Australian Government

Department of Health and Ageing

Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

National Horizon Scanning Unit
Horizon scanning prioritising summary

Volume 12, Number 7:

Breath test for the detection of lung cancer in high-risk patients (update).

March 2006

AHTA

Adelaide Health Technology Assessment

[add ISSN]
[add Publications Approval Number]

Electronic copies can be obtained from http://www.horizonscanning.gov.au

Enquiries about the content of this summary should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

The production of this *Horizon scanning prioritising summary* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This *Horizon scanning prioritising summary* was prepared by Tom Sullivan, Janet Hiller and Linda Mundy from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Department of Public Health, Mail Drop 511, University of Adelaide, South Australia, 5005.

PRIORITISING SUMMARY: UPDATE

REGISTER ID: **000122**

NAME OF TECHNOLOGY: **BREATH TEST FOR LUNG CANCER DETECTION**

PURPOSE AND TARGET GROUP: **LUNG CANCER SCREENING FOR HIGH- RISK PATIENTS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes — ARTG number
- ☒ No
- ☐ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
Europe	✓		

IMPACT SUMMARY:

This summary provides a 12 month update on the breath test developed by Menssana Research (USA). The original Prioritising Summary for this device was completed in October 2004.

BACKGROUND

The breath test is a non-invasive test that measures volatile organic compounds (VOCs) in exhaled breath to predict the probability of lung cancer. A portable collection apparatus captures the VOCs in one litre of breath into an absorbent trap. The absorbent trap is then analysed by gas chromatography and mass spectroscopy.

The breath collection apparatus is shown adjacent. The high-risk subject wears a nose clip and breathes in and out through a disposable

mouthpiece. The long tube is the breath reservoir, and the small tube affixed to its end is the absorbent trap. The front panel of the breath collection apparatus shows the flowmeter on the left and a digital timer on the top right (Menssana Research 2004).

Previous research has identified breath markers of oxidative stress, the breath methylated alkane contour, which distinguishes breath of patients with and without lung cancer (Phillips et al 1999, Phillips et al 2003, Gordon et al 1985, Menssana Research 2004).

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer is the most common cause of cancer death in males and the fourth leading cause of cancer in Australia (AIHW 2003). In 2001, 5278 males and 2782 females were newly diagnosed with cancer of the lung, bronchus or trachea (AIHW, 2004). The mortality rate for lung cancer is high with approximately 90% of patients diagnosed with lung cancer succumbing to the disease. Five-year survival rates are poor at approximately 10% (AIHW, 2003).

Similar statistics have also been reported in New Zealand. Lung cancer is the most common cause of cancer death in males and the fifth most prominent type of cancer in New Zealand (NZHIS, 2005). In 2001, 1529 lung cancer registrations were reported, accounting for 8.5 per cent of total cancer registrations in New Zealand that year (NZHIS, 2005). Mortality rates for lung cancer were also high in 2001, with a total of 1435 people succumbing to the disease (NZHIS, 2005).

DIFFUSION

Population lung screening utilising the breath test is not offered in Australia. The manufacturer suggests the breath test may serve as a primary tool in the investigation of high-risk patients, followed by secondary screening with CT and final testing with bronchoscopy.

COMPARATORS

Current methods for diagnosing lung cancer in Australia include chest X-ray, chest CT, bronchoscopy and lung biopsy.

EFFECTIVENESS AND SAFETY ISSUES

The most recent and largest study of the Menssana breath test for lung cancer compared breath samples between 178 bronchoscopy patients and 41 healthy volunteers (Phillips et al, 2003).

Breath samples from the bronchoscopy group were collected prior to the procedure and analysed to determine the alveolar gradients of particular VOCs (a cross-sectional study). The bronchoscopy determined that of the 178 patients, 91 were disease-free, 15 had metastatic lung cancer, 67 had primary lung cancer and 5 patients had an indeterminate result. The 67 primary lung cancer patients' breath samples were then compared to the 41 healthy volunteers' samples (diagnostic level III-3 evidence). A predictive model employing nine specific VOCs identified primary lung cancer with a sensitivity of 89.6% (60 of 67 patients) and a specificity of 80.5% (33 of 41 volunteers).

EFFECTIVENESS AND SAFETY ISSUES -FEBRUARY 2006 UPDATE

Since October 2004 when the original prioritising summary was compiled, three new studies into the usefulness of breath tests for the detection of lung cancer have been published (Deng et al 2004, Yu et al 2005, and Machado et al 2005). All studies were level III-3 diagnostic evidence, involving a total of 53 participants diagnosed with lung cancer and 185 control participants. Each

study demonstrated to some extent the validity of using breath tests for the detection of lung cancer. Deng et al (2004) reported that hexanal and heptanal detected in the breath originated from the blood, and values of these VOCs were substantially higher in lung cancer patients (n=10) in comparison to control subjects (n=10). Yu et al (2005) reported that certain alkanes and aromatic hydrocarbons were detected in 73 per cent of lung cancer patients (11/15), but only in 13% of controls (2/15). Finally, Machado et al (2005) developed a predictive model for the detection of lung cancer, again through the measurement of VOCs using gas chromatography and mass spectroscopy. In the study, 14 participants with bronchogenic carcinoma and 45 controls were used to develop the predictive model. Subsequently the model was applied to a separate group of 76 participants, 14 with and 62 without cancer (whose disease state was blinded to the experimenters prior to model fitting). The sensitivity and specificity for detecting lung cancer using the model was 71.4% and 91.9%, respectively.

In addition to these published studies, Phillips et al (2005) submitted an abstract describing a large scale study (level III-3 diagnostic evidence) to the Journal of Clinical Oncology (currently awaiting publication). In a follow-up to their 2003 study, the authors compared breath samples between 212 smokers older than 60 years of age who did not have lung cancer (controls) and 195 patients diagnosed with primary lung cancer (predominantly non-small-cell lung cancer). It was not specified whether the patients with lung cancer were smokers. In their analysis, two thirds of the sample was used to develop a predictive model for the detection of lung cancer, and one third of the sample was considered a test set. The authors identified 29 VOCs which acted as biomarkers for lung cancer, and using these VOCs they found the predictive model was able to detect lung cancer in the test set with a sensitivity and specificity of 90.6% and 82.7%, respectively. Assuming a 2% prevalence of lung cancer in smokers aged 60 years and over, these diagnostic characteristics translate to a positive and negative predictive value of 11.6% and 99.6% respectively. The high negative predictive value is particularly important, as it shows the breath test can correctly rule out lung cancer in the majority of patients who do not have the disease. As a result, the breath test could lower costs and reduce the need for CT screening and/or bronchoscopy in patients believed to be at high risk of lung cancer.

In addition to the detection of lung cancer, the use of breath tests are also being evaluated in a wide range of other medical applications. Menssana Research is currently evaluating the use of breath tests in the detection of breast cancer, heart transplant rejection, pulmonary tuberculosis, ischaemic heart disease, kidney disease and diabetes mellitus. For each of these applications, research is concerned with the identification of VOCs that act as specific markers for the disease of interest.

At present the breath test developed by Menssana Research has only been approved by the United States Food and Drug Administration for the detection of heart transplant rejection. However the company is currently pursuing regulatory approval for the use of the breath test in detecting lung and breast cancer in both the USA and Europe (personal communication, Menssana Research).

COST IMPACT

The manufacturer is yet to determine the cost of the test (personal communication, Menssana Research, Jan 2006).

In 1993–94 the total health care expenditure on lung cancer was estimated at A$107 million. This estimate includes hospital, medical, pharmaceuticals, nursing home and allied health services, public health programs, research, other institutional and non-institutional and administration

expenditure. During the same period total treatment costs per case of lung cancer were estimated at $14,298 (Mathers et al 2004).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

It is not known whether early detection of lung cancer can improve disease outcome. However, the study authors claim that early detection in the United States could improve the 5-year survival rate from 20% in patients with stage 3 lung cancer (see Appendix), and up to 70% in patients with stage 1 disease (Phillips et al 2003).

OTHER ISSUES

No issues were raised at the time of preparing the original prioritising summary.

CONCLUSION:

A quick, accurate and non-invasive method for detecting lung cancer in high risk patients has the potential for benefits both in terms of cost effectiveness and health related outcomes.

HEALTHPACT ACTION:

This technology is still in the developmental stage and lacks good quality evidence to support its effectiveness, despite new evidence supporting the use of breath tests in other applications it is therefore recommended that this technology be archived.

SOURCES OF FURTHER INFORMATION:

Australian Institute of Health and Welfare (AIHW) & Australasian Association of Cancer Registries (AACR) 2003. Cancer in Australia 2000. AIHW cat. no. CAN 18. Canberra: AIHW (Cancer Series no. 23).

Australian Institute of Health and Welfare (2004). *Interactive Cancer Data* [Internet] Available at [Accessed 7th October, 2004].

Cancer Council Australia (2004). *Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer.* [Internet] Available at http://www.nhmrc.gov.au/publications/pdf/cp97.pdf [Accessed 7th October, 2004].

Deng, C., Zhang, X. & Li, N. (2004). 'Investigation of volatile biomarkers in lung cancer blood using solid-phase microextraction and capillary gas chromatography-mass spectrometry', *J Chromatogr B Analyt Technol Biomed Life Sci*, 808 (2), 269-277.

Gordon, S. M., Szidon, J. P. et al (1985). 'Volatile organic compounds in exhaled air from patients with lung cancer', *Clin Chem*, 31 (8), 1278-1282.

Machado, R. F., Laskowski, D. et al (2005). 'Detection of lung cancer by sensor array analyses of exhaled breath', *Am J Respir Crit Care Med*, 171 (11), 1286-1291.

Mathers, C., Penm, R., Sanson-Fisher, R., Carter, R., Campbell, E. [Internet] *Health Systems costs of cancer in Australia 1993 -1994.* Available at http://www.aihw.gov.au/publications/hwe/hscca93-94/hscca93-94-c03.pdf Accessed 22nd September, 2004].

Medline Plus (2002). *Stages of Cancer* [Internet]. American Accreditation HealthCare Commission. Available from: http://www.nlm.nih.gov/medlineplus/ency/imagepages/19222.htm [Accessed 19th October 2004].

Menssana Research (2004). *Breathtaking Technology* [Internet] Available at http://www.menssanaresearch.com/ [Accessed 22nd September, 2004]

Ost, D., Shah, R. D. et al (2003). 'To screen or not to screen: a volatile issue in lung cancer', *Chest,* 123 (6), 1788-1792.

Phillips, M., Altorki, N. et al (2005). 'Prediction of lung cancer using volatile biomarkers in breath', Conference Proceeding: 2005 ASCO Annual Meeting, Orlando, Florida, In: *Journal of Clinical Oncology,* 23(16S), 839S.

Phillips, M., Cataneo, R. N. et al (2003). 'Detection of lung cancer with volatile markers in the breath', *Chest,* 123 (6), 2115-2123.

Phillips, M., Gleeson, K. et al (1999). 'Volatile organic compounds in breath as markers of lung cancer: a cross-sectional study', *Lancet,* 353 (9168), 1930-1933.

Yu, H., Xu, L. & Wang, P. (2005). 'Solid phase microextraction for analysis of alkanes and aromatic hydrocarbons in human breath', *J Chromatogr B Analyt Technol Biomed Life Sci,* 826 (1-2), 69-74.

SEARCH CRITERIA TO BE USED:

Alkanes/metabolism

Breath Tests/ methods

Bronchoscopy

Lung Neoplasms/ diagnosis/secondary

Tumor Markers, Biological/ analysis

APPENDIX:

Stages of cancer

The staging of a carcinoma has to do with the size of the tumour, and the degree to which it has penetrated. When the tumour is small and has not penetrated the mucosal layer, it is said to be stage I cancer. Stage II tumours are into the muscle wall, and stage III involves nearby lymph nodes. The rare stage IV cancer has spread (metastasised) to remote organs (Medline Plus 2002).