Review Article

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The electronic nose technology in clinical diagnosis: A systematic review

Mariana Valente Farraia, MSc[a,*], João Cavaleiro Rufo, PhD[b], Inês Paciência, MSc[a,b,c], Francisca Mendes, MSc[a], Luís Delgado, PhD[d,e], André Moreira, PhD[a,b,f]

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 Cyranose 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.[1] 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.[2,3] 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.[3]

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.[4] 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 patter-recognition system, capable of recognizing simple or complex odours" (1994).[5] This device mimics the mammalian olfactory system and can identify different complex odors comparing the incoming odor with patterns previously learnt.[6] 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.[5] The rise and decline of the signal depends on some parameters: nature of the odor (type and concentration of the compounds), reaction

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[a] Faculdade de Medicina da Universidade do Porto & Centro Hospitalar Universitário de S. João EPE, Porto, [b] EPIUnit—Instituto de Saúde Pública, Universidade do Porto, [c] Institute of Science and Innovation in Mechanical Engineering and Industrial Management (INEGI), [d] Imunologia Básica e Clínica, Departamento de Patologia, Faculdade de Medicina, Universidade do Porto, [e] Departamento de Imunoalergologia, Centro Hospitalar Universitário S. João EPE, Porto, [f] Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto, Porto, Portugal

[*] Corresponding author. Imunologia Básica e Clínica, Departamento de Patologia, Faculdade de Medicina, Universidade do Porto, Porto, Portugal. E-mail address: mariana.farraia@gmail.com (Mariana Valente Farraia).

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and diffusion between odor and sensors, type of sensor, and ambient conditions.[5] Methods based on mass spectrometry analysis can detect and identify which compounds are present in air samples being useful for pathophysiologic research.[7] Yet, these methods are time consuming, expensive, and depend on a skilled operator which makes them unpractical 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.[5] 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.[8–10] 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.[11] 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).[12] 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, colonrectal 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.[13] 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.

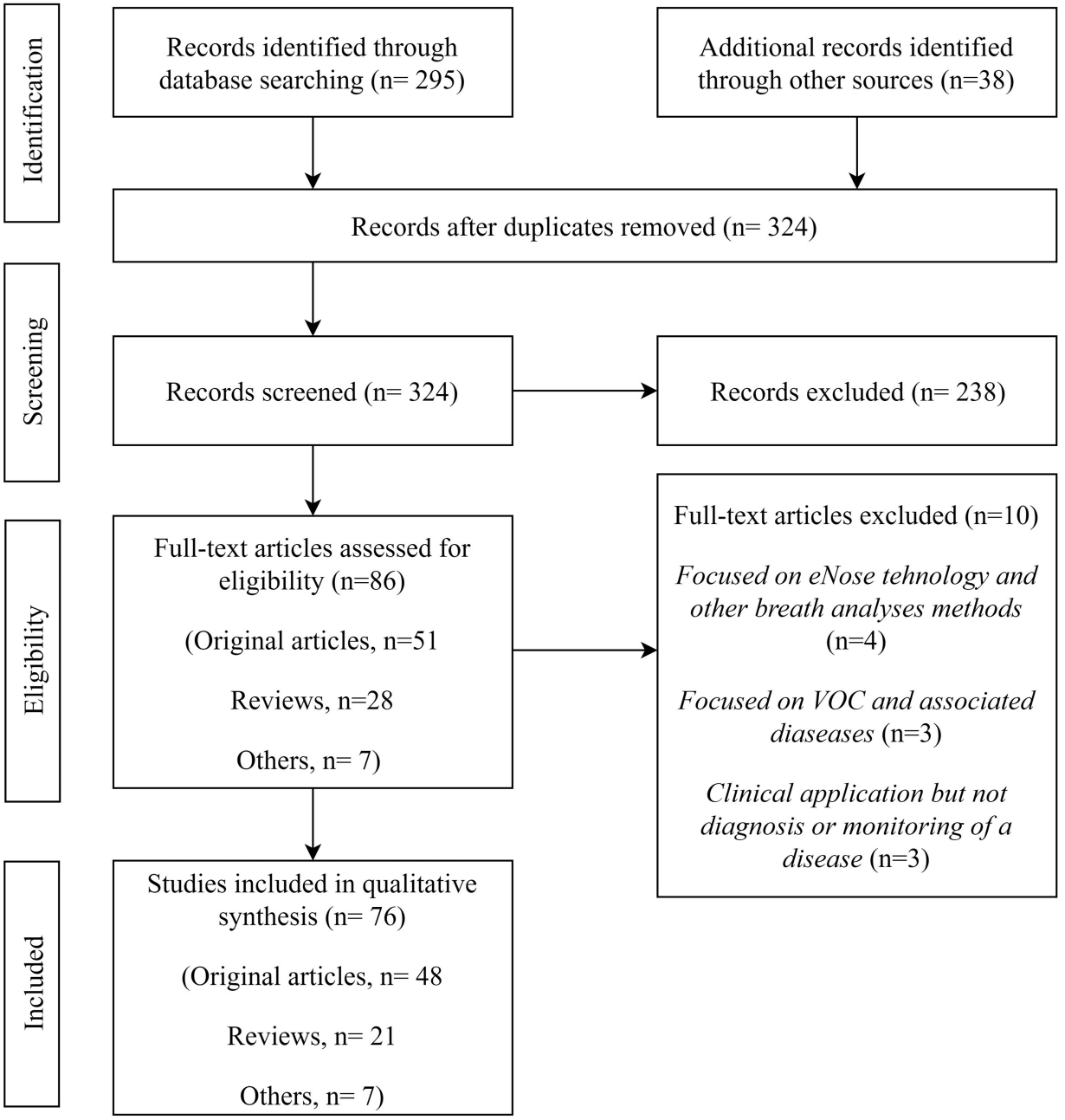

Figure 1. Summary of the literature search.

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%.[14] 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.[15] 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.[16] 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	eNose	Matrix	Short conclusions	Tests efficacy
[14]	2009	The Netherlands	Differential diagnosis (lung cancer and COPD)	10 patients with nonsmall cell lung cancer; 10 patients with COPD; 10 healthy controls	Cyranose 320	EB	VOC patterns of EB discriminates 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 nonsmoking controls; 20 smoking controls	Cyranose 320	EB	eNose distinguished patients with COPD and asthma and control subjects. EB profiles of patients with COPD partially overlapped 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), 39 with reversible obstruction (classic asthma), and 40 COPD patients (GOLD stages II–III)	Cyranose 320	EB	External validation of EB molecular profiling showed high accuracy to distinguish asthma and COPD	*Sensitivity*: Fixed asthma/COPD: 85%; Classic asthma/COPD: 91% *Specificity*: Fixed asthma/COPD: 90%; Classic asthma/COPD: 90% *AUC*: Fixed asthma/COPD: 0.95; Classic asthma/COPD: 0.93 *CVV*: Fixed asthma/COPD: 88%; classic asthma/COPD: 83%
[17]	2011	The Netherlands	Discriminate inflammatory subtype in mild and moderate COPD	28 COPD patients	Cyranose 320	EB	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	*AUC*: 0.86
[18]	2013	The Netherlands	COPD phenotyping	157 patients with different stages of COPD	Cyranose 320	EB	Taxonomy for mild to moderate COPD reinforces clusters found in previous studies and thereby allows better phenotyping of COPD in the general (ex-) 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	20 healthy controls; 10 patients with COPD with AATD (AATD); 23 patients with COPD without AATD (COPD)	Cyranose 320	EB and EBC	Smellprints of patients with AATD were different from those with COPD in EBC and EB	*Sensitivity*: EBC: AATD/COPD: 1.00 EB: AATD/COPD: 1.00 *Specificity*: EBC: AATD/COPD: 1.00 PEB: AATD/COPD: 1.00
[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	EB	An eNose can identify the presence of airway BC in clinically stable patients with COPD	*Sensitivity*: With BC/without BC: 82%; with BC/controls: 80%; Without BC/controls: 81% *Specificity*: With BC/without BC: 96%; with BC/controls: 93%; Without BC/controls: 86% *AUC*: With BC/without BC: 0.92; With BC/controls: 0.98; Without BC/controls: 0.93 *CVV*: With BC/without BC: 89%; with BC/controls: 88% Without BC/controls: 83%
[21]	2016	The Netherlands	Detect a viral or bacterial cause of acute exacerbations of COPD	43 patients: 13 with viral infection, 9 with bacterial infection, 9 with viral and bacterial infection, 12 with no infection	Aeonose	EB	The eNose was able to detect the presence or absence of a viral or bacterial respiratory infection during an acute exacerbation of COPD	*Sensitivity*: Viral/no viral: 83%; bacterial/no bacterial: 73% *Specificity*: Viral/no viral: 72%; bacterial/no bacterial: 76% *AUC*: Viral/no viral: 0.74; bacterial/no bacterial: 0.72
[22]	2012	Australia	Discriminate COPD and asthma with and without GORD	44 patients: 7 controls; 11 asthmatics; 9 asthmatics with GORD; 8 with COPD; 9 with COPD with GORD	Cyranose 320	EB	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 COPD with GORD	—
[13]	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	EB	eNose can discriminate EB of patients with asthma from controls but was less accurate in distinguishing asthma severities	Mild vs controls = 100% Severe vs controls = 90% Mild vs severe = 65%
[23]	2010	Hungary	Identify if breathprints are independent of changes in airway caliber in asthma	10 patients: 7 healthy, 3 with asthma	Cyranose 320	EB	Breathprints were not confounded by the level of airway obstruction	—
[24]	2013	The Netherlands	Asthma diagnosis	25 patients with mild/ moderate asthma	Cyranose 320	EB	eNose can identify asthmatic patients and may be used to predict their response to steroids with greater accuracy than sputum eosinophils or FeNO	*AUC*: 0.766
[25]	2015	Spain	Asthma phenotypes diagnosis		Cyranose 320	EB		

(*continued*)

Table 1
(continued).

Ref.	Year	Country	Aim	Demographics	eNose	Matrix	Short conclusions	Tests efficacy
				52 patients with persistent asthma: 24 eosinophilic, 10 neutrophilic, 18 paucigranulocytic			eNose can discriminate inflammatory phenotypes in patients with persistent asthma in a regular clinical setting	*Sensitivity*: Neutrophilic vs paucigranulocytic: 94% Neutrophilic vs eosinophilic: 60% Eosinophilic vs paucigranulocytic: 55% *Specificity*: Neutrophilic vs paucigranulocytic: 80% Neutrophilic vs eosinophilic: 79% Eosinophilic vs paucigranulocytic: 87% *AUC*: Neutrophilic vs paucigranulocytic: 0.88 Neutrophilic vs eosinophilic: 0.92 Eosinophilic vs paucigranulocytic: 0.79
26	2017	The Netherlands	Asthma diagnosis	23 patients with (partly) controlled mild to moderate persistent asthma using ICS	Cyranose 320	EB	Loss of asthma control can be discriminated from clinically stable episodes by longitudinal monitoring of EB using an eNose	*CVV*: Baseline vs loss of control: 95% Loss of control vs recovery: 86%
27	2015	Morocco	Allergic rhinitis	21 individuals: 5 patients with allergic rhinitis, 16 healthy controls	6 chemical gas sensors	EB	An eNose system based on 6 gas sensors discriminated the breath samples of rhinitis patients and controls	—
28	2013	Hungary	OSAS diagnosis	18 children with OSAS; 10 non-OSAS subjects with habitual snoring	Cyranose 320	EB	OSAS patients had a different breathprint that might reflect accelerated airway and/or systemic inflammation	*Sensitivity*: 78% *Specificity*: 70% *AUC*: 0.83 *CVV*: 64%
29	2013	Germany	OSAS diagnosis	20 healthy volunteers; 40 OSAS patients	Cyranose 320	EB	eNose can distinguish the EB of OSAS patients and control subjects	*Sensitivity*: 0.93 *Specificity*: 0.70 *AUC*: 0.85
30	2015	Italy	OSAS diagnosis (obese population)	19 obese patients with OSA; 14 obese controls without OSA; 20 nonobese healthy controls	Cyranose 320	EB	The presence of OSAS alters the exhaled VOC pattern in obese subjects	*AUC*: Controls/obese with OSA: 1,00; Controls/obese without OSA: 0.94; Obese with OSA/obese without OSAS: 0.77
31	2016	Italy	Differential diagnosis (OVS, OSAS, and COPD	13 patients with OSAS; 15 patients with COPD; 13 with OVS.	Cyranose 320	EB	Breathprints of patients with OSAS clustered distinctly from those with OVS as well as those with COPD. Breath prints from OVS were not significantly separated from those of COPD	*AUC*: OSAS/COPD: 0.83 OSAS/OVS: 1.00 OVS/COPD: 0.60 *CVV*: OSAS/COPD: 96.2% OSAS/OVS: 82.1% OVS/COPD: 67.9%
32	2004	USA	VAP diagnosis	23 patients who were receiving mechanical ventilation	Cyranose 320	Breath samples	Potential diagnostic adjunct in the diagnosis of pneumonia and other infectious diseases	*CVV*: 80%
33	2005	USA	VAP diagnosis	38 ventilated patients	Cyrano Sciences	30 mL of expired air	eNose breathprints correlated with a clinical pneumonia score	—
34	2005	USA	VAP diagnosis	44 patients with VAP	Cyranose 320	EB	eNose could discriminate between the 2 groups (pneumonia scores of 7 or greater vs pneumonia scores of 6 or less)	—
35	2015	The Netherlands	VAP diagnosis	72 patients: Gp1-33 with VAP and positive BAL test; Gp2: 39 with negative BAL test. Gp3: 53 controls	DiagNose	EB	eNose lacked sensitivity and specificity in the diagnosis of VAP	*Sensitivity*: Gp1/Gp3: 88%; Gp1/Gp2: 76% *Specificity*: Gp1/Gp3: 66%; Gp1/Gp2: 56% *AUC*: Gp1/Gp3: 0.82; Gp1/Gp2: 0.69
36	2014	The Netherlands	Lung cancer diagnosis	38 lung cancer patients and 39 COPD controls	Cyranose 320	EB	When used in concert, RASSF1A hypermethylation in sputum and EB analysis are complementary for lung cancer diagnosis	*Sensitivity*: 80% *Specificity*: 48% *AUC*: 0.66
37	2015	Canada	Lung cancer diagnosis	25 lung cancer patients; 166 high-risk smoker control subjects without cancer	Cyranose 320	EB	eNose measurements could distinguish lung cancer patients from high-risk control subjects	*AUC*: 0.84 (training set); 0.77 (test set)
38	2012	Australia	MM diagnosis	20 MM, 18 ARDs and 42 control subjects	Cyranose 320	EB	Patients with MM, ARDs, and control subjects were correctly identified with good accuracy	*CVV*: 95%
39	2012	Italy	MPM diagnosis	Gp1: 13 patients with MPM; Gp2: 13 subjects with asbestos exposure; Gp3: 13 controls	Cyranose 320	EB	EB analysis can correctly distinguish patients with MPM from subjects with similar occupational asbestos exposure without MPM and from healthy controls	*Sensitivity*: Gp1/Gp2: 92.3%; Gp1/Gp3: 92.3% *Specificity*: Gp1/Gp2: 85.7%; Gp1/Gp3: 69.2% *AUC*: Gp1/Gp2: 0.917; Gp1/Gp3: 0.893 *CVV*: Gp1/Gp2: 80.8%; Gp1/Gp3: 84.6%
40	2004	UK	ENT infections diagnosis	90 patients with ENT infections	Cyranose 320	Headspace of a vial (with a swab)	Breathprints were compared with microbiology diagnosis and it was found that eNose was correct in 88.2% of the cases	*CVV*: 88.2%

(*continued*)

Table 1
(continued).

Ref.	Year	Country	Aim	Demographics	eNose	Matrix	Short conclusions	Tests efficacy
41	2005	UK	ENT infections diagnosis	150 patients: 50 different patients for each type of bacterial subclass	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	*CW*: 99.69%
42	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	*CW*: 72%
43	2004	Japan	Oral malodor	29 healthy controls; 49 patients with oral malodor	FF-1 odor analyzer	EB	eNose may be useful for the measurement of nonsulfur gaseous compounds	AUC: 0.879
44	2015	Italy	Monitoring the treatment of patients with halitosis	10 treated patients with *Lactobacillus brevis* (CD2)-containing lozenges and 10 with placebo	BIONOTE	EB	BIONOTE can be used in addition to OralChroma to assess the initial condition of halitosis	—
45	2013	The Netherlands	Differential diagnosis (CF and PCD)	25 children with CF, 25 with PCD and 23 controls	Cyranose 320	EB	Exhaled molecular profiles significantly differ between patients with CF, PCD, and controls	*Sensitivity*: CF/controls: 84%; PCD/controls: 88%; CF/PCD: 84% *Specificity*: CF/controls: 65%; PCD/controls: 52%; CF/PCD: 60% *AUC*: CF/controls: 0.76; PCD/controls: 0.80; CF/PCD: 0.77
46	2014	Denmark	Differential diagnosis (CF and PCD)	64 patients with CF; 21 with PCD; 21 healthy controls	Cyranose 320	EB	This method significantly discriminates CF patients with a CPI from CF patients without any chronic pulmonary infection	*Sensitivity*: CF/controls: 50%; PCD/controls: 57.1%; CF w/CPI/without CPI: 71.4% *Specificity*: CF/controls: 95.2%; PCD/controls: 85.7%; CF w/CPI/without CPI: 63.3% *AUC*: CF/controls: 0.75; PCD/controls: 0.75; CF w/CPI/without CPI: 0.69
47	2016	The Netherlands	Discriminate CF patients with and without *Aspergillus fumigatus* colonization (AC)	27 patients: 9 CF with AC; 18 CF without AC	Cyranose 320	EB	eNose can detect AC with moderate to good accuracy	*Sensitivity*: 78% *Specificity*: 94% *AUC*: 0.89 *CW*: 89%
48	2014	The Netherlands	ARDS diagnosis	58 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	*AUC*: 0.71
49	2013	The Netherlands	Sarcoidosis diagnosis	11 sarcoidosis patients; 20 patients with treated pulmonary sarcoidosis; 25 healthy controls	Cyranose 320	EB	Patients with untreated 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%	*AUC*: 0.825 *CW*: 83.3%
50	2014	The Netherlands	CRC and adenomas diagnosis	100 patients: 40 with CRC, 60 with adenomas; 57 healthy controls	Cyranose 320	Fecal gas	eNose was able to differentiate between advanced adenomas and CRC by fecal gas analysis	*Sensitivity*: CRC/controls: 85%; adenomas/controls: 62%; CRC/adenomas: 75% *Specificity*: CRC/controls: 87%; adenomas/controls: 86%; CRC/adenomas: 73% *AUC*: CRC/controls: 0.92; adenomas/controls: 0.79; CRC/adenomas: 0.82
51	2015	Germany	BCa diagnosis	36 patients: 15 with the clinical suspicion of BCa; 21 without BCa but benign urological condition	Not specified	Urine samples	High potential of the eNose in the detection of BCa	*Sensitivity*: 75% *Specificity*: 86%
52	2014	Finland	Prostate cancer diagnosis	65 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
53	2016	Italy	ALS diagnosis	20 ALS patients; 20 healthy controls	Cyranose 320	EB	Breathprints from patients with ALS were discriminated from healthy controls	*AUC*: 0.795 *CW*: 75%
54	2013	The Netherlands	IA diagnosis	6 controls and 5 patients with IA	Cyranose 320	EB	Patients with IA had an exhaled VOC profile distinct from the controls	*Sensitivity*: 100% *Specificity*: 83.3% *AUC*: 0.933 *CW*: 90.9%
55	2005	Germany	Renal dysfunction diagnosis	42 patients with end-stage renal failure; 20 patients with chronic renal failure; 11 healthy controls	Not specified	Sensor head (volume 5 mL) of the eNose was placed on patient's leg	Application of an eNose system for analyzing human body odor allowed the distinction between different stages of renal dysfunction	—
56	2016	The Netherlands	Predict LOS at a preclinical stage	36 infants with LOS; 40 controls	Cyranose 320			

(*continued*)

Table 1
(continued).

Ref.	Year	Country	Aim	Demographics	eNose	Matrix	Short conclusions	Tests efficacy
						Fecal samples (fecal gas)	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% *Specificity*: 61.5% *AUC*: 0.70
[57]	2014	The Netherlands	Differential diagnosis (CD and UC).	26 patients with UC; 29 patients with CD; 28 controls	Cyranose 320	Fecal samples (fecal gas)	Fecal VOC analysis allowed discrimination of pediatric patients with IBD from controls, both during active disease and remission	*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% *Specificity*: *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: 0.96 *Clinical remission*: UC vs controls: 0.94 CD vs controls: 0.94 CD vs UC: 0.81
[58]	2016	The Netherlands	Differential diagnosis (RA and PsA).	21 RA patients; 18 PsA patients; 21 control subjects	Cyranose 320	EB	eNose is suggested to differentiate to some extent between the breathprints of patients with active RA, active PsA, and healthy controls	*Sensitivity*: RA vs controls: 76% PsA vs controls: 72% Ra vs PsA: 71% *Specificity*: RA vs controls: 67% PsA vs controls: 71% 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: 69% Ra vs PsA: 69%
[59]	2011	Germany	Detect inflammatory airway response induced by ozone inhalation.	14 healthy subjects	Cyranose 320	EB	EB profiles as measured by the eNose did not reflect airway responses to ozone	—
[60]	2014	Germany	Differentiate between preterm neonates with or without laboratory-confirmed bloodstream infections	28 intubated preterm neonates	Cyranose 320	Tracheal aspirates	Smellprints of VOC from tracheal aspirates can discriminate between preterm neonates with or without laboratory-confirmed bloodstream infection	—

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, CPI = 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, FeNO = fractional exhaled nitric oxide, GC-MS = gas chromatography coupled to mass spectrometry, GOLD = global initiative for chronic obstructive lung disease, GORD = gastroesophageal reflux disease, IA = invasive aspergillosis, IBD = inflammatory bowel disease, ICS = inhaled corticosteroid, LOS = late-onset sepsis, MM = malignant mesothelioma, MPM = malignant pleural mesothelioma, OSAS = obstructive sleep apnea syndrome, OVS = overlap syndrome, PCD = primary ciliary dyskinesia, PsA = psoriatic arthritis, RA = rheumatoid arthritis, ROC = receiver operating characteristic, UC = ulcerative colitis, VAP = ventilator associated pneumonia, VOC = volatile organic compounds.

Table 2

Characteristics and main results of the included studies (reviews, comments, and book chapters)

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 glycemic status in diabetes
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	eNose and NMR-based metabolomics of EBC can distinguish patients with respiratory diseases such as asthma, COPD, and lung cancer, or diseases with a clinically relevant respiratory component including cystic fibrosis and primary ciliary dyskinesia, and healthy individuals
68	2011	Review	Summarize the major eNose technologies developed for healthcare and biomedical applications since the late 1980s	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
69	2011	Comment	—	Should we replace mammalian scent detection with a machine or return to teaching physicians to sniff?
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	Describe the current status on clinical validation and application of breath analysis by eNose in the diagnosis and monitoring of chronic airways 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 endovenous 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
10	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
76	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, VOCs in urine may also be a trend in research on the early detection

(*continued*)

Table 2
(continued).

Ref.	Year	Type of document	Objectives	Conclusions
			using breath analysis, and summarize the advances in the study of eNoses based on gas sensitive sensors	of lung cancer. Traditional gas analysis techniques are too sophisticated and expensive for clinical use, and eNoses are now facing challenges in solving their own limitations
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
79	2014	Comment	—	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
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	Analysis of exhaled volatiles by eNoses holds promise for complementing diagnosis, phenotyping, and monitoring of lung diseases
81	2015	Review	Summarize and analyze past research and outlines future directions to improve understanding of both canine olfaction and eNose technology	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
9	2015	Systematic review	Summarize the current evidence of exhaled breath analysis for cancer detection using standard analysis techniques and eNose	Analyses of exhaled breath yielded promising results, although standardization of breath collection, sample storage, and data handling remain critical issues
82	2015	Review	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	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
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 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.
8	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	There is a clear need for noninvasive biomarkers in patient stratification. eNoses can provide an instant probabilistic result but do not selectively measure any specific VOC
84	2016	Review	Provide a clinical background of VOC identification, eNose development, and review gastroenterology applications toward diagnosis	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	Evaluate the potential role of VOC analysis as a mass screening tool for colonrectal cancer (CRC)	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.[18] 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.[19] 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.[20,21]

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.[13] 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%.[24] 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.[23] A recent study involving asthmatic subjects was conducted in Spain and aimed to phenotype the disease using the eNose.[25] The eNose was able to differentiate inflammatory phenotypes (eosinophilic, neutrophilic, and paucigranulocytic) in patients with persistent asthma with sensitivities and specificities ranging from 55% up to 94% and 79% up to 87%, respectively. Exhaled breath profiles of patients with asthma were also evaluated in a longitudinal study using 2 different approaches to analyze breath samples (GC-MS and eNose).[26] 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).[28] These results are similar to those reported by Greulich et al (sensitivity: 93%, specificity: 70%, AUC: 0.85).[29] 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%).[30] In a pilot study, OSAS breathprints were compared to OVS (overlap syndrome) and COPD.[31] 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.[34] 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.[35]

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.[40] 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).[41] A more specific study was conducted in patients with a positive diagnosis for bacterial sinusitis.[42] 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.[54,56] In the first one, eNose could established distinct VOC profile in patients with IA and controls with an AUC of 0.93.[54] In the last one, fecal VOC profile of preterm infants with LOS was discriminated from matched controls with a reasonable AUC of 0.70.[56]

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.[49] 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.[48] 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.[57] 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.[58]

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.[38] These results were similar to another study performed by Dragonieri et al.[39] 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).[39] 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 colonrectal 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 colonrectal cancer, 60 patients with advanced adenomas, and 57 healthy controls.[50] 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.[45,46] 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.[43]

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 exhale 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.[13,15] 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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