Horizon Scan Report 0006 **20 May 2009**

Diagnostic Technology:
A portable handheld electronic nose in the diagnosis of cancer, asthma and infection

Clinical Questions:

1. In community-based settings, is an electronic nose effective in the diagnosis of patients with lung cancer compared to standard practice
2. In community-based settings, is an electronic nose effective in the diagnosis of patients with mild asthma compared to standard practice
3. In community-based settings, is an electronic nose effective in the identification of bacterial infections (ear, nose and throat; urinary tract; bacterial vaginosis), compared to laboratory analysis

Device:
Cyranose 320
Smiths Detections, Pasadena, CA, USA;
UK Office: Watford, Herts WD17 1DA

Other devices:
Osmetech microbial analyser, Osmetech plc, Crewe, UK
E-nose 1 model BH114, Bloodhound Sensors Ltd., Leeds, UK

Advantages over Existing Technology:
Early diagnosis of lung cancer is desirable, but available evidence does not support screening programmes with current techniques, such as chest radiography, sputum cytology or computed tomography (5,6). Breath analysis using electronic nose (e-nose) technology is a simple, non-invasive technique that can be easily performed and has the potential to be validated for use in screening for the early diagnosis of lung cancer.

Asthma is currently diagnosed and monitored by symptoms and physiological measurements, including lung function tests and the assessment of responses to inhaled pharmacological agents (9). These tests have been internationally standardized and are reliable. However, they may be complex and time-consuming, and in some cases mild asthma may be difficult to diagnose. E-nose as a new diagnostic method in asthma is simple, fast, accurate, and may be more cost-effective (3).

Sinusitis may be cause by bacterial or viral pathogens and can be difficult to diagnose. Bacterial sinusitis is currently diagnosed by clinical criteria combined with identification of bacterial pathogens in cultures of sinus secretions (14). Antibiotics are frequently prescribed presumptively as bacterial cultures require 48h for identification. Rapid and accurate diagnosis of bacterial sinusitis would reduce unnecessary prescription of antibiotics and provide a real time guide for physicians in the choice of antibiotics.

Urinary tract infections are currently diagnosed by clinical symptoms with confirmation by urinalysis and sometimes urine culture (14). E-nose would allow for the rapid evaluation of the specific bacterial pathogen, improving antibiotic choice. Bacterial vaginosis may be confused with yeast infections, is therefore often unrecognised and may be asymptomatic. E-nose technology could be integrated into routine examinations, improving the recognition of bacterial vaginosis (16).

Details of Technology:
The electronic nose was first developed by NASA to test the air onboard the International Space Station for dangerous compounds. The Cyranose 320 is a handheld portable chemical vapour analyzer, containing a nano-composite array with

32 polymer sensors. When exposed to a gas mixture the sensors swell, thereby changing the electrical resistance, resulting in a unique "smell-print". Exhaled breath contains thousands of gaseous volatile organic compounds (VOCs) that may be used as non-invasive biomarkers of disease (2,3). E-nose devices allow online recognition of complex VOC mixtures by composite nanosensor arrays in combination with learning algorithms. Patients exhale into a non-reactive gas sampling bag against pressure to ensure closure of the vellum. The VOCs in the bag are then analysed by the e-nose. For bacterial infections, swab samples are taken, which are placed into a closed clinical vial and tested using the e-nose after 5 min (8).

Patient Group and Use:

- Diagnosis of lung cancer and discrimination of patients with lung cancer from COPD patients (1)
- Diagnosis of patients with mild asthma (3)
- Real time, rapid diagnosis of ear, nose and throat infections (8, 13)
- Real time, rapid diagnosis of urinary tract infections and bacterial vaginosis (15,16)

Importance:

Lung cancer is the second most common cancer diagnosed in the UK and each year more than 38,000 people are diagnosed (7). Lung cancer survival rates are higher the earlier the cancer is diagnosed. More than two-thirds of lung cancers are diagnosed at a late stage and survival rates for these patients are lower. Overall, only 7% of lung cancer patients survive for at least five years after diagnosis.

5.4 million people in the UK are currently receiving treatment for asthma: 1.1 million children (1 in 11) and 4.3 million adults (1 in 12). It is the most common long-term medical condition and early diagnosis can facilitate management and reduce admission to emergency care (10).

Ear, nose and throat infections are some of the most common afflictions presenting to general practice. Urinary tract infection (UTI) is one of the bacterial infections most frequently managed in general practice, and is the reason for between 1% and 3% of all GP consultations (17). About 1 in 2 women will be treated for a symptomatic UTI during their lifetime. Bacterial vaginosis is the most common cause of vaginal discharge and may progress to pelvic inflammatory disease (17). It can be associated with preterm labour. Approximately 50% of women with bacterial vaginosis are asymptomatic.

Previous Research:

A cross-sectional blinded validation study in patients with confirmed bronchogenic carcinoma compared to controls, testing the potential of e-nose technology (Cyranose 320) for the diagnosis of lung cancer, showed that the e-nose had 71% sensitivity and 92% specificity for detecting lung cancer; positive and negative predictive values were 67% and 93%, respectively (4).

A further small case-control study examined the difference in VOC-pattern of exhaled breath between patients with a confirmed diagnosis of lung cancer and patients with COPD (1). The study population was divided into 3 groups of 10, i.e. patients affected by non-small cell lung cancer (NSCLC), patients with chronic obstructive pulmonary disease (COPD) and a healthy control group. The study concluded that the e-nose could distinguish the pattern of VOCs present in exhaled breath of lung cancer patients from that of patients with COPD. Furthermore, the e-nose could adequately discriminate patients with lung cancer from control subjects.

A cross-sectional case-control study with 40 participants showed that the e-nose could discriminate exhaled breath of patients with asthma from controls, but is less accurate in distinguishing asthma severities (3). Patients with severe asthma were older than patients with mild asthma ($P < 0.01$), therefore 2 control groups with ages below and above 45 years, respectively were used. "Smell-prints" of patients with mild asthma were fully separated from young controls (Cross-validation value [CVV], 100%), and patients with severe asthma could be distinguished from old controls (CVV, 90%). Patients with mild and severe asthma could be less well discriminated (CVV, 65%), whereas the 2 control groups were indistinguishable (CVV, 50%).

One study explored the use of the e-nose to identify and classify pathogens associated with ear, nose and throat (ENT) infections (8). Bacterial swab samples were collected from 90 patients with ENT infections. Samples were analysed with the Cyranose C320 and swabs taken from the same site of infection were sent for microbiology culture. The e-nose diagnosis was compared with microbiology culture and the electronic nose identification was correct in 88% of cases. Another study investigated the use of e-nose to diagnose bacterial sinusitis (13). The study compared 34 patients with clinically confirmed sinus infections and 34 control patients and, using a cross-validation approach, the e-nose accurately predicted the diagnosis in 72% of samples.

Other applications of e-nose technology include the diagnosis of urinary tract infections (UTI) and bacterial vaginosis. In UTI diagnosis, e-nose technology was able to distinguish four groups, i.e. normal urine, *Escherichia coli*, *Proteus* spp. and *Staphylococcus* spp. infected (15). Only one normal patient sample was mis-identified as an *E. coli* infected sample. The ability of e-nose to distinguish between bacterial species is particularly important in diagnosis, as it may inform the choice of antibiotic. In the diagnosis of bacterial vaginosis, e-nose technology had a sensitivity and specificity of 83% and 77% compared with Gram stain, and 81% and 76% compared to Amsel criteria (16). These studies, however, did not employ the handheld Cyranose 320, but used laboratory-based e-nose technology (Osmetech Microbial Analyser; Bloodhound BH114). The Osmetech Microbial Analyser received FDA approval as a laboratory-based screening device (18). The FDA study on 1038 urine samples for UTI reported a sensitivity of 81% (95% CI 74% to 87%), specificity 83% (95% CI 80 to 85%), PPV 44% (95% CI 38% to 50%), NPV 96% (95% CI 95% to 98%) and accuracy 83% (95% CI 80% to 85%). This may pave the way for the approval of other devices with similar applications.

Previous Research Overview:

Device	Disease	Population		PPV*	NPV*	Sensitivity	Specificity	Ref.
		Patients/Samples	Control/ Comparator					
Cyranose 320	Lung Cancer	14 patients, active nonresected, untreated lung cancer	30 non-smoking healthy; 12 with COPD; 2 with resected lung cancer in remission; 11 with asthma; 7 with pulmonary hypertension	66.6%	93.4%	71.4%	91.9%	4
		10 patients, non-small cell lung cancer (NSCLC)	10 healthy; 10 COPD	Not available. Cross Validation Values reported. CVV of 85% for distinction between Lung cancer and COPD patients CVV 80% and 90% (duplicate measurements) for distinction between Lung cancer patients and healthy controls				1
	Asthma	10 young patients (±25 years) with asthma; 10 old patients (±50 years) with asthma	10 young (±26 years) healthy; 10 old (±57 years) healthy	Not available. Cross Validation Values reported. CVV of 100% for distinction between mild asthma and young controls CVV of 90% for distinction between severe asthma and old controls CVV of 65% for distinction between mild and severe asthma CVV of 50% between 2 control groups i.e. no distinction				3
	ENT infection	90 patients with ENT infection	Compared to microbiological culture identification	88.2%	Not reported	Not reported	Not reported	8
	Bacterial sinusitis	34 patients with sinus infection	34 healthy	72%	Not reported	Not reported	Not reported	13
BH114	Urinary tract infection	45 urine samples	Compared to microbiological culture identification	95%	Not reported	Not reported	Not reported	15
Osmetech Microbial Analyser	Bacterial vaginosis	642 tested; 182 positive 665 tested; 188 positive	Compared to Gram Stain Compared to Amsel criteria	Not reported	Not reported	83% 81%	77% 76%	16
	Urinary tract infection	1038 urine samples	Standard culture and Uriscreen (Diatech Diagnostics, Inc)	81%	83%	44%	96%	18

*PPV = Positive predictive value; NPV = Negative predictive value

Research Questions:

Does e-nose technology accurately diagnose early stages of lung cancer?
What diagnostic value does e-nose technology provide in addition to usual clinical assessment of patients with mild asthma in primary care?
Does e-nose technology accurately diagnose bacterial infection (e.g. sinusitis, UTI, bacterial vaginosis) in primary care?
Is the use of e-nose technology in primary care cost effective?

Suggested next step:

1. Regarding lung cancer diagnosis, the studies reported are of limited size and show insufficient sensitivity. Larger studies are required, as well as studies using smokers, rather than healthy controls.
2. Regarding diagnosis of UTIs, the e-nose appears to be as effective as the currently employed dip sticks, however substantial advantages of the use of e-nose compared to dip sticks need to be demonstrated, as these are cheap and effective.
3. Overall, current research has not established the test accuracy of the e-nose. The technology is at the early stages of development and substantial further research in required to assess the utility in diagnosis.

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Comments:

This report was prepared by the Primary Care Diagnostic Horizon Scanning Centre Oxford
Contact details: Dr. Annette Plüddemann; Email: horizonscanning@dphpc.ox.ac.uk