The electronic nose technology in clinical diagnosis: A systematic review

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**Abstract**

**Background:** Volatile organic compounds (VOC) are end products of human metabolism (normal and disease-associated) that can be mainly excreted in breath, urine, and feces. Therefore, VOC can be very useful as markers of diseases and helpful for clinicians since its sampling is noninvasive, inexpensive, and painless. Electronic noses, or eNoses, provide an easy and inexpensive way to analyze gas samples. Thus, this device may be used for diagnosis, monitoring or phenotyping diseases according to specific breathprints (breath profile).

**Objective:** In this review, we summarize data showing the ability of eNose to be used as a noninvasive tool to improve diagnosis in clinical settings.

**Methods:** A PRISMA-oriented search was performed in PubMed and Cochrane Library. Only studies performed in humans and published since 2000 were included.

**Results:** A total of 48 original articles, 21 reviews, and 7 other documents were eligible and fully analyzed. The quality assessment of the selected studies was conducted according to the Standards for Reporting of Diagnostic Accuracy. Airway obstructive diseases were the most studied and Cyanose 320 was the most used eNose.

**Conclusions:** Several case–control studies were performed to test this technology in diverse fields. More than a half of the selected studies showed good accuracy. However, there are some limitations regarding sampling methodology, analysis, reproducibility, and external validation that need to be standardized. Additionally, it is urgent to test this technology in intend-to-treat populations. Thus, it is possible to think in the contribution of VOC analysis by eNoses in a clinical setting.

**Keywords:** breathomics, diagnosis, electronic nose, volatile organic compounds

**Introduction**

Biochemical and biomolecular diagnostic methods used in medicine have their focus on blood and urine analysis. Breath analysis using electronic nose technology (eNose) could integrate the current examination procedures to assist clinicians in diagnosis and monitoring, since it is a noninvasive sampling technique, painless, inexpensive and that can be easily performed by sick patients, children, and elderly alike. The potential of exhaled breath analysis appeared with Hippocrates when he described an odor of fetor hepaticus as a clinical marker which is now related with hepatic diseases. The compounds related with that smell were later discover by gas chromatography coupled with mass spectrometry (GC-MS). Breath of patients with hepatic conditions showed higher levels of dimethyl sulfide, acetone, 2-butanone, and 2-pentanone and lower levels of indole and dimethyl selenide.

Nowadays, exhaled breath is not the only type of sample used for gas analysis which can include fecal and urine headspaces. The term “headspace” is referred as the gas directly surrounding a sample. The constituents of the sample which have a high volatility will generally be present in the headspace in higher concentrations. Low volatile compounds are less likely to be found in a sample. Consequently, the concentration of molecules present in the headspace is not proportional to the concentration of the same molecules in liquid or solid sample.

The electronic nose or eNose is “an instrument which comprises an array of electronic chemical sensors with partial specificity and an appropriate pattern-recognition system, capable of recognizing simple or complex odours” (1994). This device mimics the mammalian olfactory system and can identify different complex odors comparing the incoming odor with patterns previously learnt. When an odor (chemical input) is presented to the eNose causes a physical change in the sensors which is detected by the transducers and converted into an electrical signal creating a specific signature or smellprint. The rise and decline of the signal depends on some parameters: nature of the odor (type and concentration of the compounds), reaction
and diffusion between odor and sensors, type of sensor, and ambient conditions. Methods based on mass spectrometry analysis can detect and identify which compounds are present in air samples being useful for pathophysiological research. Yet, these methods are time consuming, expensive, and depend on a skilled operator which makes them impractical to be applied at clinical settings. Electronic noses have the potential to overcome these disadvantages because they are relatively inexpensive, easy to use and provide a rapid analysis. To achieve this goal, it is necessary to create a prediction model with a training set of samples and external validate the model for further application.

The aim of this systematic review was to investigate how eNose technology may be applied as a noninvasive tool to improve diagnostic in clinical settings, based on published evidence. The clinical application of eNoses has been reviewed by some authors with special focus on pulmonary diseases, cancer, and gastroenterology. In this review, all published studies using eNose to diagnosis, phenotyping or monitoring diseases, pulmonary and extra pulmonary, are listed and discuss.

**Methods**

**Search strategy**

This systematic review was conducted following the PRISMA statement for authors of systematic reviews by searching for studies using the eNose technology as a diagnostic tool in medicine. The search was performed until the end of September 2017 in PubMed and Cochrane Library. The keywords “electronic nose” or “enose” and “diagnosis” or “diagnostic” or “phenotyping” or “phenotype” or “monitoring” were used. Full-text manuscripts in English published since January 2000, independently of the type of document (original article, review, comment, conference paper, letters, and book chapters), were assessed for eligibility. The adopted inclusion criteria were (a) diagnosis using electronic nose technology in clinical and medical applications; and (b) clinical trials. The exclusion criteria consisted of (a) trials not performed on human patients.

**Quality assessment**

The quality assessment of the selected studies was conducted according to the Standards for Reporting of Diagnostic Accuracy (STARD). The STARD statement was created to improve the quality of reporting diagnostic accuracy studies and incorporates a checklist of 30 items divided in 5 groups, covering the main sections of a scientific article, that should be included in the report of those studies. To better represent the quality assessment, STARD quality scores were defined: items reported in the study were classified as “Yes” and added 1 point to the score; items not reported or unclear were classified as “No” and “Unclear,” respectively, and added 0 points to the score (see Supplemental Digital Content, http://links.lww.com/PBJ/A1).

**Results**

**Study selection, characterization, and quality assessment**

The systematic search using the aforementioned methodology yielded 295 studies. After removal of duplicates, 286 studies were accepted for screening. However, this number was increased to 324 after the inclusion of studies found by reference list searching. During the screening of titles and abstracts using the prespecified inclusion criteria, 238 studies were rejected, yielding 86 studies for full revision. Each of those studies was then reviewed. Ten studies were later excluded: 4 articles were focused on eNose technology and other breath analysis methods, 3 were focused on volatile organic compounds (VOC) and associated diseases, and 3 studies regarded clinical application but not diagnosis or monitoring of a disease. Reasons to exclude the studies at this stage were discussed with members of the review team. Thus, 76 studies were included: 48 original articles, 21 reviews, and 7 other documents (comments, letters, and book chapter). Figure 1 shows the flow diagram of search and selection process.

The eNose technology applied in health field was tested in several diseases to verify its potential on diagnosis or monitoring. The diseases in which this technology was tested can be divided into 5 groups: airway obstructions, respiratory infections, inflammatory diseases, cancer, and other diseases. Airway obstructions group is the one which includes more research and published studies (18 original articles). Chronic obstructive pulmonary disease (COPD) and asthma are the most studied diseases using the eNose technology as a diagnostic tool, followed by obstructive sleep apnea syndrome (OSAS). The second group with 9 studies includes ear, nose, and throat (ENT) infections, ventilator-associated pneumonia (VAP), invasive aspergillosis (IA), and late-onset sepsis (LOS). The inflammatory diseases with only 5 studies are sarcoidosis, inflammatory bowel disease, arthritis, inflammatory answer to ozone, and acute respiratory distress syndrome (ARDS). Furthermore, this technology has been applied to investigate the possibility of diagnosis different type of cancers, such as lung cancer, prostate cancer, colorectal cancer, and malignant pleural mesothelioma (MPM). The other diseases that have been under investigation are cystic fibrosis, halitosis, amyotrophic lateral sclerosis (ALS), and renal dysfunction. The most commonly used eNose, in 81% of the studies, was the Cyranose 320 (Sensigent, Baldwin Park, CA) and the most current methodology for sampling collection consisted of using Tedlar Bags for trapping the exhaled breath after 5 minutes of tidal breathing through a VOC filter, to eliminate the influence of environmental VOC in the samples and was primarily described by Dragonieri et al. This methodology was used in 44% of the studies. Considering a cross-validation value (CVV) or an area under the curve (AUC) of 80% or more, 50% of the studies achieved those requirements (65% if we consider only-studies that presented CVV or AUC values). However, only 10% of all studies performed external validation in a new recruited population. The summarized overview of the collected information is presented at Table 1, and most important outcomes are presented in the discussion (Table 1). Table 2 presents the main results of reviews, comments, and book chapters found in the literature (Table 2).

**Study population**

An overview of the included studies is presented in Table 1. The population used in each study vary significantly, from 10 (3 cases and 7 controls) to 171 participants (25 cases and 166 controls). In several studies, control group was composed by healthy subjects but in some cases participants with other health conditions or with smoking habits were included. The studies were conducted in several countries of Europe, North America, Asia, and Australia. The leader country with more investigation in this field was the Netherlands, with 19 studies. Seven studies evaluated more than 1 condition per survey, supporting the potential of using eNose for differential diagnosis.
Discussion

Diagnosis of airway obstructive diseases

The present review study presents an overview of eNose performance on diagnosis and phenotyping of diseases. Most of the included studies (18 original articles) concerned common airway obstructive diseases, such as COPD and asthma, and the VOC patterns were analyzed to differentiate these conditions, or to compare them with breathprints of other airway diseases, such as lung cancer.

Dragonieri et al found that COPD and nonsmall cell lung cancer have different exhaled VOC patterns which could be distinguished by eNose with a CVV of 85%.\(^1\) Furthermore, patients with nonsmall cell lung cancer could also be distinguished from healthy controls with a CVV of 80% or 90% when duplicates measurements were analyzed. At the same year, Fens et al published a study aiming to separate VOC profiles between COPD and asthma patients.\(^2\) They found different breath profiles between asthma subjects and COPD patients with an accuracy of 96%, as well as between nonsmoking controls and smoking controls with accuracies values of 95% and 92.5%, respectively. Later, the same group of authors conducted a study to externally validate the previous results, following STARD guidelines.\(^3\) The external validity of breath profiles showed that fixed asthma and classic asthma can be discriminated from COPD patients with high accuracy (88% and 83%, respectively) and sensitivity and specificity values varied from 85% up to 91% and 90%, respectively. Fens et al were able to differentiate mild and moderate types of COPD not only using eNose technology but also using mass spectrometry (GC-MS) and computed...
Table 1
Characteristics and main results of the included original studies

| Ref. | Year | Country | Aim | Demographics | Matrix | Short conclusions | Tests ef. efficacy |
|------|------|---------|-----|--------------|--------|-------------------|-------------------|
| 14   | 2009 | The Netherlands | Differential diagnosis (lung cancer and COPD) | 10 patients with neoplastic cell lung cancer; 10 patients with COPD; 10 healthy controls | Cyranose 320 | VOC patterns of EB distinguished patients with lung cancer from COPD patients as well as healthy controls | — |
| 15   | 2009 | The Netherlands | Differential diagnosis (COPD and asthma) | 90 patients: 30 with COPD, 20 with asthma, 20 non-smoking controls, 20 smoking controls | Cyranose 320 | eNose distinguished patients with COPD and asthma and control subjects. EB profiles of patients with COPD partially overlaps with those of asymptomatic smokers | CVV Asthma/COPD: 96% |
| 16   | 2011 | The Netherlands | Differential diagnosis (COPD and asthma) | 60 asthma patients: 21 with fixed obstruction (fixed asthma), 9 with reversible obstruction (classic asthma), and 40 COPD patients (GOLD stages II-IV) | Cyranose 320 | External validation of EB molecular profiling showed high accuracy to distinguish asthma and COPD | — |
| 17   | 2011 | The Netherlands | Discriminate inflammatory subtype in mild and moderate COPD | 28 COPD patients | Cyranose 320 | Exhaled molecular profiling by GC-MS and by eNose is closely associated with cell counts and markers of inflammatory cell activation in induced sputum of patients with COPD. ROC analysis for eNose showed high sensitivity and specificity for inflammatory activity in mild COPD but not for moderate COPD | — |
| 18   | 2013 | The Netherlands | COPD phenotyping | 157 patients with different stages of COPD | Cyranose 320 | Taxonomy for mild to moderate COPD reinforces clusters found in previous studies and thereby allows better phenotyping of COPD in the general smoking population. Symptoms, spirometry, computed tomography lung density and exhaled molecular profiling all contributed significantly to distinguish COPD subphenotypes | — |
| 19   | 2011 | Germany | COPD with and without AATD diagnosis | 30 healthy controls; 10 patients with COPD with AATD (AATD); 23 patients with COPD without AATD (COPD) | Cyranose 320 | Sensitivity of patients with AATD were different from those with COPD in EBC and EB | — |
| 20   | 2014 | Spain | Discriminate COPD patients with and without airway BC | 37 clinically stable COPD patients: 10 with BC, 27 without BC; 13 healthy controls | Cyranose 320 | An eNose can identify the presence of airway BC in clinically stable patients with COPD | — |
| 21   | 2016 | The Netherlands | Detect a viral or bacterial cause of acute exacerbations of COPD | 43 patients: 13 with viral infection, 9 with bacterial infections, 9 with viral and bacterial infection, 12 with no infection | Aeroneose | The eNose was able to detect the presence or absence of a viral or bacterial respiratory infection during an acute exacerbation of COPD | — |
| 22   | 2012 | Australia | Discriminate COPD and asthma with and without GORD | 44 patients: 7 controls, 11 asthmatics, 9 with GORD, 8 with COPD, 9 with COPD with GORD | Cyranose 320 | The eNose distinguished EB profiles of asthmatic patients with reflux from asthmatics without GORD but did not produce a robust profile for patients with COPD and GORD. | — |
| 23   | 2007 | The Netherlands | Asthma diagnosis | 40 patients: 10 young with mild asthma, 10 young controls, 10 older with severe asthma, 10 older controls | Cyranose 320 | The eNose distinguished EB profiles of patients with asthma from controls but was less accurate in distinguishing asthma severities. Mild vs controls = 100%; Severe vs controls = 96%; Mild vs severe = 65% | — |
| 24   | 2010 | Hungary | Identify if breathprints are independent of changes in airway caliber in asthma | 10 patients: 7 healthy, 3 with asthma | Cyranose 320 | Breathprints were not confounded by the level of airway obstruction | — |
| 25   | 2013 | The Netherlands | Asthma diagnosis | 25 patients with mild/moderate asthma | Cyranose 320 | Breathprints can identify asthmatic patients and may be used to predict their response to steroids with greater accuracy than sputum eosinophils or FeNO | — |
| 26   | 2015 | Spain | Asthma phenotypes diagnosis | | Cyranose 320 | | — |

(continued)
| Ref | Year | Country | Aim | Demographics | eNose | Matrix | Short conclusions | Tests efficacy |
|-----|------|---------|-----|--------------|-------|--------|------------------|----------------|
| 26  | 2017 | The Netherlands | Asthma diagnosis | 52 patients with persistent asthma: 24 eosinophilic, 10 neutrophilic, 18 paucigranulocytic | Cyranose 320 | EB | eNose can discriminate inflammatory phenotypes in patients with persistent asthma in a regular clinical setting | — |
| 27  | 2015 | Morocco | Allergic rhinitis | Neutrophilic vs eosinophilic: 60% | Cyranose 320 | EB | Loss of asthma control can be discriminated from clinically stable episodes by longitudinal monitoring of EB using an eNose | Sensitivity: 28%; Specificity: 70% |
| 28  | 2013 | Hungary | OSAS diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | An eNose system based on 6 gas sensors discriminated the breath samples of rhinitis patients and controls | Sensitivity: 69%; Specificity: 92% |
| 29  | 2015 | Italy | OSAS diagnosis (obese population) | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | OSAS patients had a different breathprint that might reflect accelerated airway and/or systemic inflammation | Sensitivity: 82%; Specificity: 80% |
| 30  | 2015 | Germany | OSAS diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 31  | 2016 | Italy | Differential diagnosis (OVS, OSAS, and COPD) | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 32  | 2004 | USA | VAP diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 33  | 2005 | USA | VAP diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 34  | 2015 | The Netherlands | VAP diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 35  | 2014 | The Netherlands | Lung cancer diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 36  | 2015 | Canada | Lung cancer diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 37  | 2012 | Australia | MM diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 38  | 2012 | Italy | MPM diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |
| 39  | 2004 | UK | ENT infections diagnosis | Neutrophilic vs eosinophilic: 60%; Eosinophilic vs paucigranulocytic: 55% | Cyranose 320 | EB | — | — |

(continued)
Table 1 (continued).

| Ref. | Year | Country | AIM | Demographics | eNose | Matrix | Short conclusions | Test efficacy |
|------|------|---------|-----|--------------|-------|--------|------------------|--------------|
| 47   | 2005 | UK      | ENT infections diagnosis | 150 patients; 50 different patients for each type of bacterial subspecies | Cyranose 320 | Headspace of a vial with a swab | eNose is able to identify 3 bacteria subclasses with 99.69% accuracy with the application of the RBF network along with Cyranose 320 | CVV: 99.69% |
| 48   | 2006 | USA     | Bacterial sinusitis diagnosis | 45 patients with sinus infections, 34 controls | Cyranose 320 | EB | eNose was able to predict the diagnosis of sinusitis in at least 72% of the samples using the external validation methodology | CVV: 72% |
| 49   | 2004 | Japan   | Oral malodor | 29 healthy controls; 49 patients with oral malodor treated with Lactobacillus brevis CDDs-containing tablets and 10 with placebo | FF-1 odor analyzer | EB | eNose can be used in addition to OralChroma to assess the initial condition of halitosis | AUC: 0.879 |
| 50   | 2015 | Italy   | Monitoring the treatment of patients with halitosis | 10 treated patients with Lactobacillus brevis CDDs-containing tablets and 10 with placebo | BIONOTE | EB | BIONOTE can be used in addition to OralChroma to assess the initial condition of halitosis | — |
| 51   | 2013 | The Netherlands | Differential diagnosis (CF and PCD) | 25 children with CF, 25 with PCD and 25 controls | Cyranose 320 | EB | eNose can detect AC with moderate to good accuracy | Sensitivity: CF/controls: 84%; PCD/controls: 67%; PCD/CF: 71%; AUC: 0.75; Specificity: CF/controls: 63%; PCD/controls: 67%; PCD/CF: 62%
| 52   | 2014 | Denmark | Differential diagnosis (CF and PCD) | 64 patients with CF: 21 with PCD; 21 healthy controls | Cyranose 320 | EB | eNose can discriminate between patients with and without ARDS with modest accuracy. Diagnostic accuracy increased when only moderate and severe ARDS patients were considered | Sensitivity: CF/controls: 68%; PCD/controls: 67%; PCD/CF: 71%; AUC: 0.75; Specificity: CF/controls: 63%; PCD/controls: 67%; PCD/CF: 65% |
| 53   | 2014 | The Netherlands | ARDS diagnosis | 98 patients with ARDS, 92 controls | Cyranose 320 | EB | eNose can discriminate between patients with and without ARDS with modest accuracy. Diagnostic accuracy increased when only moderate and severe ARDS patients were considered | Sensitivity: CF/controls: 68%; PCD/controls: 67%; PCD/CF: 71%; AUC: 0.75; Specificity: CF/controls: 63%; PCD/controls: 67%; PCD/CF: 65% |
| 54   | 2013 | The Netherlands | Sarcoidosis diagnosis | 11 sarcoidosis patients; 20 patients with treated pulmonary sarcoidosis; 25 healthy controls | Cyranose 320 | EB | Breathprints from patients with sarcoidosis could be distinguished from healthy controls. However, breathprints of untreated sarcoidosis patients were barely separated from those of the treated sarcoidosis group, with cross-validated accuracy of 74.2% | Sensitivity: CF/controls: 78%; PCD/controls: 71%; AUC: 0.87 | Specificity: CF/controls: 94%; PCD/controls: 84% | AUC: 0.87 |
| 55   | 2014 | The Netherlands | CRC and adenomas diagnosis | 100 patients: 40 with CRC; 60 with adenomas; 57 healthy controls | Cyranose 320 | EB | Fecal gas can be used to differentiate between advanced adenomas and CRC by fecal gas analysis | Sensitivity: CRC/controls: 86%; adenomas/controls: 82%; CRC/adenomas: 75%; Specificity: CRC/controls: 87%; adenomas/controls: 86%; CRC/adenomas: 73%; AUC: 0.89; AUC CRC/controls: 0.92; adenomas/controls: 0.80; CRC/adenomas: 0.68 | Sensitivity: 79%; Specificity: 80% | AUC: 0.89 |
| 56   | 2015 | Germany | BCa diagnosis | 36 patients: 15 with the clinical suspicion of BCa; 21 without BCa but benign urological condition | Cyranose 320 | EB | Breathprints from patients with BCa were discriminated from healthy controls. However, breathprints of patients with BCa were barely separated from those of the treated BCa group, with cross-validated accuracy of 74.2% | Sensitivity: CF/controls: 78%; PCD/controls: 71%; AUC: 0.87 | Specificity: CF/controls: 94%; PCD/controls: 84% | AUC: 0.87 |
| 57   | 2014 | Finland | Prostate cancer diagnosis | 50 patients: 50 with prostate cancer; 15 with benign prostatic hyperplasia | ChemPro 100-eNose | Urine sample headspace | The eNose was able to discriminate prostate cancer and benign prostatic hyperplasia | Sensitivity: 78%; Specificity: 67%; AUC: 0.77 | Sensitivity: 78%; Specificity: 80%; AUC: 0.87 |
| 58   | 2016 | Italy | ALS diagnosis | 20 ALS patients; 20 healthy controls | Cyranose 320 | EB | Breathprints from patients with ALS were discriminated from healthy controls | Sensitivity: 100%; Specificity: 85.3%; AUC: 0.93 | Sensitivity: 78%; Specificity: 80%; AUC: 0.87 |
| 59   | 2013 | The Netherlands | IA diagnosis | 6 controls and 5 patients with IA | Cyranose 320 | EB | Breathprints from patients with IA had an elevated VOC profile distinct from the controls | Sensitivity: 78%; Specificity: 80%; AUC: 0.87 | Sensitivity: 78%; Specificity: 80%; AUC: 0.87 |
| 60   | 2004 | Germany | Renal dysfunction diagnosis | 42 patients with end-stage renal failure; 20 patients with chronic renal failure; 11 healthy controls | Cyranose 320 | EB | Breathprints from patients with IA had an elevated VOC profile distinct from the controls | Sensitivity: 78%; Specificity: 80%; AUC: 0.87 | Sensitivity: 78%; Specificity: 80%; AUC: 0.87 |
| 61   | 2016 | The Netherlands | Predict LOS at a preclinical stage | 36 infants with LOS; 40 controls | Cyranose 320 | EB | Breathprints from patients with IA had an elevated VOC profile distinct from the controls | Sensitivity: 78%; Specificity: 80%; AUC: 0.87 | Sensitivity: 78%; Specificity: 80%; AUC: 0.87 |

(continued)
| Ref. | Year | Country     | Aim                                      | Demographics                                                                 | eNose       | Matrix      | Short conclusions                                                                                           | Tests efficacy |
|------|------|-------------|------------------------------------------|-------------------------------------------------------------------------------|-------------|-------------|----------------------------------------------------------------------------------------------------------|----------------|
| 57   | 2014 | The Netherlands | Differential diagnosis (CD and UC). | 26 patients with UC, 26 patients with CD, 28 controls                             | Fecal samples (fecal gas) | Cyranose 330 | Fecal VOC profiles of preterm infants with LOS could be discriminated from matched controls, up to 3 days before clinical onset of the disease | Sensitivity: 57.1% Specifity: 61.5% AUC: 0.70 Sensitivity: Active disease: UC vs controls: 100% CD vs controls: 86% CD vs UC: 97% Clinical remission: UC vs controls: 94% CD vs controls: 94% CD vs UC: 88% Specifity: Active disease: UC vs controls: 100% CD vs controls: 67% CD vs UC: 92% Clinical remission: UC vs controls: 94% CD vs controls: 94% CD vs UC: 72% AUC: Active disease: UC vs controls: 1.00 CD vs controls: 0.85 CD vs UC: 0.86 Clinical remission: UC vs controls: 0.94 CD vs controls: 0.94 CD vs UC: 0.84 CD vs UC: 0.81 Sensitivity: RA vs controls: 76% PsA vs controls: 72% RA vs PsA: 71% Specifity: RA vs controls: 67% PsA vs controls: 77% RA vs PsA: 72% AUC: RA vs controls: 0.75 PsA vs controls: 0.77 RA vs PsA: 0.72 CVV: RA vs controls: 71% PsA vs controls: 63% RA vs PsA: 69% |  |
| 58   | 2016 | The Netherlands | Differential diagnosis (RA and PsA). | 21 RA patients; 18 PsA patients; 21 control subjects                                    | EB          | Cyranose 330 | EB profiles as measured by the eNose did not reflect airway responses to ozone |  |
| 59   | 2016 | Germany      | Detect inflammatory airway response induced by ozone inhalation. | 14 healthy subjects                                                               | EB          | Cyranose 330 | EB profiles as measured by the eNose did not reflect airway responses to ozone |  |
| 60   | 2014 | Germany      | Detect inflammatory airway response induced by ozone inhalation. | 28 intubated preterm neonates                                                      | Tracheal aspirates | Cyranose 330 | Tracheal aspirates can discriminate between preterm neonates with or without laboratory-confirmed bloodstream infections |  |

Notes: 57-60 = Fecal samples (fecal gas), 57 = Fecal VOC profiling of preterm infants with LOS could be discriminated from matched controls, up to 3 days before clinical onset of the disease. 58-60 = EB profiles as measured by the eNose did not reflect airway responses to ozone.

**Abbreviations:** AATD = alpha 1-antitrypsin deficiency, AC = Aspergillus fumigatus colonization, ALS = amyotrophic lateral sclerosis, ARDS = acute respiratory distress syndrome, ARDs = asbestos-related diseases, AUC = area under the ROC curve, BAL = bronchoalveolar lavage, BC = bacterial colonization, BCA = bladder cancer, CD = Crohn disease, CF = cystic fibrosis, COPD = chronic obstructive pulmonary disease, CP = chronic pulmonary Pseudomonas aeruginosa infection, CRC = colorectal cancer, CVV = cross-validation value, EB = exhaled breath, EBC = exhaled breath condensate, eNose = electronic nose, ENT = ear, nose, and throat, IA = invasive aspergillosis, IBD = inflammatory bowel disease, ICS = inhaled corticosteroid, LOS = late-onset sepsis, MM = malignant mesothelioma, MPM = malignant pleural mesothelioma, OVS = obstructive sleep apnea syndrome, OSAS = obstructive sleep apnea syndrome, PaO2 = primary oliguric nephritis, PsA = psoriatic arthritis, RA = rheumatoid arthritis, ROC = receiver operating characteristic, UC = ulcerative colitis, VAP = ventilator-associated pneumonia, VOC = volatile organic compounds.
| Ref. | Year | Type of document | Objectives | Conclusions |
|------|------|------------------|------------|-------------|
| 61   | 2000 | Review           | Discuss current status of electronic nose technology and its link to medicine | The diagnostic power of odors is a very old practice which is being rediscovered due to new advances in gas sensor technology and artificial intelligence. |
| 62   | 2004 | Review           | Describe and evaluate electronic olfaction technology to monitor the presence of VOC from human body and breath that can be used to evaluate status of diabetes | Despite the potential advantages of electronic olfaction blood glucose, monitoring remains the major method for monitoring glycometabolic status in diabetics. |
| 63   | 2004 | Review           | Present an overview of the most important recent developments, illustrates some applications for the diagnosis of infections and discusses future trends | The development of robust instrumentation, coupled with remote data acquisition and central processing powered by hybrid intelligence systems, could see eNose technology in common use in the next 5 years. |
| 64   | 2005 | Book chapter    | Bronchogenic carcinoma diagnosis | The exhaled breath of patients with lung cancer has distinct characteristics that can be identified with an eNose. |
| 65   | 2010 | Review           | eNose as a diagnostic tool in otolaryngology | eNose technology holds significant potential for enabling rapid, noninvasive, bedside diagnosis of otolaryngologic disease. |
| 66   | 2011 | Review           | To review the fast-developing topic of assessment of exhaled breath components to improve the diagnosis and monitoring of respiratory and systemic diseases | Examination of exhaled breath has the potential to change the existing routine approaches in human medicine. |
| 67   | 2011 | Review           | Specific profiles of volatile compounds in exhaled breath and metabolites in EBC are potentially useful markers of inflammatory respiratory diseases | There are several current limitations that have hindered the development of eNose medical applications in the medical industry. One major problem is that there has not been sufficient trial in-hospital testing of eNose instruments to determine the capabilities, feasibility, and performance of these instruments for specific tasks. |
| 68   | 2011 | Review           | Summarize the major eNose technologies developed for healthcare and biomedical applications since the late 1980s | Should we replace mammalian scent detection with a machine or return to teaching physicians to sniff? |
| 69   | 2011 | Comment          | — | — |
| 70   | 2012 | Review           | Techniques potentially useful for identifying biomarkers of pulmonary inflammation and oxidative stress | Different techniques could enable an early identification of subgroups of healthy smokers at higher risk for tobacco-induced lung damage. eNose differentiates healthy smokers from healthy nonsmokers based on breath VOC patterns. |
| 71   | 2013 | Review           | To review the current status on clinical validation and application of breath analysis by eNose in the diagnosis and monitoring of chronic airway diseases | Several proofs of concept studies have shown promising results for diagnosing different (airway) diseases, but there are still a lot of limitations. |
| 72   | 2013 | Editorial        | Review breathomics in sleep apnea | Taken together, composite metabolomics analysis of exhaled breath can become an aid in the diagnostic work-up and monitoring of OSAS, similar to inflammatory airways diseases. |
| 73   | 2013 | Editorial        | What method would you use to identify asthma in a symptomatic patient, and how would you attempt to predict treatment response? | So far, no single indicator has been identified as definitive of asthma, and pattern recognition approaches have promising properties. Following larger population studies and further technological advances, the eNose certainly has the potential to become a good tracker of asthma, initially in the hands of researchers and perhaps in the longer term also in clinical practice. |
| 74   | 2013 | Letter to editor | eNose can detect changes in exhaled breath molecular profiles during the endonasal laser ablation (EVLA) procedure | In conclusion, in this small study we did not find an association between the breathprints and changes of perceived taste or smell. |
| 75   | 2014 | Review           | Cover various upper and lower airway sampling methods | eNose and breath condensate have potential biomarker application but still require standardization and additional study. |
| 76   | 2014 | Review           | Review current sensor instruments and their application in the detection of gas phase volatile compound biomarkers in medicine—focusing on gastroenterology | Gas phase volatile compound biomarkers offer the potential for future diagnostics in gastroenterology. The eNose stands up to the challenge as evidence mounts in favor of its support. |
| 77   | 2014 | Review           | Analyze the limitations of traditional imaging techniques in the early detection of lung cancer, illustrate possible mechanisms of the production of VOC in cancerous cells, present evidence that supports the detection of such disease | The analysis of breath VOC is a choice for the early detection of lung cancer compared to imaging techniques. We recommend a more comprehensive technique that integrates the analysis of VOC and non-VOC in breath. In addition, VOlaw in urine may also be a trend in research on the early detection of lung cancer. |
| Ref. | Year | Type of document | Objectives | Conclusions |
|------|------|------------------|------------|-------------|
| 77   | 2014 | Book chapter     | Review the current state of the metabolomics of asthma and airway inflammation with a focus on the different methods and instrumentation being used for the discovery of biomarkers in research and their future translation into the clinic as diagnostic aids for the choice of patient-specific therapies. | — |
| 78   | 2014 | Review           | Discuss recent improvements and directions in the development of breath VOC analysis and diagnosis platforms that offer the potential for disease biomarker discovery and disease prognosis. | Exhaled VOC have the potential to aid rapid disease detection, prognostication, and drug response. However, a major challenge limiting the application of this approach is the lack of standardization in breath collection, profiling detection platforms, and robust statistical analyses. The eNose offers the prospect of noninvasive, standardized detection of prostate cancer in any setting. Further studies are required to optimize the detection protocol and to determine whether the eNose is also capable of providing a measure of cancer aggressiveness. |
| 79   | 2014 | Comment          | —          | — |
| 80   | 2015 | Review           | To describe a wide range of eNoses and summarize data on the methodological issues in eNose research. Review studies which show the ability of eNoses to distinguish pulmonary and extrapulmonary disorders. | Most studies using eNoses have compared cancer patients to healthy controls. It is possible that VOC patterns in the breath change as the result of poor health in general, and not specifically because of cancer. |
| 81   | 2015 | Review           | Summarize and analyze past research and outline future directions to improve understanding of both canine olfaction and eNose technology. | Analyses of exhaled breath yielded promising results, although standardization of breath collection, sample storage, and data handling remain critical issues. This empirical evaluation showed that it is not meaningful to estimate the diagnostic performance on a training set alone, even after internal validation. Therefore, we recommend the inclusion of an external validation set in all future eNose projects in medicine. |
| 82   | 2015 | Systematic review | Summarize the current evidence of exhaled breath analysis for cancer detection using standard analysis techniques and eNose. Empirically evaluate and compare the influence of different dimension reduction, classification, and validation methods found in published studies on the diagnostic performance in several datasets. | VOC profile seems to be able to accurately diagnose and monitor various diseases. However, multiple limitations, including validation and standardization of sampling and analysis, need to be overcome before VOC can be used in clinical practice. |
| 83   | 2015 | Review           | Review the currently technologies in breathomics with a special focus on technical issues, such as sampling, sample analysis, and data processing. | VOC has the potential role of VOC analysis as a mass screening tool for colorectal cancer (CRC). |
| 84   | 2016 | Review           | Evaluate the data obtained by using breathomics in (1) predicting the inception of asthma or COPD, (2) inflammatory phenotyping, (3) exacerbation prediction, and (4) treatment stratification. | Despite the limitations of VOC analysis, greater clinical interest and wider adoption will allow for more clinical trials to independently validate many observations already reported. |
| 85   | 2016 | Review           | Provide a clinical background of VOC identification, eNose development, and review gastroenterology applications toward diagnosis. | The reliability of a metabolomic approach in CRC screening as a noninvasive biomarker is supported by this review despite several limitations due to the number of patients included in each study, the different analytical platforms and the biological material used, and different VOC identified. |

COPD = chronic obstructive pulmonary disease, EBC = exhaled breath condensate, eNose = electronic nose, EVLA = endovenous laser ablation, NMR = nuclear magnetic resonance, OSAS = obstructive sleep apnea syndrome, VOC = volatile organic compounds.
tomography scanning. Interestingly, the group found that eNose breathprints could be related with activation markers of eosinophils and neutrophils in mild asthma, suggesting that the eNose may not only be useful for asthma diagnosis, but also for phenotyping. Another successful application of the eNose was demonstrated in a study where individuals with COPD were discriminated according to their alpha 1-antitrypsin deficiency. The eNose was also able to discriminate COPD patients with and without airway bacterial colonization or identify the presence of a viral or bacterial cause in acute exacerbations.

However, the first study using breathprint analysis of exhaled VOC by an eNose in airway obstructions was conducted in patients with mild and severe asthma. In this study, the degree of asthma severity was not discriminated by eNose, although it was able to distinguish asthma patients from controls with an accuracy of 90%. These results were further confirmed by another group and a sensitivity of 80% was reached, despite the low specificity of 65%. These results can be explained by the differences in methodologies, namely due to the effects of treatment that was discontinued in one of the studies. Nevertheless, changes in the airway caliber in asthma have been shown to not affect the breathprints. A recent study involving obese patients without OSAS (CVA: 67.6%). In a pilot study, we were able to distinguish asthma patients from controls with an accuracy [CVA: 97.4%], but were only moderate distinct from obese patients with OSAS [CVA: 67.6%]. Both technologies were able to distinguish breathprints of patients with asthma were also evaluated in a longitudinal study using 2 different approaches to analyze breath samples (GC-MS and eNose). Both technologies were able to distinguish breathprints of patients collected during baseline, loss of control, and during recovery time. eNose technology had a higher accuracy than mass spectrometry (86–95% and 68–77%, respectively).

OSAS was primarily investigated by Benedek et al that discovered the potential of the eNose technology in discriminating OSAS from non-OSAS patients in a pediatric population (sensitivity: 78%, specificity: 70%, AUC: 0.80). These results are similar to those reported by Greulich et al sensitivity: 93%, specificity: 70%, AUC: 0.85). Obesity was also found to affect the pattern of exhaled breath since obese patients with OSAS were discriminated from health controls (cross validation accuracy [CVA]: 97.4%), but were only moderate distinct from obese patients without OSAS (CVA: 67.6%). In a pilot study, OSAS breathprints were compared to OVS (overlap syndrome) and COPD. Patients with OSAS clustered distinctly from those with OVS as well as from those with COPD (AUC: 1.00 and 0.83), but patients with OVS were not significantly different from those with COPD (AUC: 0.60).

The significant interest of researchers in studying eNose technology as a diagnosis tool is notable, especially concerning airway obstructive diseases. Clinical diagnosis can be difficult because of related symptoms between different diseases, which makes breathprint analysis very useful if further research confirms these primary results. Diagnosis is not the only application of breathprint analysis, as it also appears to be promising for the phenotyping and monitoring of diseases.

Diagnosis of Infectious Diseases
Infectious diseases are caused by pathogenic microorganisms that are known to produce specific VOC. Several groups hypothesized that eNose could be used as a noninvasive tool to identify specific signatures of these health conditions.

The most studied condition was VAP, a type of lung infection. A group in the United States discovers that Cyranose 320 was capable to correlate different breathprints to a pneumonia score. However, it was Schnabel et al that presented a more detailed study revealing a sensitivity of 88% and a specificity of 66% in the discrimination between VAP patients with a positive bronchoalveolar lavage test and healthy controls. ENT infections are very common and the eNose technology, in a preliminary study with 90 patients, was able to identify the presence of bacterial infections in 88.2% of the cases.

This result was also obtained by Dutta et al that, additionally, was capable to distinguish between 3 classes of Staphylococcus aureus infections (MRSA, MSSA, and C-NS). A more specific study was conducted in patients with a positive diagnosis for bacterial sinusitis. The eNose could predict the diagnosis of sinusitis in at least 72% of the samples using the external validation methodology. However, no further studies aiming to predict ENT infections by eNose in patients were conducted since 2006.

The most recent studies focused on diagnosis of IA and the prediction of LOS at a preclinical stage. In the first one, eNose could establish distinct VOC profile in patients with IA and controls with an AUC of 0.93. In the last one, fecal VOC profile of preterm infants with LOS was discriminated from matched controls with a reasonable AUC of 0.70.

Microorganisms produce different VOC that can be detected in air samples by eNose. These studies showed that exhaled breath can be analyzed by eNose, but also fecal gas which showed distinct VOC profiles. The results are promising but further investigation is required.

Diagnosis of Inflammatory Diseases
There is some recent research in this field; however, the number of studies is still low. Dragonieri et al started to study sarcoidosis in 11 untreated patients, 20 treated pulmonary sarcoidosis patients and 25 healthy controls. Patients with untreated sarcoidosis were distinguished from healthy controls with an AUC of 0.825 and a CVA of 83.3%. This number decreased when breathprints of untreated patients were compared with the treated group (CVA: 74.2%). ARDS was also a condition investigated in 58 patients and 92 controls. The 2 groups were separated with an AUC of 0.71. Differential diagnosis of Crohn disease and ulcerative colitis yielded a promising result in a pediatric population during active and remissive disease. The values of sensitivity and specificity varied from 88% up to 100% and 67% up to 100%, respectively. The eNose was also tested in rheumatoid arthritis and psoriatic arthritis yielded moderate to poor values of sensitivity and specificity.

Inflammatory diseases are less investigated, and more studies are required to confirm the aforementioned observations. Nevertheless, these results are promising, especially for sarcoidosis.

Diagnosis of Cancer
More recently, the eNose technology has been tested to diagnose some types of cancer. Surprisingly, lung cancer was not the first research target. An Australian group reported that, in 88% of the cases, eNose could separate MPM patients from controls. These results were similar to another study performed by Dragonieri et al. Both studies included patients with significant asbestos exposure but without MPM to compare with the MPM
group. MPM subjects could be discriminated from those with asbestos exposure (sensitivity: 92.3%, specificity: 85.7%, AUC: 0.917) and from controls (sensitivity: 92.3%, specificity: 69.2%, AUC: 0.893).50 Lung cancer was then explored by McWilliams et al and it was found that in 80% of the cases, eNose measurements were able to distinguish lung cancer patients from high-risk smoking control subjects without cancer.37 These results were similar to a previous study where eNose reached a performance of 80% of sensitivity and 48% of specificity.36

Pilot studies in prostate, bladder, and colorectal cancer using the air scape of urine and feces samples for analysis were conducted recently.50–52 The ChemPro 100-eNose could discriminate prostate cancer and benign prostatic hyperplasia with moderate values of sensitivity and specificity of 78% and 67%, respectively.52 Electronic nose could also separate bladder cancer and patients with benign urological condition with moderate to good sensitivity and specificity (75% and 86%, respectively).51 Finally, Cyranose 320 was able to distinguish the fecal gas profile of 40 patients with colorectal cancer, 60 patients with advanced adenomas, and 57 healthy controls.36 Sensitivity and specificity varied from 62% up to 85% and 73% up to 87%.

Cancer diagnosis using air analysis of exhaled breath, urine, and fecal samples is a recent focus of investigation, revealing promising results. Although cancers related to the respiratory system have been further studied, only pilot studies have been performed so far, and a validation of these results is still required.

**Other diseases**

The diagnosis by eNose was also applied to differentiate breathprints of cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) patients in 2 different studies, showing different results.43,46 The first reached a sensitivity of 84% and a specificity of 60%, when breathprints of both diseases were compared. Comparing both diseases with control group, similar results were observed (sensitivity: 88% and 84%; specificity: 52% and 60%).45 The other study did not compare the 2 diseases.46 Comparisons between CF or PCD and the control group showed a lower sensitivity when compared to the previous study (50% and 57%, respectively) but with a higher specificity (95% and 85%, respectively). The samples were analyzed with Cyranose 320 and both used a VOC filter to minimize the influence of environmental VOC on the breath profiles. The major difference was among the population, the first used children’s breathing samples, while the last studied samples from young adults.

Only 1 study evaluated the capacity of eNose to separate healthy subjects from patients with renal failure, yielding a correct classification of 95.2%.55 However, a completely different methodology was used. Authors investigated body odor with the sensor head on the leg of patients. More recently, ALS was also investigated and breath profiles from patients were moderately discriminated from healthy controls (CVA: 75%).53 Finally, oral malodor was assessed, and an AUC of 0.879 was reached comparing control subjects and malodor patients.45

This technology can be explored and investigated to diagnose several diseases. Further research in other health conditions is expected to test the potential use of this diagnostic tool.

**Limitations**

There are some limitations in studies using eNose technology as a possible noninvasive diagnosis tool. The most evident is that eNose cannot identify and quantify the compounds present in the sample. Electronic noses are used to detect patterns and not individual molecules. Some studies have demonstrated an association between the eNose technology and mass spectrometry, yielding a more complete analysis.17,18 However, breathprint analysis allows the quick and easy assessment of an exhaled breath sample with thousands of volatile molecules. Another limitation is related to exhaled breath sampling since exogenous VOC can be present in samples. Breathprints are critically dependent on the methods of collection and sampling of exhaled breath. The most commonly used technique was described by Dragonieri et al.13 Sample collection consists of asking patients to breath normally for 5 minutes through a 3-way nonrebreathing valve with a VOC filter at the inspiratory port and a silica filter at the expiratory port to promote inspiratory VOC filtering and air drying, respectively. Therefore, it is possible to minimize any influence of humidity and environmental VOC on exhaled VOC patterns.13,17 After a maximal deep inspiration, patients exhaled a single vital capacity volume into a 10 L Tedlar bag connected to the expiratory port and silica reservoir.13 Almost 50% of the studies described in this review used this sampling methodology. In addition to this method, researchers should also adopt a restrict protocol regarding to food and beverage intake prior to sampling. Sampling methods should be standardized to achieve comparable results between studies and to improve diagnostic accuracy.

As a pioneer area, much of research involves pilot studies to evaluate the potential of eNose to discriminate breathprints of controls from patients with a specific disease. However, in the airway obstructions group, there are some recent studies that try to distinguish different stages and severities of a disease (mainly COPD and asthma).17,25 This type of research is expected to increase once its clinical application becomes more evident, as well as studies to help in treatment management and guidance of therapies.

The external validation allows to confirm and provide robustness to the obtained results. Unfortunately, only 5 studies performed external validation. External validation requires a training set and a validation set with newly recruited patients to assess the diagnostic accuracy.16 In the future, this validation methodology should be more recurrent to give strength to the results and introduce this tool into real clinical practice. Additionally, STARD guidelines for diagnostic accuracy studies should be followed to increase transparency and strength of results.

There are some limitations regarding to the methodology that should be solved to enable comparisons of results across studies. Still, it is necessary to do studies in larger populations to achieve robust results and include pediatric subjects, not just adults.

**Future perspectives**

In the future, research in this field is expected to increase due to the promising results demonstrated in previous studies, especially in airway obstructive diseases. The main objective is to achieve a universal methodology, with adequate reproducibility and repeatability, to enable comparisons between studies. External validation should be performed to increase robustness of the results. Subsequently, studies on larger, representative, and intend-to-treat populations are needed to evaluate this technology in a real clinical setting in the presence of several confounders. It should be emphasized that pediatric population must be included in further studies. Thereby, it is possible to think about a
clinical application of eNose technology, firstly as a complementary diagnostic approach for other traditional tools.

**Conclusions**

In conclusion, there is a need for a simple, noninvasive, inexpensive, and easy-to-perform technique to assess complex biological samples. GC-MS studies already proven that air analysis, especially of exhaled breath, can be a tool to evaluate an individual’s metabolic status (normal or disease-associated). In recent years, several studies using eNose technology to analyze gas samples have shown promising results to diagnose different diseases, not only respiratory but also infectious and inflammatory diseases and various types of cancers. Electronic nose analysis could be useful in a clinical setting because they are portable, easy to perform, inexpensive, rapid and do not require a specialized technician. Many of the previous studies have shown the moderate to good accuracy of this technology to differentiate several conditions from controls, especially airway obstructive diseases. However, it is a priority to create guidelines for standardized breath sampling, analysis and interpretation of the results. Additionally, it is necessary to externally validate the results in independent datasets of newly recruited patients to strengthen the results. Finally, studies on larger and representative populations are needed to test this technology in a real clinical setting. Reproducibility and repeatability of measurements using eNoses should also be studied and optimized to ensure comparable results.

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**Conflicts of interest**

The authors declare no conflicts of interest.

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