

Diagnostic Performance of Electronic Nose Technology in Sarcoidosis



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BACKGROUND: Diagnosing sarcoidosis can be challenging, and a noninvasive diagnostic method is lacking. The electronic nose (eNose) technology profiles volatile organic compounds in exhaled breath and has potential as a point-of-care diagnostic tool.

RESEARCH QUESTION: Can eNose technology be used to distinguish accurately between sarcoidosis, interstitial lung disease (ILD), and healthy control subjects, and between sarcoidosis subgroups?

STUDY DESIGN AND METHODS: In this cross-sectional study, exhaled breath of patients with sarcoidosis and ILD and healthy control subjects was analyzed by using an eNose (SpiroNose). Clinical characteristics were collected from medical files. Partial least squares discriminant and receiver-operating characteristic analyses were applied to a training and independent validation cohort.

RESULTS: The study included 252 patients with sarcoidosis, 317 with ILD, and 48 healthy control subjects. In the validation cohorts, eNose distinguished sarcoidosis from control subjects with an area under the curve (AUC) of 1.00 and pulmonary sarcoidosis from other ILD (AUC, 0.87; 95% CI, 0.82-0.93) and hypersensitivity pneumonitis (AUC, 0.88; 95% CI, 0.75-1.00). Exhaled breath of sarcoidosis patients with and without pulmonary involvement, pulmonary fibrosis, multiple organ involvement, pathology-supported diagnosis, and immunosuppressive treatment revealed no distinctive differences. Breath profiles differed between patients with a slightly and highly elevated soluble IL-2 receptor level (median cutoff, 772.0 U/mL; AUC, 0.78; 95% CI, 0.64-0.92).

INTERPRETATION: Patients with sarcoidosis can be distinguished from ILD and healthy control subjects by using eNose technology, indicating that this method may facilitate accurate diagnosis in the future. Further research is warranted to understand the value of eNose in monitoring sarcoidosis activity.

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KEY WORDS: breath test; diagnostic tool; electronic nose; interstitial lung disease; sarcoidosis

ABBREVIATIONS: AUC = area under the curve; eNose = electronic nose; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; PLS-DA = partial least squares discriminant analysis; sIL-2R = soluble IL-2 receptor; VOC = volatile organic compound

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Take-home Points

Study Question: Can eNose technology be used to distinguish accurately between sarcoidosis, ILD, and healthy control subjects, and between sarcoidosis subgroups?

Results: In a study cohort of 252 patients with sarcoidosis, 317 with ILD, and 48 healthy control subjects, eNose accurately distinguished sarcoidosis from control subjects (AUC, 1.00 in the validation cohort), and pulmonary sarcoidosis from other ILD (AUC, 0.87; 95% CI, 0.82-0.93 in the validation cohort).

Interpretation: Patients with sarcoidosis can be distinguished from ILD and healthy control subjects by using eNose technology, indicating that this method may facilitate accurate diagnosis in the future.

Sarcoidosis is a granulomatous inflammatory disease without a known cause that can affect roughly any organ. The lungs are involved in the vast majority of patients (89%-99%).¹ Diagnosis can be challenging because no standardized diagnostic procedure exists. The three major criteria for diagnosis are compatible clinical features, pathology tissue assessment, and exclusion of other granulomatous diagnoses.²

Due to the heterogeneity of sarcoidosis, disease course and treatment outcomes are difficult to predict. Severity of symptoms, organs affected, disease progression, and treatment response vary widely between individuals.^{1,3} In clinical practice, patients may be divided into those with limited disease (ie, involution or stable) and (potentially) progressive disease with threat to organ function.⁴

Current serum biomarkers for diagnosing, monitoring, or predicting disease course of sarcoidosis lack validity and/or reliability.⁵ Nonetheless, serum levels of soluble

IL-2 receptor (sIL-2R) are often used in clinical practice as a follow-up marker for disease activity.⁶ sIL-2R also correlates with inflammatory activity on PET scans.⁵ The sIL-2R value is not specific for a sarcoidosis diagnosis and not available worldwide.

Breath biomarkers are increasingly studied in respiratory diseases, as exhaled volatile organic compounds (VOCs) reflect pathophysiological processes in the human body.^{7,8} Techniques such as gas chromatography and mass spectrometry can be used to identify individual VOCs but are time-consuming and complex. To the best of our knowledge, three studies have identified individual VOCs in sarcoidosis using these techniques.⁹ However, VOC identification lacked reproducibility in external validation cohorts.¹⁰ It is more likely that analysis of a profile of VOCs (a “breathprint”) using electronic nose (eNose) technology will be of added value in clinical practice. This breath analysis tool is quick, easier, and cheaper than gas chromatography and mass spectrometry analysis.^{8,11} eNose devices contain multiple gas sensors that react to a broad range of exhaled VOCs.¹² An individual breathprint is created following pooling and processing data of the gas sensor deflections.

Until now, only one small pilot study has evaluated the potential of eNose technology to detect sarcoidosis.¹³ A cohort of 11 patients with untreated sarcoidosis could be distinguished from 25 healthy control subjects. Further research in larger patient groups is warranted to confirm these promising results.

The aim of the current study was to evaluate the reliability and validity of exhaled breath analysis using eNose technology to differentiate between sarcoidosis, healthy control subjects, and interstitial lung disease (ILD). Moreover, we aimed to evaluate whether breathprint data could distinguish between subgroups of patients with sarcoidosis based on clinical characteristics.

Study Design and Methods

Study Design and Population

This single-center cross-sectional study was performed in the Erasmus Medical Center (Rotterdam, The Netherlands) between August 2019 and March 2021. Outpatients with an established diagnosis of sarcoidosis according to the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders criteria or ILD according to the American Thoracic Society/European Respiratory Society criteria were eligible for inclusion.^{2,14-16} Data of a subset

of patients in this study were also used in a previous publication by Moor et al.¹⁷ Healthy control subjects were recruited among health care staff of the Erasmus Medical Center. Subjects in the healthy control group had a negative history of respiratory diseases and did not use pulmonary medication.

The study was conducted in accordance with the amended Declaration of Helsinki. Patients and control subjects with pulmonary infection were excluded. All participants signed informed consent before participating. The medical ethics committee approved the study protocol (MEC-2019-0230).

Data Collection

The SpiroNose (Breathomix) was used for exhaled breath analysis. The SpiroNose is a validated eNose device containing seven different metal-oxide semiconductor sensors.^{18,19} Measurements were performed as described previously.¹⁷ Participants were instructed to perform five tidal breaths, followed by an inhalation to total lung capacity, a 5 s breath hold, and a slow expiration. Data were stored and processed in a secured, certified online database and data processing platform (BreathBase).¹⁸

Participants completed a short questionnaire, including ethnicity, smoking, recent food or drink intake, inhaler use, and signs of pulmonary infection. Information on patient characteristics, medical history, medication use, and most recent available diagnostic test results (eg, spirometry, chest imaging, pathologic assessment, blood samples) were collected from medical files. If available, the most recent chest high-resolution CT scan was evaluated for the presence of pulmonary fibrosis. Patients were classified as having pulmonary fibrosis when reticulations with traction bronchiectasis were present on high-resolution CT scan as reviewed by an experienced thoracic radiologist. Clinical subgroups were defined depending on organ involvement, presence of pulmonary fibrosis, current immunosuppressive treatment, availability of histology for diagnosis, and sIL-2R level. To explore if breathprints correlate with disease activity, the sIL-2R level was used as a marker for activity. In our laboratory, an sIL-2R value ≤ 550 U/ml is considered normal. The median value of elevated sIL-2R levels was used as a cutoff to define the lower and upper 50% groups.

Data Analysis

Sensor data resulting from the measurements were extracted from the database. Prior to statistical analysis, eNose sensor signals were processed. Sensor signals were corrected for ambient air, peak values were normalized to the most stable sensor, and inter-array differences were reduced.^{18,19} Sensor peak values and ratios between peak value and breath hold were both used for analysis. The sensor data of each patient were labeled with the patient and disease characteristics. Partial least squares discriminant analysis

(PLS-DA) was used for evaluating sensor data. This method reduces the dimensionality of data and results in a set of multivariate components. Each PLS-DA component is a weighted combination of the original sensor variables. The first two components explain the greatest variance of sensor data. PLS-DA components 1 and 2 were therefore used for comparing data between diagnosis groups. Component 1 was used for analysis within the sarcoidosis groups to avoid overfitting the model. For linear regression analysis, PLS-DA component 1 was used. Results from the PLS-DA analyses were visualized as scatterplots, with component 1 on the x-axis and component 2 on the y-axis. Each dot represents one patient, and the center of the dot cloud represents the mean value of the components. After applying a generalized linear model prediction method to the PLS-DA components 1 and 2, receiver-operating characteristic analysis was performed using the odds (a value between 0 and 1) that a patient does belong to either of the groups based on the sensor data. The area under the curve (AUC) values and corresponding 95% CIs were derived from that analysis. In addition, sensitivity, specificity, accuracy, and negative and positive predictive values were calculated. Additional background information on sensor data processing and analysis is provided in the text and e-Figures 1 to 5 of e-Appendix 1.

Prior to analysis, diagnosis groups were randomly divided into a training and an independent validation set (2:1), following recommendations for metabolomics experiments.²⁰ The PLS-DA components 1 and 2 derived from the training set were applied to the independent validation set to validate the results. For analysis within the sarcoidosis cohort, subgroups were not split into a training set and validation set. Descriptive statistics were used to analyze baseline data. Normally distributed data are displayed as mean values with SDs and non-normally distributed data as median with interquartile range. Between-group comparisons were conducted by using χ^2 tests, Kruskal-Wallis tests, and Mann Whitney tests. Analyses were performed by using R version 4.0.3 for Mac OS X GUI (PBC) using the mixOmics package version 6.14.0 and ggpubr package version 0.4.0.

Results

In total, 569 outpatients were included: 252 with sarcoidosis and 317 with ILD. A total of 48 healthy control subjects were included. The ILD cohort comprised patients with IPF (n = 124), connective tissue disease-related ILD (n = 64), hypersensitivity pneumonitis (HP; n = 50), and other ILDs (n = 79) (Table 2).

Baseline characteristics of the study groups are presented in Table 1. Patients with ILD were older than patients with sarcoidosis and the healthy control subjects ($P < .05$). Patients with sarcoidosis had a higher diffusion capacity for carbon monoxide and FVC compared with patients with ILD ($P < .05$).

Sarcoidosis vs Healthy Control Subjects

Patients with sarcoidosis and healthy control subjects were divided into a training (sarcoidosis, n = 168; control subjects, n = 32) and a validation (sarcoidosis, n = 84; control subjects, n = 16) set (Fig 1).

Differentiation between patients and control subjects resulted in an AUC of 1.00 in both the training and the validation set. Corresponding sensitivity, specificity, and accuracy are displayed in Table 3.

When comparing patients with pulmonary involvement (n = 224) vs control subjects, similar results were found in both the training set (sarcoidosis, n = 150; control subjects, n = 32; AUC, 1.00) and the validation set (sarcoidosis, n = 74; control subjects, n = 16; AUC, 1.00). Patients with sarcoidosis treated with immunosuppressive medication (training, n = 81; validation, n = 40) could also be differentiated from healthy control subjects (training, n = 32; validation, n = 16) with an AUC of 1.00 in both sets.

Pulmonary Sarcoidosis vs ILD

eNose data of patients with sarcoidosis and pulmonary involvement (n = 224) were compared to data of patients with ILD (n = 317) (Fig 2, Table 3). This

TABLE 1] Baseline Characteristics

Characteristic	Sarcoidosis (n = 252)	ILD (n = 317)	HC (n = 48)
Age, y	53.1 ± 11.4 ^a	70.0 (62.0-76.0) ^a	36.5 (27.0-48.3) ^a
Male sex	134 (53.2) ^b	195 (61.5) ^b	15 (31.3)
BMI, kg/m ²	27.1 (24.7-30.6) ^b	26.3 (24.2-29.4) ^b	22.6 (20.7-24.5)
Smoking status ^a			
Never smoker	154 (61.1)	90 (28.4)	37 (77.1)
Former smoker	83 (32.9)	217 (68.5)	7 (14.6)
Current smoker	15 (6.0)	10 (3.2)	4 (8.3)
FVC (% of predicted)	89.0 (78.0-98.0) ^c	78.8 ± 20.0	...
D _{lco} (% of predicted)	78.5 (63.0-89.0) ^c	50.2 ± 15.4	...

Data are presented as mean ± SD, No. (%), or median (interquartile range). D_{lco} = diffusion capacity for carbon monoxide; HC = healthy control subjects; ILD = interstitial lung disease.

^aSignificantly different between all groups ($P < .05$).

^bSignificantly different from HC ($P < .05$).

^cSignificantly different from patients with ILD ($P < .05$).

analysis resulted in an AUC of 0.90 (95% CI, 0.87-0.94) in the training set (sarcoidosis, n = 150; ILD, n = 212) and an AUC of 0.87 (95% CI, 0.82-0.93) in the validation set (sarcoidosis, n = 74; ILD, n = 105).

The comparison between pulmonary sarcoidosis and HP yielded an AUC of 0.95 (95% CI, 0.90-0.99) in the training set (sarcoidosis, n = 150; HP, n=34), and an AUC of 0.88 (95% CI, 0.75-1.00) in the validation set (sarcoidosis, n = 74; HP, n = 16) (Fig 3).

Sarcoidosis

Additional clinical characteristics of the sarcoidosis cohort are described in Table 4. The comparison of breathprints between sarcoidosis subgroups resulted in AUCs ranging from 0.55 to 0.64 (Table 5). The presence or absence of pulmonary involvement, and pulmonary fibrosis in particular, multiple organ involvement, pathology-supported diagnosis, or immunosuppressive treatment did not influence patients' breathprint, as all 95% CIs were close to 0.5.

The sIL-2R level was available in 132 patients. eNose data did not distinguish patients with normal sIL-2R levels from elevated levels (cutoff, 550 U/mL). In patients with elevated sIL-2R levels (n = 43), the median was 772.0 U/mL. In this group, differences in breathprint were found between the lower and upper 50% (AUC, 0.78; 95% CI, 0.64-0.92; n = 21, lower 50%; n = 22, upper 50%). Exploratory regression analysis did not show a correlation between breathprint and sIL-2R levels.

Additional subgroup analyses revealed that smoking status, age, and sex did not influence the outcomes. The

results of these analyses are shown in e-Figures 6 to 21 of e-Appendix 2.

Discussion

This study evaluated the diagnostic performance of eNose technology in a large cohort of patients with sarcoidosis. The eNose accurately differentiated between patients with sarcoidosis and healthy control subjects with an AUC of 1.00. Breathprints of patients with ILD, and HP in particular, could also be adequately distinguished from pulmonary sarcoidosis.

TABLE 2] Distribution of Diagnoses in ILD Cohort (n = 317)

Type of ILD	No. (%)
Idiopathic pulmonary fibrosis	124 (39.1)
Connective tissue disease-related ILD	64 (20.2)
Hypersensitivity pneumonitis	50 (15.8)
Idiopathic nonspecific interstitial pneumonia	20 (6.3)
Interstitial pneumonia with autoimmune features	14 (4.4)
Combined pulmonary fibrosis and emphysema	10 (3.2)
(Cryptogenic) organizing pneumonia	9 (2.8)
Unclassifiable	8 (2.5)
Granulomatosis with polyangiitis	4 (1.3)
Respiratory bronchiolitis ILD	4 (1.3)
Asbestosis	3 (0.9)
Desquamative interstitial pneumonia	3 (0.9)
Drug-induced ILD	2 (0.6)
Other	2 (0.6)

ILD = interstitial lung disease.

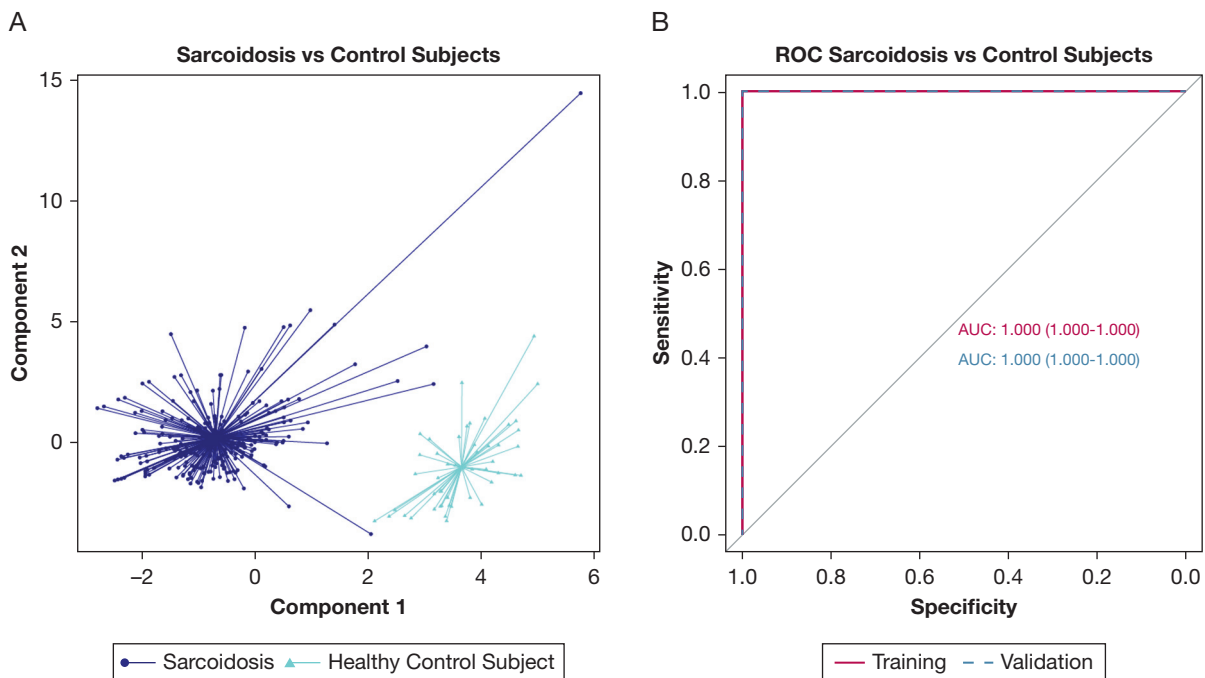


Figure 1 – Electronic nose data of patients with sarcoidosis and healthy control subjects. A, Scatterplot of electronic nose data of partial least squares discriminant analysis components 1 and 2 for full data set (sarcoidosis, $n = 252$; control subjects, $n = 48$). Each data point represents one patient; the center of the dot cloud represents the mean value of the components. B, ROC curves for training and validation set. AUC = area under the curve; ROC = receiver-operating characteristic.

These findings were confirmed in a validation cohort. Within sarcoidosis, breathprints of patient subgroups were similar, except for those with elevated sIL-2R levels.

The accuracy of eNose technology to differentiate sarcoidosis from control subjects was significantly better than in the only previous study assessing eNose technology in sarcoidosis. Dragonieri et al¹³ reported a cross-validated accuracy of 83.3% to distinguish sarcoidosis from healthy control subjects, whereas in the current study, the accuracy was 100%. Moreover, Dragonieri et al¹³ found no difference in breathprint between treated patients with sarcoidosis and healthy control subjects. The difference between the studies might be explained by the much smaller cohort size in the study of Dragonieri et al,¹³ as well as the use of a different eNose device.

Interestingly, in the current cohort, breathprints were similar in the sarcoidosis subgroups. A specific signal originating from the disease itself seems to dominate the patients' breathprints, despite clinical heterogeneity.⁴ The finding that breathprints of patients with and without pulmonary fibrosis were not

significantly different implies an influence of inflammation on exhaled VOCs. This theory is supported by increasing evidence from studies on different breath analysis techniques in other diseases.²¹ In this study, we also showed that the eNose could separate patients with sarcoidosis and high and low inflammatory activity, based on sIL-2R levels, and might serve as a new marker for inflammatory activity. However, no correlation between breathprints and sIL-2R levels was found. This could be due to a relatively small number of patients with an available sIL-2R level in the current cohort, the majority of whom had only slightly elevated levels (median, 772.0 U/mL). More extensive follow-up studies with successive within-patient measurements will lead to a better understanding of the influence of disease activity and treatment on breathprints, as well as the relation with sIL-2R levels and inflammatory activity on PET scans. According to a longitudinal study in subjects with asthma and unsupervised clustering of eNose data, it might be possible to identify changes in inflammatory activity or immunosuppressive treatment.²²

In clinical practice, it can be challenging to establish a diagnosis of sarcoidosis, and in particular to

TABLE 3] Diagnostic Performance of Electronic Nose Technology

Group 1	No.	Group 2	No.	Dataset	AUC (95% CI)	Sensitivity	Specificity	Accuracy	NPV	PPV
Sarcoidosis	168	HC	32	Training	1.00 (1.00-1.00)	100%	100%	100%	100%	100%
	<i>84</i>		<i>16</i>	<i>Validation</i>	<i>1.00 (1.00-1.00)</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>
Sarcoidosis (pulmonary)	150	HC	32	Training	1.00 (1.00-1.00)	100%	100%	100%	100%	100%
	<i>74</i>		<i>16</i>	<i>Validation</i>	<i>1.00 (1.00-1.00)</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>
Sarcoidosis (treated)	81	HC	32	Training	1.00 (1.00-1.00)	100%	100%	100%	100%	100%
	<i>40</i>		<i>16</i>	<i>Validation</i>	<i>1.00 (1.00-1.00)</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>	<i>100%</i>
Sarcoidosis (pulmonary)	150	ILD	212	Training	0.90 (0.87-0.94)	90.0%	82.1%	85.4%	92.1%	78.0%
	<i>74</i>		<i>105</i>	<i>Validation</i>	<i>0.87 (0.82-0.93)</i>	<i>85.1%</i>	<i>81.9%</i>	<i>83.2%</i>	<i>88.7%</i>	<i>76.8%</i>
Sarcoidosis (pulmonary)	150	HP	34	Training	0.95 (0.90-0.99)	92.7%	91.2%	92.4%	73.8%	97.9%
	<i>74</i>		<i>16</i>	<i>Validation</i>	<i>0.88 (0.75-1.00)</i>	<i>87.8%</i>	<i>87.5%</i>	<i>87.8%</i>	<i>60.9%</i>	<i>97.0%</i>

Results of the validation set are in italic. AUC = area under the curve; HC = healthy control subjects; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; NPV = negative predictive value; PPV = positive predictive value.

differentiate between other granulomatous diseases such as HP.²³ Notably, our results showed that sarcoidosis could be accurately separated from HP. A limitation of the current study was the absence of patients with granulomatous diseases such as TB and sarcoid-like reactions, due to the low prevalence of these diseases. Previous studies did show that TB can be accurately differentiated from healthy control subjects and from patients with suspected TB using an eNose.^{24,25} eNose technology therefore holds the potential to guide multidisciplinary team discussions in patients with a granulomatous disease. Future studies should assess the value of eNose technology in differentiating between a broader range of granulomatous entities. Especially in areas with limited access to diagnostic procedures and/or a high prevalence of TB, eNose might be of added value as an easy accessible and accurate point-of-care tool in clinical practice.

The new sarcoidosis diagnostic guideline states that histopathology is not always needed to establish the diagnosis if all other findings are consistent with sarcoidosis.² In the current study, breathprints of patients with and without a diagnosis confirmed by tissue sampling did not differ, which supports the

recommendations in the guideline. This finding emphasizes the potential of eNose technology as an accurate diagnostic tool for sarcoidosis, without the need for invasive tissue sampling.

Strengths of the current study are its large sample size and real-world population, including patients with comorbidities or medication use. We also validated the results obtained from the training set in an independent validation cohort. A limitation is that the current dataset contains some missing data. sIL-2R values were not available for all patients, which might influence the outcome and strength of the analysis. Hence, further studies to extend and confirm these results are warranted. Moreover, the compared groups were not matched regarding certain baseline variables such as sex, smoking status, and age. However, additional subgroup analyses did not show an effect of these variables on results. Lastly, the results of our single-center study still need to be confirmed and validated by external patient cohorts in a multicenter multinational study.²⁶ External validation, design of a diagnostic algorithm, and test cohorts are required steps before implementation of the SpiroNose as a diagnostic tool can be realized (Fig 4).

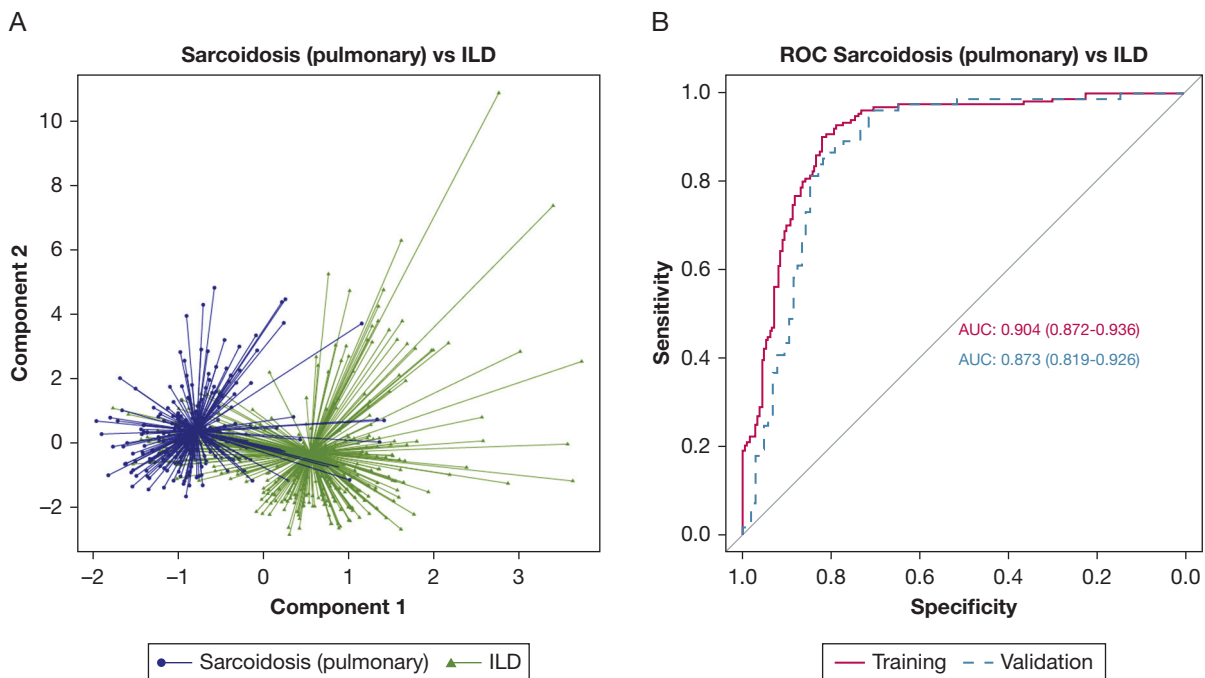


Figure 2 – Electronic nose data of patients with pulmonary sarcoidosis and ILD. A, Scatterplot of electronic nose data of partial least squares discriminant analysis component 1 and 2 for full data set (sarcoidosis, $n = 224$; ILD, $n = 317$). Each data point represents one patient; the center of the dot cloud represents the mean value of the components. B, ROC curves for training and validation set. AUC = area under the curve; ILD = interstitial lung disease; ROC = receiver-operating characteristic.

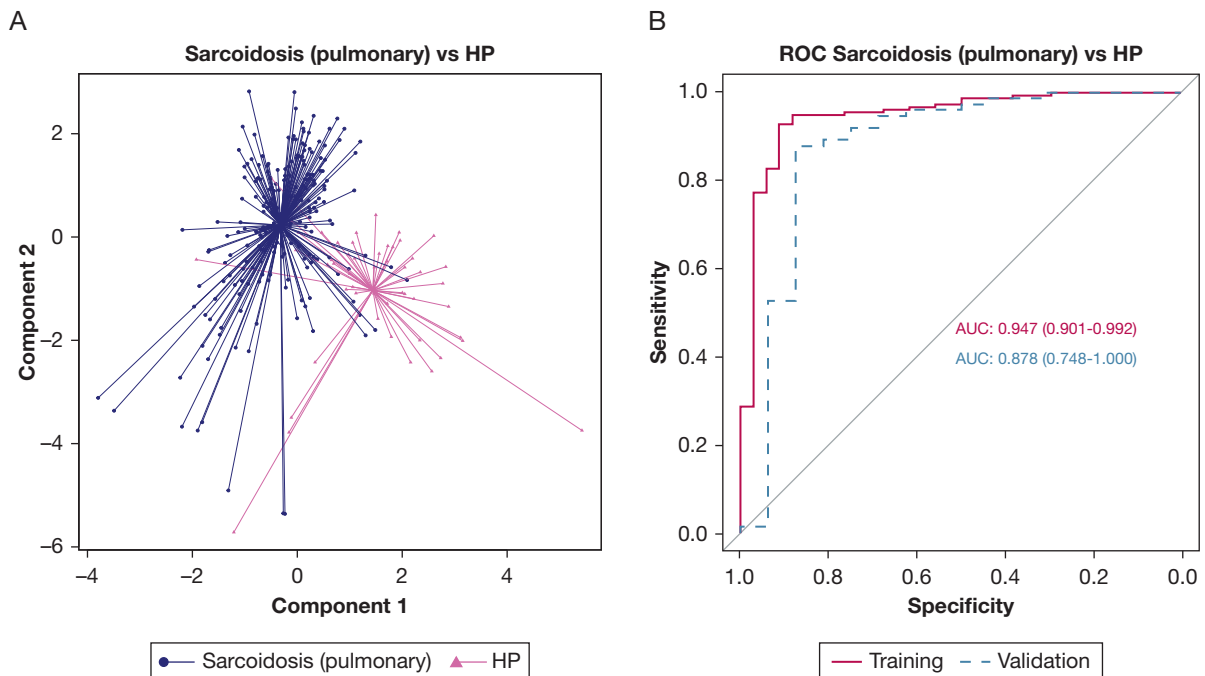


Figure 3 – Electronic nose data of patients with pulmonary sarcoidosis and HP. A, Scatterplot of electronic nose data of partial least squares discriminant analysis components 1 and 2 for full data set (sarcoidosis, $n = 224$; HP, $n = 50$). Each data point represents one patient; the center of the dot cloud represents the mean value of the components. B, ROC curves for training and validation set. AUC = area under the curve; HP = hypersensitivity pneumonitis; ROC = receiver-operating characteristic.

TABLE 4] Sarcoidosis Patient Characteristics

Characteristic	Value
Self-reported ethnicity	252 (100)
European/White	170 (67.5)
South and Latin American	59 (23.4)
Asian	11 (4.4)
Northern African	7 (2.8)
Sub-Saharan African	5 (2.0)
Time from diagnosis	252 (100)
Time, mo	68.0 (28.3-139.0)
Diagnosis supported by pathology	188 (74.6)
No. of organs involved	252 (100)
1 organ	24 (9.5)
> 1 organ	228 (90.5)
Pulmonary involvement	224 (88.9)
Pulmonary fibrosis	52 (23.2)
No pulmonary fibrosis	148 (66.1)
Fibrosis unknown ^a	24 (10.7)
Extrapulmonary involvement	250 (99.2)
Lymph nodes	232 (92.8)
Skin	48 (19.2)
Eyes	46 (18.4)
Muscle/joints	30 (12.0)
Cardiac	21 (8.4)
Small fiber neuropathy	11 (4.4)
Central nervous system	6 (2.4)
Other organs	50 (20.0)
Current immunosuppressive treatment ^b	121 (48.0)
Corticosteroids	70 (57.9)
Methotrexate	70 (57.9)
TNF inhibitors	19 (15.7)
Azathioprine	8 (6.6)
Mycophenolate mofetil	2 (1.7)
Rituximab	1 (0.8)
No current immunosuppressive treatment	131 (52.0)
sIL-2R results ^c	132 (52.4)
Level, U/mL	458.0 (325.5-625.8)
Normal sIL-2R (\leq 550 U/mL)	89 (35.3)
Level, U/mL	383.0 (297.0-458.0)
Elevated sIL-2R ($>$ 550 U/mL)	43 (17.1)
Level, U/mL	772.0 (632.5-1289.5)

Data are presented as No. (%) or median (interquartile range). Percentages calculated of subgroup total. sIL-2R = soluble IL-2 receptor; TNF = tumor necrosis factor.

^aNo high-resolution CT imaging available.

^bSome patients used a combination of different medications.

^csIL-2R level was not available for 120 (47.6%) patients with sarcoidosis.

Interpretation

The current study shows a reliable and accurate differentiation of patients with sarcoidosis from patients

with ILD and healthy control subjects, based on eNose data. The results confirm the potential of eNose technology as a noninvasive diagnostic tool to obtain an

TABLE 5] Diagnostic Performance of Electronic Nose in Sarcoidosis Subgroups

Group 1	No.	Group 2	No.	AUC (95% CI)
Disease characteristics				
Pulmonary involvement	224	No pulmonary involvement	28	0.64 (0.54-0.73)
Pulmonary fibrosis	52	No pulmonary fibrosis	148	0.59 (0.51-0.68)
1 Organ involved	24	> 1 Organ involved	228	0.64 (0.53-0.76)
Immunosuppressive treatment	121	No immunosuppressive treatment	131	0.55 (0.48-0.62)
Pathology supported	188	No pathology	64	0.61 (0.52-0.69)
sIL-2R level				
Normal	89	Elevated	43	0.61 (0.51-0.71)
Elevated lower 50%	21	Elevated upper 50%	22	0.78 (0.64-0.92)

AUC = area under the curve; sIL-2R = soluble IL-2 receptor.

early, accurate sarcoidosis diagnosis and reduce the number of invasive diagnostic procedures in the diagnostic trajectory. These findings encourage further research in external cohorts of patients with sarcoidosis to validate the diagnostic properties of eNose technology (Fig 4).

Within sarcoidosis, breathprints were similar between subgroups, except for patients with high inflammatory activity. This emphasizes the potential value of eNose technology in monitoring disease activity. Longitudinal studies need to explore the ability of this tool to monitor disease activity.

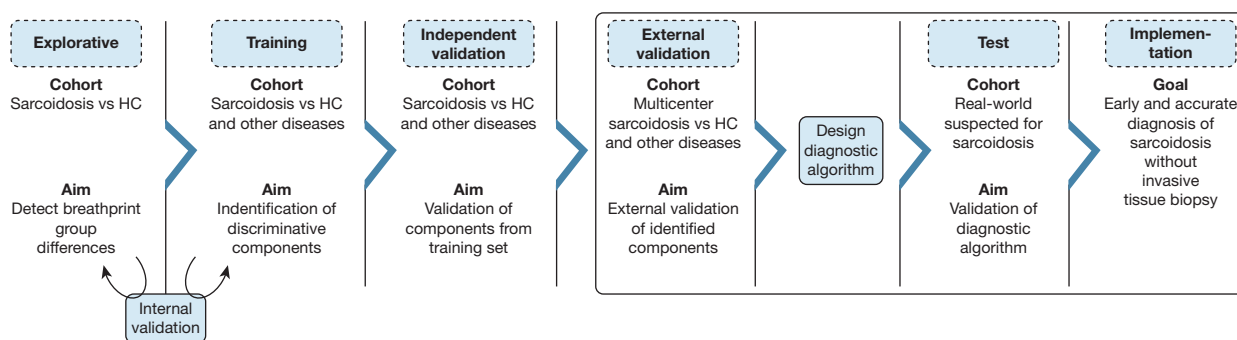


Figure 4 – Development steps of electronic nose technology toward a diagnostic tool for sarcoidosis. In the current study, data analysis of a training and independent validation cohort have been performed. Research steps in the rectangle box are still required before the SpiroNose could be used as a diagnostic tool in patients with suspected sarcoidosis. HC = healthy control subjects.

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All were involved in acquisition, analysis, and/or interpretation of the data presented in the manuscript, as well as critical revision of the manuscript. All authors approved submission of the final version of the manuscript, and all agreed to be accountable for all aspects of the submitted work.

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Additional information: The e-Appendices and e-Figures can be found in the Supplemental Materials section of the online article.

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