The smell of lung disease: a review of the current status of electronic nose technology

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Abstract

There is a need for timely, accurate diagnosis, and personalised management in lung diseases. Exhaled breath reflects inflammatory and metabolic processes in the human body, especially in the lungs. The analysis of exhaled breath using electronic nose (eNose) technology has gained increasing attention in the past years. This technique has great potential to be used in clinical practice as a real-time non-invasive diagnostic tool, and for monitoring disease course and therapeutic effects. To date, multiple eNoses have been developed and evaluated in clinical studies across a wide spectrum of lung diseases, mainly for diagnostic purposes. Heterogeneity in study design, analysis techniques, and differences between eNose devices currently hamper generalization and comparison of study results. Moreover, many pilot studies have been performed, while validation and implementation studies are scarce. These studies are needed before implementation in clinical practice can be realised. This review summarises the technical aspects of available eNose devices and the available evidence for clinical application of eNose technology in different lung diseases. Furthermore, recommendations for future research to pave the way for clinical implementation of eNose technology are provided.

Keywords: Electronic nose, Breath analysis, Respiratory medicine, Personalised medicine, Machine learning, Sensor technology

Background

The field of pulmonary medicine has rapidly evolved over the last decades, with increasing knowledge about pathophysiology and aetiology leading to better targeted treatment strategies. Nevertheless, many chronic lung diseases have non-specific, often overlapping symptoms, which delays the diagnostic process and timely start of adequate treatment. Moreover, even specific disease entities can be very heterogeneous with varying phenotypes, and thus disease courses and optimal treatment strategies vary per patient. Accurate, non-invasive, real-time diagnostic tools and biomarkers to predict disease course and response to therapy are currently lacking in most lung diseases, but are indispensable to achieve a personalised approach for individual patients.

An emerging tool that has the potential to meet this need is an electronic nose (eNose). This device ‘smells’ exhaled breath for clinical diagnostics, a concept probably as old as the field of medicine itself. Exhaled breath contains thousands of molecules, also known as volatile organic compounds (VOCs). These VOCs can be divided into compounds derived from the environment (exogenous VOCs) and compounds that are the result of biological processes in the body (endogenous VOCs).
Endogenous VOCs can be associated with normal physiology, but also with pathophysiological inflammatory or metabolic activity [1, 2]. Identification of individual VOCs using techniques as gas chromatography or mass spectrometry is a specific but time-consuming exercise. An eNose can be used in real-time to recognise patterns of VOCs and has therefore potential as point-of-care tool in clinical practice.

The aim of this paper is to review the current clinical evidence on eNose technology in lung disease, regarding diagnosis, monitoring of disease course and therapy evaluation. In addition, technical aspects and available eNose devices are discussed.

**eNose technology**

In the time of Hippocrates, it was already acknowledged that exhaled breath can provide information about health conditions [3]. For instance, a sweet acetone breath odour indicates diabetes, a fishy smell suggests liver disease, and wounds with smell of grapes point towards pseudomonas infections [4]. Initial breath analysis studies were performed using gas chromatography or mass spectrometry. Throughout the last decades, more techniques were developed for breath analysis, for example ion mobility spectrometry, selected ion flow tube mass spectrometry and laser spectrometry [5]. Although these techniques became more advanced during the years and are very precise in identifying individual VOCs, they are very complex, laborious and thus not suitable as a real-time clinical practice tool.

Exhaled breath analysis by use of eNose technology is recently gaining increasing attention. An eNose is defined as “an instrument which comprises of an array of electronic-chemical sensors with partial specificity and an appropriate pattern recognition system, capable of recognising simple or complex odours” [6]. Sensors are used in eNoses to generate a singular response pattern. The sensors can generally be divided into three categories: electrical, gravimetric, and optical sensors. Each type responds to analytes (i.e. VOCs) in a specific way, and all types have a high sensitivity. Each sensor has advantages and disadvantages, without one type being superior in general. Electrical sensors consist of an electronic circuit connected to sensory materials. Upon binding with specific analytes, an electrical response is provided [7–10]. Consequently, a variation in electrical property of the sensor surface can be detected. Electrical sensors are low-cost, but are sensitive to temperature changes and have a limited sensor life [11]. Gravimetric (or mass sensitive) sensors label analytes based on changes in mass, amplitude, frequency, phase, shape, size, or position. Gravimetric sensors contain a complex circuitry and are sensitive to humidity and temperature [11]. Finally, optical sensors detect a change in colour, light intensity or emission spectra upon analyte binding. Optical sensors are insensitive to environmental changes, but are the most technically complex sensor-array systems and are not portable due to breakable optics and components. Due to the high complexity, they are more expensive than the other sensor types [11]. For each type of sensor, a more in depth explanation can be found in the Additional file 1.

Detection and recognition of odours by an eNose is similar to the functioning of the mammalian olfactory system (Fig. 1). First, an odour is detected (by olfactory receptors in a human nose or eNose sensors), which sends off various signals (to the cortex or software). Then, these signals are pooled together and processed into a pattern. This pattern can be recognised as a particular smell (e.g. a flower) [12]. As a result, an eNose can...
differentiate between diseases by analysing and comparing the smelled ‘breathprints’ (i.e. VOC patterns) with those previously learned. The devices are hand-held, patient friendly, easy-to-use and feasible as point-of-care test.

Analysis methods
To analyse eNose breathprints, pattern recognition by machine learning is most commonly used. A machine learning model uses algorithms which automatically improve due to experience with previously presented data. These models are in general established using a five step process: data collection, data preparation, model building, model evaluation, and model improvement. Machine learning is categorised into unsupervised, supervised, and reinforcement learning [13]. In supervised learning, the algorithms are trained with labelled data input, the desired output is thus known. On the contrary, unsupervised learning allows the algorithm to recognise patterns in the data, and groups data without providing labels. Lastly, reinforcement learning encompasses the training of the machine learning models to generate decision sequences. The latter is not used in the eNose studies reviewed in this paper.

Several machine learning models have been proposed as appropriate algorithms for modelling complex non-linear relationships in medical research data, such as breathprints. These models include, amongst others, artificial neural networks (mimicking the structure of animal brains to model functions), ensemble neural networks (many neural networks working together to solve a problem), and support vector machines (SVM, creating a hyperplane which allows the modelling of highly complex relationships) [14, 15]. A comparison between eNose studies show that SVM algorithm is most frequently used (10 out of 17 studies in 2019) [15]. Possibly, this is due to the fact that this is the easiest model to use for researchers new to machine learning. Another factor can be the existence of many programming languages with well-supported libraries for SVM algorithms. SVM also possesses a high accuracy, is not very prone to overfitting, and is not overly influenced by noisy data [15]. Nonetheless, there is no consensus about the optimal model for breathprint analysis.

Available eNoses
Various eNose devices have been developed and studied in different lung diseases. Table 1 provides an overview of the specifications of devices used in studies reviewed in this paper. The choice of an eNoses device may, among others, depend on the measurement setting. For example for the BIONOTE, Cyranose 320, PEN3, and Tor Vergata eNoses the exhaled breath is captured into sample bags or cartridges which makes it possible to collect on-site and store samples for later analyses. In other settings, it could be preferable that the eNose is easily portable, like the Aeonose. The SpiroNose is the only eNose that is capable of adjusting for disturbances from ambient air using its external sensors.

The stage of development towards a clinically implemented tool differs substantially per device and disease. Before clinical implementation, each specific eNose has to be tested as a proof of concept and consecutively in substantial cohorts for each specific disease. Subsequently, data validation and clinical implementation needs to be assessed in real-life cohorts. To give more insights in the stage of development for each eNose per lung disease, we divided studies in five different stages: (1) proof of concept study; (2) cohort size of diseased participants less than fifty; (3) cohort size of diseased participants equal or more than fifty; (4) study cohort with an external validation cohort; (5) evaluation of clinical implementation. An overview of the progress per eNose and disease is visualised in Fig. 2. To the best of our knowledge, none of the devices are currently used in clinical pulmonology practice.

Current clinical application
On 21 October 2020, a systematic literature search was performed in the databases Embase, Medline (Ovid), and Cochrane Central. Search terms and selection criteria are described in the Additional file 2. Table 2 provides an overview of design and results of all studies in this review.

Asthma
Asthma is a chronic lung disease characterised by reversible airflow obstruction with airway inflammation and hyperresponsiveness. Common symptoms, such as cough, chest tightness, shortness of breath and wheezing, are variable in severity and often non-specific [17]. Various studies, both in children and adults, showed that eNose technology can differentiate asthma patients from healthy controls with a good accuracy [18–25]. Two studies also demonstrated that breathprints of asthma patients were significantly different than breathprints of chronic obstructive pulmonary disease (COPD) patients [19, 26]. Interestingly, two studies reported better performance of eNose technology than conventional investigations (spirometry or an exhaled nitric oxide (FeNO) test) for detecting asthma. These studies were performed in patients with an established asthma diagnosis [21, 22]. Diagnostic performance further increased when eNose technology was combined with a FeNO test (accuracy 95.7%) [21]. Moreover, even after loss of control and reaching stable disease with oral corticosteroids (OCS) treatment eNose technology could differentiate asthma
Table 1 Characteristics of available eNoses

| Company | Working Principle (i.e. sensors) | Sensing material | Array composition | Breath collection | Image | Image source |
|---------|---------------------------------|------------------|-------------------|-------------------|-------|--------------|
| Aeonose | The eNose company, Zutphen, the Netherlands | Electrical sensors | 1 array; 3 sensors | Tidal breathing straight into eNose | [Image](www.enose.nl) | [www.enose.nl](www.enose.nl) |
| BIONOTE | Campus Bio-Medico University, Rome, Italy | Gravimetric sensors | 1 array; 7 sensors operating at 4 different temperatures | Tidal breathing into Pneumopipe cartridge | [Image](Rocco et al. 2016 [16]) | Rocco et al. 2016 [16] |
| Cyranose 320 | Sensigent, California, United States (previously known as: Smith Detections) | Electrical sensors | 1 array; 32 different polymers | Exhalation into sample bag | [Image](www.sensigent.com/products/cyranose.html) | www.sensigent.com/products/cyranose.html |
| PEN3 | Airsense Analytics GmbH, Schwerin, Germany | Electrical sensors | 1 array; 10 different sensors | 5 min tidal breathing, deep inhale, exhalation | [Image](www.airsense.com/sites/default/files/flyer_pen.pdf) | www.airsense.com/sites/default/files/flyer_pen.pdf |
| SpiroNose | Breathomix, Leiden, the Netherlands (previously produced by: Comon Invent) | Electrical sensors | 4 exhaled breath and 4 reference arrays; 7 different sensors per array | Exhalation straight into eNose | [Image](www.breathomix.com) | www.breathomix.com |
| Tor Vergata | Tor Vergata University, Rome, Italy | Gravimetric sensors | 1 array; 8 sensors | Exhalation into sample bag | [Image](Tor Vergata University) | Tor Vergata University |

An overview of specifications of eNose devices used in studies reviewed in this paper. eNose prototypes are not included. BIONOTE biosensor-based multisensory system for mimicking nose tongue and eyes, eNose electric nose, MOS metal oxide semiconductor, PEN portable electronic nose, QCM quartz crystal microbalance. Images are used with approval of the eNose companies.
from healthy controls, while the diagnostic value of FeNO decreased. In the same study, breathprint significantly predicted response to subsequent OCS treatment, while sputum eosinophils, FeNO values and, hyperresponsiveness did not [22].

The existence of multiple asthma pheno- and endotypes with different underlying pathophysiological mechanisms is increasingly acknowledged [27]. In recent years, many eNose studies have attempted to identify different clusters of asthma patients, using both supervised and unsupervised methods [28–31]. For example, supervised clustering for eosinophilic, neutrophilic and pauci-granulocytic phenotypes revealed significant differences in breathprints between groups [30]. One study identified three clusters using unsupervised breathprint analysis in a group of severe asthmatic patients, corresponding with different inflammatory profiles. During follow-up, 30 of 51 patients migrated to another cluster; migration was associated with changes in sputum eosinophil count [31]. Two other longitudinal studies showed changes in breathprint when asthma control was lost after withdrawal of corticosteroids in previously stable asthma patients, and also after recovery [22, 32]. A pilot study, in which bronchoconstriction was induced in stable asthma patients, found that changes in airway calibre did not alter breathprints. Moreover, breathprints remained stable during the day in individual patients [20]. This implies that inflammatory processes and not (acute) airway obstruction influence breathprints. Overall, these findings suggest that eNose technology is a promising tool for phenotyping and monitoring asthmatics. Longer follow-up studies are required to examine whether cluster-migration or change in breathprint are also related to actual clinical course.

A currently ongoing study is evaluating whether eNose technology can be used to predict response to monoclonal antibody therapy (NCT03988790).

**Paediatric asthma**

In general, the diagnosis of asthma in children is challenging. Lung function tests are often difficult to perform and do not always provide a diagnosis. Interestingly, a study in 45 children demonstrated that eNose measurements were fairly well repeatable, both in healthy and asthmatic participants [33].
| Study participants | Outcome measures | Results | eNose | Statistical breathprint analysis |
|-------------------|------------------|---------|-------|---------------------------------|
| **Asthma**        |                  |         |       |                                 |
| Dragonieri, 2007 [18] | n = 20 asthma  
• n = 10 mild  
• n = 10 severe  
• n = 20 HC  
• n = 10 old  
• n = 10 young | Diagnostic accuracy | Mild vs young HC  
CVV 100%  
Severe vs old HC  
CVV 90% | Mild vs severe HC  
CVV 65% | Cyranose 320 | PCA; CDA |
| Fens 2009 [19]    | n = 20 asthma  
• n = 30 COPD  
• n = 20 non-smoking HC  
• n = 20 smoking HC | Diagnostic accuracy | COPD vs asthma  
CV 96%  
COPD vs smoking HC  
CV 66% | Non-smoking vs smoking HC  
Not significant | Cyranose 320 | PCA |
| Lazar 2010 [20]   | n = 10 asthma  
• induction of bronchoconstriction with methacholine or saline  
• n = 10 controls | Disease course | Bronchoconstriction causes no significant change in breathprint | | | |
| Montuschi 2010 [21] | n = 27 asthma  
• n = 24 HC | Diagnostic accuracy | eNose only  
Acc 87.5%  
eNose + FeNO  
Acc 95.8% | | Tor Vergata | PCA; feed-forward neural network |
| Fens 2011 [26]    | Training: [19]  
• n = 20 asthma  
• n = 20 COPD  
Validation: [19]  
• n = 60 asthma  
• n = 21 fixed obstruction  
• n = 39 classic  
• n = 40 COPD | Diagnostic accuracy | Validation: Classic asthma vs COPD  
Sens 85%  
Spec 90%  
AUC 0.93 (0.84–1.00)  
Acc 83% | Validation: Fixed asthma vs COPD  
Sens 91%  
Spec 90%  
AUC 0.95 (0.87–1.00)  
Acc 88% | | Cyranose 320 | PCA; CDA |
| Van der Schee 2013 [22] | n = 25 asthma  
• n = 20 HC  
• n = 18 asthma  
• maintenance ICS, stop ICS (4 weeks)  
effect and OCS (2 weeks) | Diagnostic accuracy | Before OCS  
Sens 80.0%  
Spec 65.0%  
AUC 0.766 ± 0.14 | After OCS  
Sens 84.0%  
Spec 80%  
AUC 0.862 ± 0.12 | Before OCS  
(FeNO only)  
AUC 0.738 ± 0.15 | | Cyranose 320 | PCA; CDA |
| Plaza 2015 [30]   | n = 24 eosinophilic asthma  
• n = 10 neutrophilic asthma  
• n = 18 paucigranulocytic asthma | Diagnostic accuracy | Neutro vs pauci  
Sens 94%  
Spec 80%  
AUC 0.88 | EoS vs neutro  
Sens 60%  
Spec 79%  
AUC 0.92  
CV 73% | | | Cyranose 320 | PCA; CDA |
| Brinkman 2017 [32] | n = 22 asthma, induced LOC  
• maintenance ICS, stop ICS (8 weeks)  
and restart ICS | Disease course | LOC vs no LOC  
Sens 90.9%  
Spec 71.4%  
AUC 0.883 (±0.16) | Correlation sputum eos— 
breathprint  
R = 0.601 | | | Cyranose 320 | PCA; CDA |
| Bannier 2019 [23] | n = 20 asthma (age > 6 years)  
• n = 22 HC | Diagnostic accuracy | Sens 74%  
Spec 74%  
AUC 0.79 | | | | Aeonose | ANN |
| Brinkman 2019 [31] | n = 78 severe asthma  
• n = 51 longitudinal follow-up | Clustering | 3 clusters (baseline), acc 93%  
Differences: chronic OCS use, percent serum eosinophil and neutrophil count | | | | | | | | |
## Table 2 (continued)

| Study participants | Outcome measures | Results | eNose | Statistical breathprint analysis |
|--------------------|------------------|---------|-------|----------------------------------|
| **Asthma**         |                  |         |       |                                  |
| Cavaleiro Rufo 2019 [34] | n = 64 suspected asthma (age 6–18 years)  
• n = 45 asthma  
• n = 29 persistent  
• n = 16 intermittent  
• n = 19 no asthma | Diagnostic accuracy  
Asthma vs no asthma  
Sens 77.8%  
Spec 84.2%  
AUC 0.81 (0.69–0.93)  
Acc 79.7% | Persistent vs no asthma  
Sens 79.7%  
Spec 68.6%  
AUC 0.81 (0.70–0.92)  
Acc 79.7% | Intermittent vs no asthma  
Not significant | Cyanose 320  
PCA; Hierarchical clustering |
| Dragonieri 2019 [24] | Training: n = 14 AAR  
n = 7 AAR  
n = 14 HC  
n = 7 HC | Validation: | Training: AAR vs HC  
AUC 0.87 (0.70–0.97)  
CVA 75.0% | Validation: AAR vs rhinitis  
AUC 0.92 (0.84–1.00)  
CVA 83.1% | Cyanose 320  
PCA; CDA |
| Abdel-Aziz 2020 [118] | Training: n = 486  
atopic asthma (age > 4 years)  
Validation: n = 169 atopic asthma (age > 4 years) | Diagnostic accuracy  
Asthma vs no asthma  
Sens 68%  
Spec 57%  
AUC 0.70 (0.55–0.84)  
Acc 63% | Persistent vs no asthma  
Sens 68%  
Spec 57%  
AUC 0.70 (0.55–0.84)  
Acc 63% | Intermittent vs no asthma  
Not significant | Cyanose 320  
PLS-DA; adaptive least absolute shrinkage and selection operator; gradient boosting machine |
| **Chronic obstructive pulmonary disease (COPD)** |                  |         |       |                                  |
| Fens 2011 [45] | n = 28 GOLD I + II  
airway inflammation (sputum eosinophil cationic protein and myeloperoxidase) | Disease course  
Correlation eosinophil cationic protein and breathprint  
r = 0.37 | Correlation myeloperoxidase and breathprint  Not significant | Airway inflammation vs no  
Sens 50–73%  
Spec 77–91%  
AUC 0.66–0.86 | Cyanose 320  
PCA |
| Hattesohl 2011 [37] | n = 23 COPD (pure exhaled breath, PEB)  
n = 10 COPD (exhaled breath condensate, EBC)  
n = 10 HC (EBC, PEB)  
n = 10 AATd (EBC, PEB) | Diagnostic accuracy  
COPD vs HC  
Sens 100%  
Spec 100%  
CVV PEB 67.6%  
CVV EBC 80.5% | COPD vs AATd  
Sens 100%  
Spec 100%  
CVV PEB 58.3%  
CVV EBC 82.0% | HC vs AATd  
Sens 100%  
Spec 100%  
CVV PEB 62.0%  
CVV EBC 59.5% | Cyanose 320  
LDA |
| Fens 2013 [42] | n = 157 COPD | Therapeutic effect  
Before vs 6 d after therapy  
Sens 100%  
Spec 100%  
CVV 53.3% | 4 clusters (acc 97.4%)  
Differences: airflow limitation, health related QoL, sputum production, dyspnoea, smoking history, co-morbidity, radiologic density, gender | Cyanose 320  
Hierarchical cluster analysis Non-hierarchical K-means clustering |
| Study participants | Outcome measures | Results | eNose | Statistical breathprint analysis |
|--------------------|-----------------|---------|-------|---------------------------------|
| **Colombia 2014**  | n = 10 COPD bacterial colonised n = 27 COPD non-colonised n = 13 HC | Diagnostic accuracy | Coloured vs non-coloured Sens 82% Spec 96% AUC 0.922 CVA 89% | HC vs non-coloured Sens 81% Spec 86% AUC 0.937 CVA 83% | Cyranose 320 | PCA; CDA |
| **Cazzola 2015**   | n = 27 COPD n = 8 AECOPD ≥ 2 per year n = 19 AECOPD < 2 per year n = 7 HC | Diagnostic accuracy | COPD vs HC Sens 96% Spec 71% CVA 91% | AECOPD ≥ 2 vs < 2 per y Not significant | Prototype (6 QMB sensors) | PLS-DA |
| **Shafiek 2015**   | n = 50 COPD n = 17 sputum PPM growth n = 93 AECOPD n = 42 sputum PPM growth n = 30 HC | Diagnostic accuracy | COPD vs HC Sens 70–72% Spec 70–73% | COPD vs AECOPD no PPM vs AECOPD PPM Sens 89% Spec 48% (with PPM not significant) Sens 88% Spec 60% | Cyranose 320 | LDA; SLR |
| **Van Geffen 2016**| n = 43 AECOPD n = 18 with viral infection n = 22 with bacterial infection | Diagnostic accuracy | With vs without viral infection Sens 83% Spec 72% AUC 0.74 | With vs without bacterial infection Sens 73% Spec 76% AUC 0.72 | Aeonose | ANN |
| **De Vries 2018**  | Training: n = 321 asthma/COPD Validation: n = 114 asthma/COPD | Clustering | 5 clusters Differences: ethnicity, systemic eosinophilia/ neutrophilia, FeNO, BMI, atopy, exacerbation rate | | SpiroNose | PCA; Unsupervised Hierarchical clustering |
| **Finamore 2018**  | n = 63 COPD n = 32 n6MWD worsened 1 year n = 31 n6MWD stable or improved 1 year | Disease course | n6MWD change predicted by eNose Sens 84% Spec 88% AUC 86% | n6MWD change predicted by eNose + GOLD Sens 81% Spec 78% AUC 79% | BIONOTE | PLS-DA |
| **Montuschi 2018**| n = 14 COPD maintenance ICS, stop ICS (4 weeks) effect and restart ICS | Therapeutic effect | Maintenance vs restart ICS Change in 15 of 32 Cyranose sensors; 3 of 8 Tor Vergata sensors | Maintenance vs restart ICS Spirometry + breathprint prediction model AUC 0.857 | Cyranose 320, Tor Vergata | Multilevel PLS; KNN |
| **Scarlata 2018**  | n = 50 COPD standard inhalation therapy (12 weeks) n = 50 COPD | Therapeutic effect | Baseline vs after 12 w Significant decline in VOCs | | BIONOTE | PLS-DA |
| **Van Velzen 2019**| n = 16 AECOPD before, during and after recovery | Disease course | Before vs during Sens 79% Spec 71% CVA 75% | During vs after Sens 79% Spec 71% CVA 75% | | Cyranose 320, Tor Vergata, Comon | PCA |
| **Rodriguez-Aguilar 2020** | n = 116 COPD n = 88 smoking, n = 28 household air pollution associated n = 64 GOLD I-II, n = 52 GOLD III-IV n = 178 HC | Diagnostic accuracy | COPD vs HC Sens 100% Spec 97.8% AUC 0.989 Acc 97.8% (CD), 100% (SVM) | Smoking vs air pollution associated Not significant | Cyranose 320 | PCA; CDA; SVM |
Table 2 (continued)

| Study participants | Outcome measures | Results | eNose | Statistical breathprint analysis |
|--------------------|------------------|---------|-------|----------------------------------|
| **Cystic fibrosis (CF)** | | | | |
| Paff 2013 [52] | n = 25 CF n = 25 primary ciliary dyskinesis (PCD) n = 23 HC | Diagnostic accuracy | CF vs HC Sens 84% Spec 65% AUC 0.76 | Exacerbation CF | Cyanose 320 PCA |
| Joensen 2014 [53] | n = 64 CF n = 14 pseudomonas infection n = 21 PCD n = 21 HC | Diagnostic accuracy | CF vs HC Sens 50% Spec 95% AUC 0.75 | | |
| Krauss 2019 [60] | n = 174 ILD n = 34 pneumonia n = 64 HC | Diagnostic accuracy | Training: Sens 64.3–67.9% Spec 88.0–92.0% AUC 0.89–0.91 Validation: Sens 33.3–66.7% Spec 71.4–78.6% AUC 0.61–0.86 Acc 65.0–70.0% | Cyanose 320 PCA; CDA |
| Yang 2018 [59] | n = 34 pneumonia n = 64 HC | Diagnostic accuracy | Training: Sens 64.3–67.9% Spec 88.0–92.0% AUC 0.89–0.91 Validation: Sens 33.3–66.7% Spec 71.4–78.6% AUC 0.61–0.86 Acc 65.0–70.0% | Cyanose 320 PCA; CDA |
| **Interstitial lung disease (ILD)** | | | | |
| Dragonieri 2013 [58] | n = 31 sarcoidosis n = 11 untreated n = 20 treated n = 25 HC | Diagnostic accuracy | Untreated vs HC AUC 0.825 CVA 83.3% | | |
| Bannier 2019 [23] | n = 13 CF (age > 6 years) n = 22 HC | Diagnostic accuracy | Sens 85% Spec 77% AUC 0.87 | | |
| De Heer 2014 [54] | n = 9 CF colonised A. fumigatus n = 18 CF not colonised | Diagnostic accuracy | Sens 78% Spec 94% AUC 0.80–0.89 CVA 88.9% | | |
| Dragonieri 2013 [58] | n = 31 sarcoidosis n = 11 untreated n = 20 treated n = 25 HC | Diagnostic accuracy | Untreated vs HC AUC 0.825 CVA 83.3% | | |
| **Lung cancer (LC)** | | | | |
| Machado 2005 [75] | n = 14 LC n = 20 HC n = 27 other lung disease | Diagnostic accuracy | Training: LC vs HC + other CVA 71.6% (CDA) Validation: LC vs HC + other Sens 71.4% Spec 91.9% Acc 85% (SVM) | Cyanose 320 SVM PCA CDA |
| Hubers 2014 [71] | n = 20 LC n = 31 HC | Diagnostic accuracy | Training: Sens 80% Spec 48% Validation: Sens 94% Spec 13% | | |

Note: The table includes details of study participants, outcome measures, results, eNose outcomes, and statistical breathprint analysis.
| Study participants                          | Outcome measures | Results                  | eNose               | Statistical breathprint analysis |
|--------------------------------------------|------------------|--------------------------|---------------------|---------------------------------|
| Schmekel, 2014 [88] n = 22 LC              | Disease course   | <1 y vs HC R = 0.95–0.98 | Prediction model survival days R = 0.96–0.97 | Applied Sensor AB model 2010 | PCA; PLS; ANN |
| McWilliams, 2015 [68] n = 25 LC            | Diagnostic accuracy | Sens 84–96% Spec 63.3–81.3% AUC 0.84 | | | |
| Gasparri, 2016 [76] Training: n = 51 LC n = 54 HC Validation: n = 21 LC n = 20 HC | Diagnostic accuracy | | | | |
| Rocco, 2016 n = 100 (former) smokers [16]  | Diagnostic accuracy | Detection LC Spec 86% AUC 0.79 | | | |
| Van Hooren, 2016 [81] n = 32 LC            | Diagnostic accuracy | Sens 84–96% Spec 85–88% AUC 0.88–0.98 Acc 85–93% | | | |
| Shlomi, 2017 [67] n = 30 benign nodule n = 89 LC n = 53 EGFR tested (n = 19 mutation) | Diagnostic accuracy | Early stage LC vs benign Sens 75% Spec 93.3% AUC 87.0 | | | |
| Tirzite, 2017 [83] n = 165 LC n = 79 HC n = 91 other lung disease | Diagnostic accuracy | LC vs HC Sens 87.3–88.9% Spec 66.7–71.2% CV 72.8% | | | |
| Huang, 2018 [70] Training: 80% of n = 56 LC n = 188 HC Validation: 20% of n = 56 HC n = 188 HC | Diagnostic accuracy | Validation: LC vs HC Sens 100, 92.3% Spec 88.6, 92.9% AUC 0.96, 0.95 Acc 90.2, 92.7% | | | |
| Van de Goor, 2018 [73] Training: n = 52 LC n = 93 HC Validation: n = 8 LC n = 14 HC | Diagnostic accuracy | Training: Sens 83% Spec 84% AUC 0.84 Acc 83% | | | |
| Tirzite, 2019 [77] n = 119 LC smoker n = 133 LC non-smoker n = 223 HC + other lung disease n = 91 smoking | Diagnostic accuracy | LC non-smoker vs HC + other Sens 96.2% Spec 90.6% | | | |
| Kononov, 2020 [78] n = 65 LC n = 53 HC | Diagnostic accuracy | Sens 85.0–95.0% Spec 81.2–100% CVA 88.9–97.2% AUC 0.95–0.98 | | | |
| Krauss, 2020 n = 91 LC active disease n = 51 incident LC n = 29 LC complete response n = 33 HC n = 23 COPD | Diagnostic accuracy | LC active vs HC Sens 84% Spec 97% AUC 0.92 | | | |
| Lung cancer—(non-)small cell lung cancer (NSCLC) | | | | | |
| Dragonieri, 2009 [69] n = 10 NSCLC n = 10 COPD | Diagnostic accuracy | NSCLC vs HC CV 90% | | | |
| | | NSCLC vs COPD CV 85% | | | |
| Study participants | Outcome measures | Results | eNose | Statistical breathprint analysis |
|---------------------|------------------|---------|-------|---------------------------------|
| **Kort 2018 [72]**  |                  |         |       |                                 |
| n = 144 NSCLC      | Diagnostic        |NSCLC vs HC | Aeonose | ANN                            |
| n = 18 SCLC        | accuracy          | Sens 92.2% |        |                                 |
| n = 85 HC          |                  | Spec 51.2% |        |                                 |
| n = 61 suspected, LC excluded | AUC 0.85 |                  |        |                                 |
| De Vries 2019 [87] | Training:        |Therapeutic | SpiroNose | LDA                            |
| n = 92 NSCLC       | Diagnostic        |NSCLC vs HC |        |                                 |
| n = 51 SCLC        | accuracy          | Sens 94.2% |        |                                 |
| • n = 42 response  |                  | Spec 44.1% |        |                                 |
| • n = 50 no response|                  | AUC 0.75  |        |                                 |
| Mohamed 2019 [80]  | Diagnostic        |NSCLC vs controls | PEN3 | PCA; ANN                        |
| n = 50 NSCLC       | accuracy          | Sens 92.9% |        |                                 |
| n = 50 HC          |                  | Spec 90%   |        |                                 |
| n = 50 NSCLC       |                  | Acc 97.7%  |        |                                 |
| **Kort 2020 [74]** |                  |         |       |                                 |
| n = 138 NSCLC      | Diagnostic        |NSCLC vs controls | Aeonose | ANN; Multivariate logistic regression |
| n = 143 controls   | accuracy          | Sens 94.2% |        |                                 |
| • n = 59 suspected, LC excluded | Spec 44.1% |        | |                                 |
| • n = 84 HC        |                  | AUC 0.75  |        |                                 |
| Fielding 2020 [82] |                  |         |       |                                 |
| n = 20 bronchial SCC | Diagnostic       |BSCC in situ vs HC | Cyanose | 320                             |
| • n = 10 in situ   | accuracy          | Sens 77%  |        |                                 |
| • n = 10 advanced stage | Spec 80%        |        |        |                                 |
| n = 22 laryngeal SCC |                  | Misclassification rate 10% | Cyanose | 320                             |
| • n = 12 in situ   |                  | Spec 80%  |        |                                 |
| • n = 12 advanced stage |              |        |        |                                 |
| n = 13 HC          |                  | Misclassification rate 10% | Cyanose | 320                             |
| Chapman 2012 [86]  |                  |         |       |                                 |
| Training:          | Diagnostic        |MPM vs ARD | Cyanose | 320                             |
| n = 10 MPM         | accuracy          | Sens 90%  |        |                                 |
| n = 10 MPM         |                  | Spec 88%  |        |                                 |
| n = 32 HC          |                  | Acc 65.2% |        |                                 |
| n = 18 benign ARD  |                  | (44.5–82.3)|        |                                 |
| Dragonieri 2012 [85]|                  |         |       |                                 |
| n = 13 MPM         | Diagnostic        |MPM vs AEx | Cyanose | 320                             |
| • internal validation with training set: | accuracy         | Sens 92.3% |        |                                 |
| n = 8, validation set: n = 5 |                  | Spec 69.2% |        |                                 |
| n = 13 HC          |                  | AUC 0.893 |        |                                 |
| n = 13 AEx         |                  | CVA 84.6% |        |                                 |
| Lamotte 2017 [84]  |                  |         |       |                                 |
| n = 11 MPM         | Diagnostic        |MPM vs benign ARD | Cyanose | 320                             |
| n = 12 HC          | accuracy          | Sens 75.0% (45.9–93.2) | PCA |                               |
| n = 15 AEx         |                  | Spec 64%  |        |                                 |
| n = 12 benign ARD  |                  | AUC 0.758 (0.582–0.913) | PCA |                               |
| Pulmonary infections|                  |         |       |                                 |
| De Heer 2016 [100] |                  |         |       |                                 |
| n = 168 bottles with strain | Diagnostic       |Mould vs other | Cyanose | 320                             |
| • n = 135 bacteria + yeast | accuracy      | Sens 91.9% |        |                                 |
| • n = 30 medium only |                  | Spec 95.2% |        |                                 |
| • n = 62 mould (A. fumigatus and R. oryzae) | AUC 0.970 (0.949–0.991) | Cyanose | 320                             |
| n = 62 mould (A. fumigatus and R. oryzae) |                | Acc 92.9% |        |                                 |
### Table 2 (continued)

| Study participants | Outcome measures | Results | eNose | Statistical breathprint analysis |
|--------------------|------------------|---------|-------|----------------------------------|
| **Pulmonary infections—Tuberculosis (TB)** |
| Suarez-Cuartin 2018 [101] | n = 73 bronchiectasis  • n = 41 colonised (n = 27 pseudomonas)  • n = 32 non-colonised | Diagnostic accuracy | Collonised vs non-colonised AUC 0.75  CVA 72.1% | Cyanose 320 | PCA |
| **Pulmonary infections—Ventilator-associated pneumonia (VAP)** |
| Hanson 2005 [104] | n = 19 VAP (clinical pneumonia score, CPIS ≥ 6)  n = 19 controls (CPIS < 6) | Diagnostic accuracy | Correlation CPIS-breathprint R² = 0.81 | Cyanose 320 | PLS |
| Hockstein 2005 [105] | n = 15 VAP (pneumonia score ≥ 7)  n = 29 HC (ventilated) | Diagnostic accuracy | Acc 66–70% | Cyanose 320 | KNN |
| Humpleys 2011 [99] | n = 44 VAP suspected  • 98 BAL samples  • Groups: gram-positive, gram-negative, fungi, no growth  n = 6 HC (ventilated) | Diagnostic accuracy (in vitro) | Differentiation groups (LDA)  Sens 74–95%  Spec 77–100%  Acc 83% | Prototype (24 MOS) | PCA, LDA |
| Schnabel 2015 [106] | n = 72 VAP suspected  • n = 33 BAL +  • n = 39 BAL –  n = 53 HC (ventilated) | Diagnostic accuracy | BAL + VAP vs HC  Sens 88%  Spec 66%  AUC 0.82 (0.73–0.91) | DiagNose | Random Forest, PCA |
| Chen 2020 [15] | Training: 80% of n = 33 VAP  • n = 26 HC (ventilated)  Validation: 20% of n = 33 VAP  • n = 26 HC (ventilated) | Diagnostic accuracy | Training: AUC 0.823 (0.70–0.94) | Cyanose 320 | KNN, Naive Bayes, decision tree; neural network; SVM; random forest |
| **Pulmonary infections—Tuberculosis (TB)** |
| Fend 2006 [109] | n = 188 TB  n = 142 TB excluded | Diagnostic accuracy (in vitro) | Sens 89% (80–97)  Spec 88% (85–97) | Bloodhound BH-114 | PSA, DFA, ANN |
| Bruins 2013 [107] | Training: n = 15 TB  • n = 14 TB excluded  Validation: n = 34 TB  • n = 114 TB excluded  n = 46 HC | Diagnostic accuracy | Training: Sens 95.9% (92.9–97.7)  Spec 98.5% (96.2–99.4) | Validation: TB vs HC  Sens 93.5% (91.1–95.4)  Spec 85.3% (82.7–87.5) | ANN |
| Coronel Teixeira 2017 [108] | Training: n = 23 TB  • n = 46 HC  Validation: n = 47 TB  • n = 63 HC + asthma + COPD | Diagnostic accuracy | Training: Sens 91%  Spec 93% | Validation: Sens 88%  Spec 92% | Aeonose 3-like algorithm, ANN |
| Mohamed 2017 [110] | n = 67 TB  n = 56 HC | Diagnostic accuracy | Sens 98.5% (92.1–100)  Spec 100% (93.5–100)  Accuracy 99.2% | PEN3 | PCA, ANN |
| Saktiawati 2019 [111] | Training: n = 85 TB  • n = 97 HC + TB excluded | Diagnostic accuracy | Training: Sens 85% (75–92)  Spec 55% (44–65)  AUC 0.82 (0.72–0.88) | Validation: Sens 78% (70–85)  Spec 42% (34–50) | Aeonose | ANN |
| Zetola 2017 [112] | n = 51 TB  • n = 20 HC | Diagnostic accuracy | Sens 94.1% (83.8–98.8)  Spec 90.0% (68.3–98.8) | Prototype (QMB sensors) | PCA, KNN |
Table 2 (continued)

| Study participants                                                                 | Outcome measures                                                                 | Results                                                                 | eNose       | Statistical breathprint analysis |
|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------|---------------------------------|
| **Pulmonary infections—Aspergillosis**                                             |                                                                                   |                                                                        |             |                                 |
| De Heer 2013 [102]                                                                  | n = 11 neutropenia                                                               | Diagnostic accuracy                                                    | Cyranose    | PCA, CDA                        |
|                                                                                     | • n = 5 probable/proven aspergillosis                                           | Sens 100% (48–100) Spec 83.3% (36–100) AUC 0.933 CVA 90.9% (59–100) |             |                                 |
| De Heer 2016 [54]                                                                  | n = 9 CF colonised A. fumigatus                                                 | Diagnostic accuracy                                                    | Cyranose    | PCA, CDA                        |
|                                                                                     | n = 18 CF not colonised                                                          | Sens 78% Spec 94% AUC 0.80–0.89 CVA 88.9%                               |             |                                 |
| **Pulmonary infections—Corona Virus Disease (COVID-19)**                            |                                                                                   |                                                                        |             |                                 |
| Wintjens 2020 [114]                                                                | n = 219 screened                                                                  | Diagnostic accuracy                                                    | Aeonose ANN |                                 |
|                                                                                     | • n = 57 COVID-19 positive                                                       | Sens 86% (74–93) Spec 54% (46–62) AUC 0.74 CVA 62%                     |             |                                 |
| **Obstructive sleep apnoea (OSA)**                                                 |                                                                                   |                                                                        |             |                                 |
| Greulich 2013 [89]                                                                  | n = 40 OSA                                                                       | Diagnostic accuracy                                                    | Cyranose    | PCA                             |
|                                                                                     | n = 20 HC                                                                        | OSA vs HC Sens 93% Spec 70% AUC 0.85 CVA 97.4                           |             |                                 |
|                                                                                     | N = 40 OSA                                                                       | Therapeutic effect                                                     |             |                                 |
|                                                                                     | • 3 months CPAP ventilation                                                       | Before vs after CPAP Sens 80% Spec 65% AUC 0.82                          |             |                                 |
| Incalzi 2014 [95]                                                                  | n = 50 OSA                                                                       | Therapeutic effect                                                     | BIONOTE PCA|                                 |
|                                                                                     | • 1 night CPAP ventilation                                                       | Change in breath-print (visually different, no statistical analysis)   |             | PLS-DA                          |
| Dragonieri 2015 [90]                                                               | n = 19 OSA                                                                       | Diagnostic accuracy                                                    | Cyranose    | PCA, CDA, KNN                    |
|                                                                                     | n = 14 obese                                                                      | Obese OSA vs HC Sens 79% Spec 68% AUC 97.4 CVA 96.1                    |             |                                 |
|                                                                                     | n = 20 HC                                                                        | (Non-)OSA 7AM vs HC 7PM Not significantly different Acc 77–81%         |             |                                 |
| Kunos 2015 [96]                                                                    | n = 17 OSA                                                                       | Diagnostic accuracy                                                    | Cyranose    | PCA                             |
|                                                                                     | n = 9 non-OSA sleep disorder                                                     | Obese OSA vs HC Sens 87% Spec 70% AUC 94.1 CVA 94.1                    |             |                                 |
|                                                                                     | n = 10 HC                                                                        | Non-OSA or HC 7AM vs 7PM Significantly different Acc 77–81%            |             |                                 |
|                                                                                     | • 7AM and 7PM sample                                                             |                                                                            |             |                                 |
|                                                                                     | n = 26 HC                                                                        |                                                                            |             |                                 |
|                                                                                     | • 7AM sample                                                                     |                                                                            |             |                                 |
| Dragonieri 2016 [92]                                                               | Training: n = 13 OSA                                                              | Diagnostic accuracy                                                    | Cyranose    | PCA, CDA                        |
|                                                                                     | Validation: n = 6 OSA                                                             | OSA vs overlap CVA 92% AUC 0.98                                          |             |                                 |
|                                                                                     | n = 15 COPD                                                                      | Validation: OSA vs overlap CVA 91.7% AUC 1.00                            |             |                                 |
|                                                                                     | n = 6 overlap                                                                    | Validation: OSA vs COPD CVA 75% AUC 0.83                                |             |                                 |
| Scarlet 2017 [91]                                                                  | n = 40 OSA                                                                       | Diagnostic accuracy                                                    | BIONOTE     |                                |
|                                                                                     | • n = 20 hypoxic                                                                  | OSA vs HC Sens 98–100%                                                 |             | PLS-DA                          |
|                                                                                     | n = 20 obese                                                                      |                                                                            |             |                                 |
|                                                                                     | n = 20 COPD                                                                      | Non-hypoxic vs hypoxic OSA Acc 60–80%                                  |             |                                 |
|                                                                                     | n = 56 HC                                                                        |                                                                            |             |                                 |
| **Other—Acute respiratory distress syndrome (ARDS)**                               |                                                                                   |                                                                        |             |                                 |
| Bos 2014 [115]                                                                     | Training: n = 40 ARDS                                                             | Diagnostic accuracy                                                    | Cyranose    | Sparse-partial least             |
|                                                                                     | Validation: n = 18 ARDS                                                           | Sens 95% Spec 42% AUC 0.72                                              |             | square logistic regression      |
|                                                                                     | n = 66 HC                                                                        |                                                                            |             |                                 |
| **Other—Lung transplantation (LTx)**                                               |                                                                                   |                                                                        |             |                                 |
| Kovacs 2013 [117]                                                                  | n = 16 LTx recipients                                                             | Diagnostic accuracy                                                    | Cyranose    | PCA, Linear regression          |
|                                                                                     | n = 33 HC                                                                        | LTx recipients vs HC Sens 63% Spec 75% AUC 0.825                         |             |                                 |
Moreover, two studies showed that eNose technology distinguishes children with asthma from healthy controls [23, 25, 34]. An eNose seemed to be more accurate for diagnosing asthma than spirometry with bronchodilation only [34]. Also, uncontrolled asthma could be differentiated from controlled asthma and healthy controls [25]. Furthermore, eNose technology accurately distinguished children with persistent asthma from healthy controls, but not the ones with intermittent asthma [34]. This was possibly due to more airway inflammation reflected in the breathprints of persistent asthmatics. Hence, eNose technology could potentially facilitate easier and earlier diagnosis of asthma in children, and guide therapy in clinical practice. However, large validation studies focusing on diagnosing asthma in children are currently lacking.

**COPD**

Although COPD is one of the major causes of death worldwide, epidemiological studies indicate that it remains largely underdiagnosed [35]. COPD is a complex, heterogeneous disease with several phenotypes, which can overlap with asthma and pulmonary infections, among others. Furthermore, the diagnosis is delayed in patients whose symptoms are attributed to (undiagnosed) heart failure [36]. Hence, there is an unmet clinical need for accurate timely diagnosis. Also better disease course prediction and therapy guidance is warranted.

Several studies have evaluated the ability of eNose technology to diagnose COPD. Exhaled breath analysis discriminated between COPD and (smoking) healthy controls with an accuracy of 66–100% [19, 37–41]. Even though these are promising results, most studies were relatively small and lacked a validation cohort. Several studies aimed to distinguish subgroups within COPD by performing unsupervised analyses on breathprint data [42–44]. De Vries et al. performed unsupervised cluster analysis in a combined group of asthma and COPD patients [43]. Interestingly, they identified and validated five clusters which mainly differed based on clinical and inflammatory characteristics (eosinophil and neutrophil count) rather than diagnosis. Two other studies identified 3–4 unsupervised clusters based on breathprint data. The clusters differed regarding several clinical and demographic features [42, 44]. However, in both studies, clusters were determined by different clinical parameters, showing the need for further (validation) studies. A recent study indicated that breathprints of patients with COPD associated with air pollution did not differ from smoking-associated COPD [40]. Also, no differences in breathprint between Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I-II versus GOLD stage III-IV were detected in another study [40]. The breathprint of patients with smoking-related COPD and patients with alpha-1-antitrypsin, however, could be distinguished with an accuracy of 82% in a single-centre study [37].

**An overview of eNose technology studies in lung diseases. Studies are divided per diagnosis and displayed in chronological order. Study results shown in sensitivity/ specificity, AUC and CVA (if available). In case of a training and validation set, participant numbers and results of both set are shown. All presented results are statistical significant (p < 0.05) unless stated otherwise**

| Study participants | Outcome measures | Results | eNose breathprint analysis |
|--------------------|------------------|---------|---------------------------|
| **Diagnostic effect** | Therapeutic | Correlation breath-print—tiacrolimus levels | Cyanose 320 | PCA; Linear regression |
| **Therapeutic effect** | Correlation breath-print—tiacrolimus levels | Cyanose 320 | PCA; Linear regression |

**Other—Pulmonary embolism (PE)**

| Fens 2010 [116] | Diagnostic accuracy | Comorbidity: PE vs excluded | No comorbidity: PE vs excluded | No comorbidity: PE vs excluded (breath-print + Wells) |
|-----------------|---------------------|-----------------------------|------------------------------|--------------------------------------------------|
| n = 20 PE       | Acc 65%              | AUC 0.55                     | AUC 85%                      | AUC 0.81                                         |
| n = 20 PE excluded |                    |                             |                              |                                                  |
| n = 13 comorbidity |                   |                             |                              |                                                  |

Table 2 (continued)
eNose technology can theoretically be useful in early detection of inflammation and acute exacerbation of COPD (AECOPD), as inflammatory processes influence breathprints. This hypothesis was confirmed in a cross-sectional study evaluating the association of breathprints with different inflammation markers in sputum; eNose breathprints highly correlated with inflammatory activity [45]. In patients with an AECOPD, presence of viral and bacterial infection was accurately detected by an eNose [46]. In another group of AECOPD patients, patients with colonisation of potentially pathogenic microorganisms had a significantly different breathprint than AECOPD patients that were not colonised. Besides, AECOPD patients’ breathprints differed from stable COPD patients without microorganism colonisation [39]. Stable COPD patients with bacterial colonisation were also significantly different from those without (area under the curve (AUC) 0.922) [41]. Two prospective longitudinal studies indicated that the breathprint before, during and after recovery of an AECOPD differed [39, 47]. Confirming these results in larger cohort studies might lead the way to use breathprints for earlier detection and (targeted) treatment of infections and AECOPDs. This is interesting as treatment may improve outcomes and prevent hospitalizations [48].

Regarding prognostic value of eNose technology, one study demonstrated that eNose data correlated better to change in 6-min walking distance over one year, than the current GOLD classification [49]. A few studies evaluated the effect of initiation and withdrawal of inhalation medication on breathprints. Two studies found significant changes in breathprint after start of inhalation therapy [44, 50]. A designed multidimensional model, combining eNose technology with spirometry, gave a better indication of treatment response (AUC 0.857) than spirometry only (AUC 0.561) [50]. This small pilot study shows the potential of integrating eNose technology in standard practice. However, it remains to be elucidated whether eNose technology can serve as a marker for therapy compliance of inhaled medication.

Cystic fibrosis

Cystic fibrosis (CF) is associated with bronchiectasis, recurrent infectious exacerbations, and progressive deterioration of lung function due to exacerbations [51]. A few studies using different eNoses showed that patients with CF could accurately be distinguished from healthy controls and asthma patients based on their breathprint [23, 52, 53]. Two studies showed conflicted results regarding differentiation of CF from primary ciliary dyskinesia (PCD) patients, a bronchiectatic lung disease that mimics symptoms of CF [53]. While Paff et al. showed that CF and PCD could be adequately discriminated, Joensen et al. found no significant differences [52, 53]. This was possibly due to methodological differences, such as different breath collection methods and a more heterogeneous patient population in the latter study. Furthermore, eNose technology adequately discriminated between patients with and without exacerbations, with and without chronic Pseudomonas aeruginosa colonisation, and patients with and without Aspergillus fumigatus colonisation [52–54]. It would be of great interest to investigate whether early stage respiratory infections and exacerbations can also be detected and eventually be predicted by eNose technology. This will possibly increase the chance of successful eradication and slowing down pulmonary function decline.

Interstitial lung disease

Interstitial lung disease (ILD) is a heterogeneous group of relatively uncommon diseases causing fibrotic and/or inflammatory changes in interstitial lung tissue. Disease course and treatment strategies widely vary for different ILDs, and even within individual ILDs disease course often varies. Diagnosis is based on integration of clinical data with imaging and if needed pathology data. Diagnosis is often complex and diagnostic delays are common [55, 56]. eNose technology has the potential to replace invasive procedures, and aid the diagnostic process to facilitate timely and accurate diagnosis.

A large single centre cohort, including various ILDs, found that breathprints of ILD patients could be distinguished from healthy controls with 100% accuracy. Results were confirmed in a validation cohort [57]. A few other studies compared individual ILDs with healthy controls and COPD patients [58–61]. Breathprints of patients with idiopathic pulmonary fibrosis (IPF), ILD associated with connective tissue disease and pneumoconiosis were significantly different from healthy controls [59–61]. In sarcoidosis patients, the breathprint of patients with untreated sarcoidosis differed from healthy controls, implying that eNose technology may be used for initial diagnosis. This study found that breathprints of treated sarcoidosis patients were not significantly different from healthy controls, but the number of participants was small [58]. Comparing different ILDs, eNose technology distinguished IPF from non-IPF ILD patients with an accuracy of 91% in both training and validation cohort. Exploratory analyses indicated that individual ILDs can also be discriminated adequately [57]. However, groups were relatively small and, thus, results should be validated and confirmed in larger cohorts. A currently ongoing large multicentre study is investigating the potential of eNose technology to identify individual diseases, predict disease course, and response to treatment in fibrotic ILDs (NCT04680832).
Lung cancer

Worldwide, lung cancer is the leading cause of cancer deaths and has the highest incidence of all cancer types. More than 80% of patients suffering from lung cancer are former or current tobacco smokers [62]. Early diagnosis is clearly associated with better outcomes, and lung cancer screening has shown to reduce mortality [63, 64]. Nevertheless, early diagnosis remains challenging, since initial clinical presentation often overlaps with COPD or other smoking-related diseases, and symptoms often only appear in late stages [65]. Low-dose CT scan is currently the best available tool for screening. However, this type of screening is only cost-effective in a selected group of former and current smokers [66]. Also, differentiation of benign from malignant nodules is not possible with CT scan results; therefore, detected nodules warrant further invasive investigations. eNose could possibly serve as non-invasive and less costly screening tool to identify malignant pulmonary neoplasms. Two studies used eNose technology in high-risk patients enrolled for lung cancer screening. Both studies found a higher specificity for detecting lung cancer with eNose compared to low-dose CT scan; thus, the use of eNose technology as screening tool can potentially reduce the false-positive rate and prevent unnecessary (invasive) testing [16, 67]. It is important to note that not all lesions classified as benign were histologically proven in these studies.

Whether an eNose can differentiate lung cancer patients from healthy controls, patients with benign lung nodules or (former) smokers, has been investigated in different cohorts. All studies in (non-) small cell lung cancer ((N)SCLC) showed significant results, albeit with a wide range in reported sensitivity (71–99%) and specificity (13–100%) [68–80]. Smoking status of participants did not seem to influence accuracy of an eNose for detecting cancer [77]. One small study showed that patients with and without an EGFR (epidermal growth factor receptor) mutation had distinct breathprints [67]. It has not been evaluated whether eNoses can recognize specific types of lung cancer in a cohort with different subtypes. Recognition of subtypes seems plausible, as differentiation of lung cancer from head-neck cancer was possible with eNose technology [81, 82]. eNose technology did not discriminate between different stages of lung cancer [83]. One recent study in NSCLC combined eNose data with relevant clinical parameters (such as age, number of pack years, and presence of COPD), and showed a higher accuracy for lung cancer detection than using eNose data only. These results highlight the potential of eNose technology as additional diagnostic procedure [74]. Some small studies indicated that eNose technology was also able to differentiate patients suffering from malignant pleural mesothelioma (MPM) and healthy controls. Differentiation of MPM from benign asbestososis disease and asymptomatic asbestos exposure had a high sensitivity too [84–86].

Prediction of response to therapy is investigated for anti-programmed death (PD)-1 receptor therapy in NSCLC patients. Breathprints were collected before start of pembrolizumab or nivolumab therapy. Exhaled breath data could predict which patients would respond to therapy with an AUC of 0.89, confirmed in a validation cohort. By setting a cut-off value to obtain 100% specificity, the investigators were able to detect 24% of non-responders to anti-PD-1 therapy. In this regard, eNose seems to be more accurate than the currently used biomarker PD-L1 [87]. Another study is currently registered for recruiting until July 2021 and will evaluate the effect of immunotherapy on breathprints of exhaled breath and sweat in lung cancer patients (NCT03988192).

Schmekel et al. investigated the ability of eNose to predict prognosis in patients with end stage lung cancer. They collected breathprints before start and several times after start of palliative chemotherapy and applied different prediction models. Patients with less than one year survival and more than one year survival could be separated based on breathprint [88]. The authors suggest to use this eNose-based prediction for choosing a certain treatment strategy, but this needs confirmation in studies first.

Obstructive sleep apnoea

At the moment, the gold standard for diagnosing obstructive sleep apnoea (OSA) is (poly)somnography which is a costly and time-consuming test. eNose technology has been investigated as an alternative modality to diagnose this condition and assess treatment effect.

It was shown that breathprints from OSA patients and healthy controls can be distinguished reliably [89–91]. However, it remains questionable whether breathprints distinguishes true OSA, or if the breathprint is just a reflection of a metabolic syndrome or underlying inflammation caused by obesity. In one of the studies this question was more apparent as groups were not matched for body mass index [89]. Dragonieri et al. found that eNose technology did discriminate obese patients with and without OSA, with moderate accuracy [90]. Nevertheless, another study could not confirm those results [91].

Other researchers investigated OSA, OSA-COPD overlap syndrome and COPD. OSA could be distinguished from the overlap syndrome, but eNose technology could not discriminate well between the overlap syndrome and COPD. Also here it is not clear whether true OSA can be detected or other factors, such as COPD, are picked up [91, 92]. Whether included patients also suffer from heart failure is not clearly displayed in these studies, although
it is known that many heart failure patients suffer from OSA and that heart failure might influence breathprint [93, 94].

The effects of continuous positive airway pressure (CPAP) treatment in patients with OSA has also been studied. The breathprint of OSA patients changed significantly already after one night of CPAP treatment [95]. Significant difference in breathprint was also found before and after three months of CPAP treatment [89]. It remains to be elucidated what this change in breathprint indicates. Possibly, the alteration in breathprint could serve as a marker for metabolic success, therapeutic benefit or treatment adherence. Furthermore, it must be noted that the breathprints of patients with OSA differed between morning and evening [96]. Hence, diurnal variance must be taken into account when using an eNose for patients with OSA.

**Pulmonary infections**

Pathogenic micro-organisms, such as viruses, bacteria or fungi, can cause severe pulmonary infections. Identification of specific micro-organisms with sputum cultures can take up to several days, and is only possible if a specimen with sufficient quality is obtained. Specificity and sensitivity also depend on the causative micro-organism, experience of laboratory observer, and prior treatment [97]. Therefore, reported sensitivity of detecting bacteria in sputum culture ranges between 57 and 95%, and specificity between 48 and 87% [98]. Detection of specific micro-organisms using eNose technology can potentially reduce misuse of antibiotics and facilitate timely start of guided therapy.

Until now, two in vitro studies aimed to differentiate micro-organisms by analysing breathprints of their headspace air [99, 100]. Mould species were discriminated from other samples (bacteria, yeasts, and control medium) with a high accuracy (92.9%). Furthermore, different mould species seemed to have different breathprints [100]. Another study performed eNose analyses on bronchoalveolar lavage samples, and demonstrated accurate discrimination between Gram-positive bacteria, Gram-negative bacteria, fungi, and samples without growth of micro-organisms [99]. In vivo, breathprints of bronchiectasis patients significantly differed between those colonised with Pseudomonas Aeruginosa and those colonised with other pathogenic micro-organisms or non-colonised [101]. For detection of aspergillus colonisation or invasive aspergillosis in specific patient groups (CF and neutropenic patients), studies revealed a high accuracy of eNose breathprint analysis [54, 102]. These studies did not include a validation cohort or healthy control group.

Ventilator-associated pneumonia (VAP) is a common nosocomial infection in ventilated patients and has an incidence and mortality around 9% [98, 103]. In most eNose studies, bacterial growth in sputum or a clinical pneumonia score was used to define VAP [15, 104–106]. Two studies showed that obtained breathprints highly correlated with a clinical pneumonia score, implying that eNose technology might be used to predict the probability of a VAP [104, 105]. Two case–control studies in patients with VAP and ventilated patients without pneumonia showed conflicting results; Schnabel and colleagues concluded that eNose technology lacked sensitivity and specificity, whereas a recently published study of Chen and colleagues found a good accuracy for detecting VAP [15, 106]. This shows the need for more research on this topic before eNose can be used to determine the need for more (invasive) diagnostics in ill patients, such as performing bronchoscopy.

In pulmonary tuberculosis (TB) patients, detection and screening with eNose technology has been studied in different countries and compared to different control groups [107–112]. As TB is the leading cause of death from an infection caused by a single micro-organism, and as it has a high prevalence in developing countries, establishing a fast non-invasive cheap screening tool is much needed [113]. In one study, eNose technology differentiated TB from non-TB quite accurately, suggesting that it can potentially serve as a screening tool. Detection of TB had a sensitivity of 89% and a specificity of 91% compared to positive cultures. This sensitivity and specificity exceeded Ziehl–Neelsen staining [109]. However, all studies with proven TB and healthy participants in the training cohort, had a lower accuracy when validating the results in a cohort also including suspected TB patients [107, 108, 111]. Thus, more research is necessary before eNose technology can be used as a population-wide screening tool.

Due to the Corona Virus Disease (COVID-19) pandemic, much research effort is being put in the evaluation of eNose technology as a fast and non-invasive tool for the detection of COVID-19 (NCT04475562, NCT04475575, NCT04558372, NCT04379154, NCT04614883, NL8694). To date, one study tested the accuracy of eNose technology for COVID-19 screening prior to surgery in non-symptomatic patients and found a negative predictive value up to 0.96. Reverse transcription-polymerase chain reaction on a pharyngeal swab and antibody testing were used to confirm presence or absence of COVID-19 [114].

**Other**

A number of eNose studies have been performed in other lung diseases. In acute respiratory distress syndrome (ARDS), eNose technology could discriminate between
mechanically ventilated patients with and without ARDS, with moderate accuracy in a training and validation cohort [115].

One small proof-of-principle study has been performed in patients with suspected pulmonary embolism, defined as a high clinical probability according to the Wells’ score or elevated D-dimer. Breathprints of non-comorbid patients with and without pulmonary embolism could be distinguished with an accuracy of 85%. However, in patients with comorbidities known to influence VOCs (e.g. cancer, diabetes) the accuracy dropped [116].

Finally, eNose technology could be useful for follow-up and monitoring lung transplant recipients. One study found a significant association between breathprint and plasma tacrolimus levels, suggesting that eNoses might be used for non-invasive therapeutic drug monitoring [117].

A clinical trial in lung transplant recipients is currently conducted (NL9251) looking at discrimination of stable lung transplant recipients, acute cellular rejection, and chronic lung allograft rejection.

Discussion
In the past decades, multiple eNoses have been developed and tested in numerous clinical studies for a wide spectrum of lung diseases. So far, the vast majority of studies evaluated the ability of eNose technology to distinguish lung diseases from healthy controls, and to discriminate between different diagnoses. A small number of studies have been performed for prognostic or therapeutic purposes, and only a handful of studies have focused on clustering patients by breathprint and identifying phenotypes. Results in lung diseases are overall very promising, but several issues should be addressed before eNoses can be implemented in daily clinical practice.

One of the issues is the use of various eNose devices with different qualifications, types of sensors and breath sample collection methods as summarised in Table 1. It is not possible to point out the best eNose device or select one optimal sensor type, as each setting, disease and research aim can require different features. For example, a portable device might be optimal for an acute care setting, direct sampling without collection bags might be useful in low resource areas and as point-of-care technique, and a device that corrects for ambient air will probably generate more comparable results in multicentre use and settings with unstable or varying environmental conditions.

Given important differences between the various devices, it is difficult to compare data of the different eNose devices. Hence, each eNose needs to be validated for every clinical application. This implies that knowledge about characteristics of eNose devices is essential before initiating eNose research, as the type of device cannot easily be changed during the trajectory of developing a clinical tool. Additionally, the influence of endogenous (e.g. comorbidities, ethnicity, age) and exogenous factors (e.g. smoking, nutrition, drug use, measurement environment) on breathprints needs to be further elucidated.

Furthermore, studies differ significantly with regards to study design (e.g. patient selection, number of participants, and presence of a validation cohort). As illustrated in Fig. 2, the majority of studies so far can be considered as pilot or exploratory studies, and have small numbers of participants. The most important goal of these studies is to test new hypotheses, which can be further assessed and confirmed in larger studies with external validation. However, these validation studies are not often conducted. This lack of validation is a major issue in development of a clinical useful breath biomarker, as breath analysis results are not always interchangeable between research settings due to a combination of the above mentioned factors. To ensure optimal outcomes, comparison and generalisability of eNose studies, the design and analysis methods should ideally be based on specific predefined research aims.

Moreover, most studies do not explain the rationale for choosing a certain machine learning model for analysing eNose data. This prevents insights in and discussion regarding the optimal analysis techniques and algorithms. Machine learning models are complex to execute and interpret, and if not used in the right way are prone for overfitting. To avoid inadequate modelling, data scientists should always be involved in these complex analyses and models should be validated independently to exclude overfitting. To allow for comparison of different modelling techniques, we recommend an extensive world-wide shared database per eNose with FAIR (findable, accessible, interoperable, and reusable) and open source data, including patient characteristics and other pre-test probabilities. This database would ensure optimal training, validation, and application of models.

Finally, a factor that hampers eNose implementation is the need for a strong gold standard to establish a diagnosis or to evaluate therapeutic effect. High quality data input is required for optimal validity when developing a new technique. Some of the diseases mentioned in this review lack a gold standard, and even if a gold standard does exist, there is always a range of uncertainty. There is a potential for unsupervised machine learning models in this regard, as such analyses could help to identify previously unrecognised phenotype clusters. Discovering such new clusters can help to generate hypotheses about the existence of unravelled disease subtypes or overlap between diagnoses, and might eventually guide new diagnostic standards.
In conclusion, eNose technology in the field of lung diseases is promising and at the doorstep of the pulmonologist’s office. To facilitate clinical implementation, we recommend conducting prospective multicentre trials including validation in external cohorts with a study design and analysis method relevant for the research aim, and sharing databases on open source platforms. If supported by sufficient evidence, research can subsequently be extended to clinical implementation studies, and finally, use in daily practice.

We believe that eNose technology has the potential to facilitate personalised medicine in lung diseases through establishing early, accurate diagnosis and monitoring disease course and therapeutic effects.

Abbreviations
AECOPD: Acute exacerbation of COPD; AUC: Area under the curve; ARDS: Acute respiratory distress syndrome; CF: Cystic fibrosis; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease; EGFR: Epidermal growth factor receptor; eNose: Electronic nose; FeNO: Exhaled nitric oxide; GOLD: Global Initiative for chronic obstructive lung disease; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; MPM: Malignant pleural mesothelioma; NSCLC: Non-small cell lung cancer; OCS: Oral corticosteroids; OSA: Obstructive sleep apnoea; PCD: Primary ciliary dyskinesia; PD: Programmed cell death; SCLC: Small cell lung cancer; TB: Tuberculosis; VAP: Ventilator-associated pneumonia; VOCS: Volatile organic compounds.

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