostic accuracy of investigations for lung cancer? What major, known risk factors are predictive of lung cancer? Which factors are associated with delayed referral? Which delay factors can be attributed to patients, and which factors can be attributed to providers? Does a delay in the time to consultation affect patient outcome?

TARGET POPULATION
Patients presenting in primary care settings comprise the target population. This guideline does not provide recommendations for patients in a screening program.

INTENDED USERS
This guideline is targeted to family physicians (FPs), general practitioners, emergency room physicians, other primary care providers (PCPs) (nurse practitioners, registered nurses, and physician assistants), respirologists, thoracic surgeons, and radiologists. For the purposes of this document, we have referred to FPs, general practitioners, emergency room physicians, and other PCPs as ‘FPs and other PCPs’.

RECOMMENDATIONS
The following recommendations were adapted from the New Zealand Guidelines Group (NZGG) guideline Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities and the National Institute for Health and Clinical Excellence (NICE 2005), Referral guidelines for suspected cancer (3,4). The recommendations below reflect the integration of the NZGG 2009 and NICE 2005 recommendations, an updated systematic review of the research evidence since the NZGG 2009 or NICE 2005 guidelines, and consensus by the PEBC Primary Care Working Group for Referral for Suspected Lung Cancer (see Section 2: Appendix 1) (3,4).

Special consideration for these recommendations:

**Factors that Increase the Risk of Lung Cancer**
The following factors have been shown to increase the risk of lung cancer and will be referred to in the recommendations below:
- Current or previous smoker or second-hand exposure to tobacco smoke
- History of chronic obstructive pulmonary disease
- Previous exposure to asbestos or other known carcinogens (e.g., radon, chromium, nickel)
- Occupational exposure to dust or microscopic particles (e.g., wood dust, silica)
- Personal or family history of cancer (especially lung, head and neck cancer)
- Silicosis, tuberculosis

**Indications for Referral to the Emergency Department**
A person should be referred to the Emergency Department for the following:
- Signs of superior vena cava obstruction
- Stridor
- Massive hemoptysis
<table>
<thead>
<tr>
<th>Indications for Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>A person should have a chest X-ray within two working days if they present with any of the following:</td>
</tr>
<tr>
<td>• hemoptysis</td>
</tr>
<tr>
<td>• new finger clubbing</td>
</tr>
<tr>
<td>• suspicious lymphadenopathy</td>
</tr>
<tr>
<td>• dysphagia</td>
</tr>
<tr>
<td>• features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung</td>
</tr>
<tr>
<td>• features suggestive of paraneoplastic syndromes</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>any of the following unexplained signs or symptoms lasting more than three weeks (patients with known risk factors may be considered sooner):</td>
</tr>
<tr>
<td>o cough</td>
</tr>
<tr>
<td>o weight loss/loss of appetite</td>
</tr>
<tr>
<td>o shortness of breath</td>
</tr>
<tr>
<td>o chest and/or shoulder pain</td>
</tr>
<tr>
<td>o abnormal chest signs</td>
</tr>
<tr>
<td>o hoarseness</td>
</tr>
</tbody>
</table>

Patients with underlying chronic respiratory problems should have a chest X-ray within two weeks if they have unexplained changes in existing symptoms.

The requisition for a chest X-ray should include the presenting history, including all signs and symptoms suspicious of lung cancer and all risk factors.

Chest X-rays should be completed, reviewed and reported on by the radiologist, and the report read by the FP or other PCPs within two weeks of being ordered.

<table>
<thead>
<tr>
<th>Indications for Chest CT scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>A person should have a chest CT scan within two weeks if they have any of the following:</td>
</tr>
<tr>
<td>• an abnormal chest X-ray that raises suspicion of lung cancer</td>
</tr>
<tr>
<td>• a normal chest X-ray, but there is a high suspicion of lung cancer, based on clinical judgement</td>
</tr>
</tbody>
</table>

The ordering physician (i.e., FP or other PCPs, specialist, radiologist, or Diagnostic Assessment Program [DAP]) will depend on locally available resources and processes for expedited CT scans.

<table>
<thead>
<tr>
<th>Sputum Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum cytology is not recommended for the investigation of suspected lung cancer.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up to diagnostic investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>A person who has consolidation or unexplained pleural effusion on an initial chest X-ray should be treated and have a chest X-ray repeated within six weeks to confirm resolution.</td>
</tr>
</tbody>
</table>

| Indications for Referral to a Specialist (Respirologist or Thoracic Surgeon) or DAP |
Patients should be referred and expect a consultation to a specialist or where locally available to the DAP within one to two weeks if they have any of the following:

- Persistent hemoptysis
- A chest X-ray suggestive or suspicious of lung cancer including:
  - A nodule or mass
  - Multiple pulmonary nodules
  - Non-resolving pleural effusion
  - Mediastinal or contralateral hilar adenopathy
  - Interstitial infiltrates
  - Slowly or non-resolving pneumonia or consolidation
  - Fibroapical disease suggesting possible tuberculosis
  - Unexplained elevated diaphragm
- A normal chest X-ray, but there is a high suspicion of lung cancer, based on clinical judgement

If promptly accessible, a chest CT scan can be simultaneously ordered with the referral while awaiting the specialist’s consultation. This will depend upon locally available resources.

To expedite the diagnosis and avoid duplication of investigations, at a minimum, the following information should be provided to the specialist:

- History of patient, including all risk factors and signs or symptoms suspicious of lung cancer
- All efforts should be made for pre-existing imaging results, including chest X-rays and CT scans (films and digital images should be available at the time of consultation)
- All relevant other medical conditions and medications taken by patient
- All recent blood work

Recommendations to Reduce Diagnostic Delay

There should be appropriate educational tools developed and disseminated that highlight the signs and symptoms of lung cancer for FPs and other PCPs and for patients.

FPs and other PCPs should have a high index of suspicion with a low threshold for investigation of suspected lung cancer in ordering chest x-rays and referral to lung cancer specialists or the DAP. Decision support tools should be readily available to assist FPs and other PCPs.

FPs and other PCPs should include as much information as possible in their referral letters and should ask patients to help retrieve electronic copies of their imaging tests to bring to specialist appointments.

Counselling of patients should occur to address common fears and concerns.

Public health and other health agencies should work with local community leaders to address challenges, such as lower levels of education or demographic discrepancies in communities with high rates of lung cancer or known delays in lung cancer diagnosis.
**Lung Cancer Guideline Recommendations**

Does the patient have any of the following signs/symptoms?

- Signs of superior vena cava obstruction
- Stridor
- Massive haemoptysis (>600ml of blood in 24 hours or cup half (250ml) at one sitting)
- Haemoptysis
- New finger clubbing
- Suspicious lymphadenopathy
- Dysphagia
- Features suggestive of metastatic lung cancer that metastasize elsewhere and cancer that metastasized to the lung
- Paraneoplastic syndromes
- OR any of the following unexplained signs or symptoms lasting more than 3 weeks (patients with known risk factors* may be considered sooner):
  - Cough
  - Weight loss/loss of appetite
  - Shortness of breath
  - Chest and/or shoulder pain
  - Abnormal chest signs
  - Hoarseness

**Persistent haemoptysis**

Emergency Referral

**Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems**

Performed within 2 weeks

**Chest X-ray**

Performed within 2 working days

Read within 2 weeks

**Normal**

- High suspicion of lung cancer

Referred and seen within 1-2 weeks

- Specialist referral and CT scan

Referred and seen within 1-2 weeks

**Abnormal**

- Consolidation or unexplained pleural effusion

Repeat chest X-ray within 6 weeks to confirm resolution

*Risk factors: Current or previous smoker or second-hand exposure to tobacco smoke, history of chronic obstructive pulmonary disease, previous exposure to asbestos or other known carcinogens, occupational exposure to dust or microscopic particles, personal or family history of cancer (especially lung, head and neck cancer), silicosis, tuberculosis.*
KEY EVIDENCE

- Many of these recommendations were adapted or endorsed from the NZGG 2009 or NICE 2005 recommendations (3,4). Signs and symptoms listed in the NZGG 2009 or NICE 2005 recommendations were derived from their systematic reviews which mainly included case-series studies (3,4). The development of the recommendations in this guideline can be found in Section 3 of this report.

- There was no evidence found on wait times and their effects on patient outcomes. Therefore, all wait times were chosen by the Working Group because they considered them to be achievable targets in the Ontario health care system.

- The list of risk factors was broadened to include all risk factors summarized by NZGG 2009 based on the review by NICE 2005 (3,4).

Indications for Referral to Emergency Department

- This recommendation was adapted from the NICE 2005 guidelines for immediate referral. Massive hemoptysis was included based on common practice in Ontario as well as the Time-to-Treat Program (9).

Indications for Chest X-ray

- This recommendation was adapted from the NZGG 2009 guidelines for urgent referral for a chest X-ray (4). Based on expert opinion, it was felt that, for new finger clubbing, features suggestive of lung cancer that has metastasized elsewhere or other cancers that have metastasized to the lung, and suspicious lymphadenopathy, the three-week time frame was not required for referral for a chest X-ray. The Working Group chose to include dysphagia as an indicator for a chest X-ray because it was reported in the NICE 2005 review as a symptom of lung cancer and was found to be a major clinical symptom among lung cancer patients in a tertiary care setting (3,10). Furthermore, paraneoplastic syndromes were included as indications for chest X-ray based on the review by Spiro et al 2007 that reported that paraneoplastic syndromes may occur in 10% of patients with lung cancer (11).

- For patients with underlying chronic respiratory problems, the Working Group chose to adapt the recommendation from NICE 2005 (3).

Indications for CT Scan

- There was little evidence to inform these recommendations, therefore the Working Group decided to develop their own recommendations based on experiences within their own practices.

Sputum Cytology

- The updated literature search found high specificity but variable sensitivity of sputum cytology in detecting lung cancer (5,7,8,12,13). Therefore, this recommendation was endorsed from the NZGG 2009 referral guidelines (4).

Follow-up to Diagnostic Investigations

- The recommendation for follow-up to consolidation on a chest X-ray was
adapted from the NZGG 2009 referral guideline which was based on the experience of their guideline development team (4). The Working Group chose to modify the NZGG’s 2009 recommendation by including all patients rather than specifying only patients with risk factors for lung cancer. In addition to consolidation, the Working Group also included unexplained pleural effusion based on their experience in their practices.

Indications for Referral to a Specialist (Respirologist or Thoracic Surgeon) or the DAP

- These recommendations were adapted from the NZGG 2009 and NICE 2005 referral guidelines which were based on expert opinion (3,4). Additional abnormal chest X-ray results were included from the Time-to-Treat Program (9). Unexplained elevated diaphragm was included based on the suggestion of an expert panel member.

Recommendations to Reduce Diagnostic Delay

- There is evidence to suggest that the following may delay the diagnosis of lung cancer (3,4,11,14,15):
  - Patient Related Delay:
    - patient’s lack of appreciation regarding the association of symptoms with lung cancer
    - fear of cancer diagnosis
  - Family Physician related delay:
    - not recognizing signs and symptoms suggestive of lung cancer
    - co-morbidity of conditions increased delay
    - multiple consecutive investigations in primary care
    - over-reliance on chest X-ray results to diagnose lung cancer
    - imaging follow-up failure
    - initial referral to a non-respiratory physician

Algorithm

- The process used to develop this algorithm can be found in Section 3.

FUTURE RESEARCH

Further studies could be designed to investigate the diagnostic performance of signs, symptoms, or tests for lung cancer in the primary care setting. In addition, studies are needed to determine which educational initiatives would be best at decreasing practitioner or patient-related delay.

GLOSSARY

Abnormal Chest Signs

e.g., crackles or wheezes

Abnormal Chest X-ray that Raises Suspicion of Lung Cancer

e.g., nodule(s), infiltrates, non-resolving consolidation or effusion despite treatment

Features Suggestive of Metastatic Disease

Family physicians can refer to the American College of Chest Physicians (ACCP) Clinical Practice Guidelines for features of a standardized evaluation for systematic
metastases (available at: http://chestjournal.chestpubs.org/content/132/3_suppl/149S.full.pdf)(11)

Massive Hemoptysis
>600 mL of blood in 24 hours or one cup full of blood (250 mL) at one sitting

Features Suggestive of Paraneoplastic Syndromes
Family physicians can refer to the ACCP Clinical Practice Guidelines for a list of paraneoplastic syndromes associated with lung cancer (available at: http://chestjournal.chestpubs.org/content/132/3_suppl/149S.full.pdf)(11)

Signs of Superior Vena Cava Obstruction
Swelling of the face and or neck with fixed elevation of jugular venous pressure

Methods
Targeted Peer Review: During the guideline development process, seven targeted peer reviewers from Ontario and Manitoba considered to be clinical and/or methodological experts on the topic were identified by the Lung Cancer Referral Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on May 19, 2011. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Lung Cancer Referral Working Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All health care professionals with an interest in lung cancer including family physicians, thoracic surgeons and radiologists in the PEBC database were contacted by email to inform them of the survey. Also, members of the Canadian Cancer Society, the Nurses Practitioner Association of Ontario, the Ontario College of Family Physicians, the Ontario Hospital Association, the Ontario Medical Association, and the Uniting Primary Care and Oncology Leads at Cancer Care Manitoba were invited to review this guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on May 19, 2011. The consultation period ended on June 20, 2011. The Lung Cancer Referral Working Group reviewed the results of the survey.

Results
Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 2.
Table 2. Responses to nine items on the targeted peer reviewer questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Reviewer Ratings (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest Quality (1)</td>
</tr>
<tr>
<td>1. Rate the guideline development methods.</td>
<td>0</td>
</tr>
<tr>
<td>2. Rate the guideline presentation.</td>
<td>0</td>
</tr>
<tr>
<td>3. Rate the guideline recommendations.</td>
<td>0</td>
</tr>
<tr>
<td>4. Rate the completeness of reporting.</td>
<td>0</td>
</tr>
<tr>
<td>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
<td>0</td>
</tr>
<tr>
<td>6. Rate the overall quality of the guideline report.</td>
<td>0</td>
</tr>
</tbody>
</table>

|                                                                         | Strongly Disagree (1) | (2) | Neutral (3) | (4) | Strongly Agree (5) |
| 7. I would make use of this guideline in my professional decisions.     | 0 | 0 | 1 | 0 | 2 |
| 8. I would recommend this guideline for use in practice.                | 0 | 0 | 1 | 0 | 2 |

9. What are the barriers or enablers to the implementation of this guideline report?
The targeted peer reviewers indicated that the document is informative and not too lengthy. They mentioned that algorithms should be readily available at point of care, not just on the CCO website. Also, the recommendations should be coordinated with diagnostic imaging departments and specialists/hospital care. Furthermore, a validation study to evaluate effectiveness is needed.

Table 3. Summary of Written Comments by targeted peer reviewers and Modifications/Actions Taken

<table>
<thead>
<tr>
<th>Summary of Written Comments</th>
<th>Modifications/Actions/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I would harmonize the three weeks of symptoms versus the two weeks of worsening in patients with chronic symptoms. It’s unduly confusing to have different time thresholds. Doing X-rays for every flare up of COPD may not be warranted. I’d recommend both recommendations be harmonized at three weeks.</td>
<td>For patients with underlying chronic respiratory problems and unexplained changes in existing symptoms, the working group chose to change the timeframe to “have a X-ray from two weeks to three weeks.”</td>
</tr>
<tr>
<td>2. I would also include criteria for referral based on CT scan results, unless you are sure you want every CT scan ordered to be accompanied by specialist referral. In practice, I suspect CTs are often ordered without such referral.</td>
<td>The recommendation “If the CT scan is entirely negative, then further referral to a specialist can be cancelled.” was added.</td>
</tr>
</tbody>
</table>
Professional Consultation: One-hundred and fifteen of 428 (27%) responses were received. Key results of the feedback survey are summarized in Table 4.

Table 4. Responses to four items on the professional consultation survey.

<table>
<thead>
<tr>
<th>General Questions: Overall Guideline Assessment</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rate the overall quality of the guideline report.</td>
<td>Lowest Quality (1) 0 (2) 5 (3) 13 (4) 51 (5) 30</td>
</tr>
<tr>
<td></td>
<td>Strongly Disagree (1) (2) (3) (4) Strongly Agree (5)</td>
</tr>
<tr>
<td>2. I would make use of this guideline in my professional decisions.</td>
<td>4 (2) 3 (3) 15 (4) 33 (5) 44</td>
</tr>
<tr>
<td>3. I would recommend this guideline for use in practice.</td>
<td>1 (2) 4 (3) 15 (4) 34 (5) 46</td>
</tr>
</tbody>
</table>

4. What are the barriers or enablers to the implementation of this guideline report?
The professional consultants stated that the recommendations are simple to use and are very practical, and that the algorithm is useful and a great teaching aid for students. They mentioned that there are resource issues with obtaining a CT because they are not always accessible/available and not always possible to be completed in two weeks, especially in rural areas. There are also resource issues in terms of access to specialists and demand for services. They also noted the lack of evidence to support the recommendations and believed that more patient awareness may also help.

Table 5. Summary of Written Comments by professional consultants and Modifications/Actions Taken.

<table>
<thead>
<tr>
<th>Summary of Written Comments</th>
<th>Modifications/Actions/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I would have added “severe dyspnea or hypoxia” to the list of indications for referral to the Emergency Department.</td>
<td>The working group chose not to add severe dyspnea or hypoxia because the definition of severe would have to be explained.</td>
</tr>
<tr>
<td>2. I would argue that in most cases someone with chest pain should go to emergency room and not be sent for a chest X-ray in three weeks. I imagine most family physicians know this though.</td>
<td>The working group chose to exclude chest pain as an indicator for referral to the emergency room, because it would indicate cardiac concerns and not lung cancer.</td>
</tr>
</tbody>
</table>
| 3. I think it is hard to justify insisting on a chest X-ray within two days for finger clubbing (which has likely arisen over months). | The working group decided that new finger clubbing should prompt a chest X-ray. There is no point confusing things by saying “for this presentation of lung cancer, two days is appropriate, and for this presentation,
4. I would suggest that something needs to be added to “suspicious adenopathy”. It needs to be qualified as lower neck or supraclavicular.

5. I have some concerns about the indications for chest X-ray. I believe that there are circumstances where a low risk individual could have a cough for more than three weeks (e.g. viral/post-viral/asthma) where the degree of suspicion would be sufficiently low that a chest X-ray would not be ordered. This guideline would introduce an “absolute” recommendation which may lead to a lot more chest X-rays being done in low risk people. Similarly, I don't believe that every patient with "shoulder pain" for three weeks or more requires a chest X-ray. Obviously a 60 year old smoker would be managed quite differently from a 20 year old, non-smoking baseball pitcher.

6. The guideline states that the requisition for chest X-ray should include all signs and symptoms and risk factors for chest X-ray. This seems to me to be an unfair expectation. It is unclear that this would be of much help to radiologists over and above a brief summary statement that listed the main symptoms.

7. Many reviewers felt that a chest X-ray report should be available and read by the family physician within a few days of being ordered and that two weeks is an excessive delay.

8. CT’s are not available within two weeks in many rural places; patients need to travel >300 km.

9. It would be useful to have algorithms based on some of the symptom presentations that we struggle with - e.g. “approach to patient with hemoptysis and normal chest X-ray”, “approach to a pleural effusion in the absence of obvious cause on chest X-ray”, and “follow-up strategy for an incidental pulmonary nodule (I think that the radiologists have recommendations on this topic and this might be referred to in this document).”
10. DAPs would certainly make it easier. Continuing to generate awareness of the DAP to family physicians in the various local health integration networks would also be helpful (maybe acknowledge them in the document).

A description of a DAP was added to the glossary.

11. Access to specialty care is still a problem and a delaying factor. The treating physician will not treat without a "tissue diagnosis" and in the very ill this can be a difficult problem to resolve. The early finding of positive sputum cytology can help move everything along faster.

The working group chose not to modify the recommendation based on the evidence that sputum cytology has high specificity but variable sensitivity.

12. Consolidations in the lung may be associated with fever or not. If there is a fever then there is likely an infection requiring antibiotics and follow up to ensure complete clearing. There could still be an underlying cancer hence the need to ensure complete clearing. If there is a consolidation without fever then I would recommend proceeding to a CT scan immediately. So I would add "...has a fever and consolidation...should be treated with antibiotics and have... To confirm complete resolution". It is important to emphasize complete resolution as too often incomplete resolution leads to a second or third course of antibiotics.

The working group chose not to include fever as a criterion because cancers can cause fever. Also, the working group decided not to include treatment options for pneumonia and effusions and left that decision to the FP and other PCPs based on their clinical judgement. The working group decided to include the word “complete resolution.”

13. For referral of “nodule”, if we referred every nodule before a CT scan, then specialists would be overwhelmed.

The recommendation “If the CT scan is entirely negative, then further referral to a specialist can be cancelled.” was added.

Conclusion
This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Lung Cancer Referral Expert Panel and the Director of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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Contact Information
For further information about this report, please contact:

Dr. Lisa Del Giudice, Family Physician
Sunnybrook Family Practice Unit, Room A112
2075 Bayview Ave, Toronto, M4N 3M5
Phone: 416-480-4939   Fax: 416-480-6038   Email: Lisa.DelGiudice@sunnybrook.ca

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