MASTER THESIS

Ability of the electronic nose to discriminate between patients with rheumatoid arthritis and controls

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I.M. Hulshof (S1764373)
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Examination committee

Dr. P.M. ten Klooster

Prof. Dr. J.A.M. van der Palen

Dr. H.E. Vonkeman

M.C. Hegeman

University of Twente

Drienerlolaan 5

7522NB Enschede

The Netherlands

Medisch Spectrum Twente

Koningstraat 1

7512KZ Enschede

The Netherlands

Abstract

Introduction Early detection in rheumatoid arthritis (RA) is crucial to obtain optimal treatment results, yet complicated due to lacking definitive diagnostic criteria. Therefore, diagnosis is based on extensive clinical evaluation and laboratory results. Faster and less burdensome diagnostic alternatives are desired. Breath analysis through an electronic nose that measures volatile organic compounds (VOCs) showed promising results in other chronic conditions. This research explored the potential and feasibility of the electronic nose as a diagnostic tool in RA.

Method Participants were included between June 2020 and July 2021. They provided demographic, medical and lifestyle related data and a breath sample through the Aeonose electronic nose. Breath data were analyzed by the eNose company through machine learning and leave 10%-out cross-validation in order to develop an optimal discriminating model. Multivariate logistic regression was executed to explore whether prediction accuracy could be improved by incorporating additional participant characteristics.

Results Data of 83 RA patients and 48 controls showed discrimination was possible with a receiver operating curve (ROC) area under the curve (AUC) of 0.80, a sensitivity of 0.89 and a negative predictive value (NPV) of 0.76. Incorporation of age and smoking history increased the ROC AUC to 0.85 with a sensitivity of 0.95 and a NPV of 0.83.

Conclusion The Aeonose can discriminate between RA patients and controls with a high sensitivity and NPV. These promising findings might contribute to the future RA diagnostic process. However, external validation in larger independent test samples, which takes the limitations and recommendations of this study into account, is desired to confirm these results and gain further insights.

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Introduction

Dutch healthcare costs are rising rapidly with an expected expense of 174 billion Euros in 2040, doubling the costs in 2015. [1] This growth is partly caused by the increasing prevalence of chronic conditions. [2-4] Rheumatoid Arthritis (RA) is among these chronic conditions and was prevalent in almost 260.000 Dutch individuals in 2019. [5] This inflammatory and autoimmune condition is characterized by chronic symmetric inflammation of multiple joints, also known as polyarthritis. [6] Most affected individuals are between 35 and 60 years of age and women are three times more likely to be diagnosed than men. [7]

Although RA is currently incurable, it is now well treatable through more aggressive strategies and the increasing availability of new pharmacological options. According to the window of opportunity concept, faster detection, and thus early treatment, leads to reduced progression or even remission with better long-term results. [8-11] Therefore, early diagnosis of RA is increasingly recognized as an essential step towards better outcomes. [12]

However, early detection proves to be challenging due to lacking definitive diagnostic criteria. Therefore, diagnosis is based on clinical presentation and physicians usually support their diagnostic decision with the American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) classification criteria. [13] This labour intensive process, the involved inconclusive serological factors and the pressure to spend financial resources more efficiently contribute to the ongoing quest for effective disease detection alternatives. [14, 15] More accessible, faster and less burdensome diagnostic options could contribute to achieve early-stage diagnosis and treatment to prevent irreversible damage and a decreased quality of life. [16, 17]

A diagnostic tool that transferred from the industry and gained popularity in the medical field is the electronic nose. [18] Electronic noses measure volatile organic compounds (VOCs) in exhaled breath. This method showed promising results in detecting different types of cancer, such as breast cancer, gastric cancer, lung cancer and prostate cancer. [19-21] For example, lung cancer patients could be differentiated from healthy controls with a cross-validation accuracy value of 80% up to 90%. [22] Also, studies regarding airway related conditions were executed, resulting in discrimination between patients with COPD and asthma with an accuracy (ACC) of 96% [23, 24] Furthermore, studies regarding the detection of infectious diseases showed positive results. [25, 26] Recently, as a pre-screening tool for the corona virus disease (COVID-19), the electronic nose achieved a sensitivity of 86% and a negative predictive value of 92%. [18]

Inflammations in RA are hypothesized to alter the metabolism, which might allow discrimination by VOC measurement similar to previous studies. The single study that investigated this hypothesis identified differences between RA patients and healthy controls with an ACC of 71%. [27] However, the examined groups were fairly small, consisting of only 21 observations each. Secondly, the groups differed significantly in some baseline characteristics, such as age. Also, relevant baseline characteristics were either missing or not reflecting the typical RA population; data about BMI was not taken into account and all patients were non-smokers. Finally, participant evaluation of the test was not addressed, although this is an essential factor in determining future feasibility.

Therefore, further research is necessary to confirm or dismiss previous findings, address the limitations and gain insight into the possible use of the electronic nose as a diagnostic tool for RA. This study aims to investigate the ability of an electronic nose to discriminate between RA patients and controls.

Method

Study design

The research protocol was submitted to and approved by the local medical ethics committee, which ruled that the Dutch law regarding scientific research involving humans (WMO) did not apply. Participant recruitment and data collection were executed from June 2020 until July 2021 through breath analysis using an electronic nose in a research lab at Medisch Spectrum Twente (MST) in Enschede.

Study population

Adult RA patients with scheduled appointments at the rheumatology outpatient clinic were invited to participate in this research. In order to participate, patients furthermore had to have sufficient understanding of the Dutch language to understand the informed consent and sign this once they determined to participate. Lastly, the patient had to be able to perform the Aeonose procedure. The control group consisted of individuals that were not diagnosed with an inflammatory rheumatic condition. They were recruited among employees of MST and the general practitioner emergency center, located in MST. Although all employees were welcome to participate, women over 50 were especially encouraged. The reason for this is that the majority of RA patients are women.

Data collection

All eligible participants received written information regarding the study after which informed consent was obtained (Appendix A). Afterwards, data was collected as summarized in Table 1. The case report form (CRF) was available in different versions for RA patients and controls (Appendix B). Both contained questions regarding demography, smoking, comorbidities and medication use. Comorbidities were according to the known disease treatment combination (DTC) (Appendix C).

The patient CRF also collected RA related details, such as positivity of rheumatoid factor (RF) and anticyclic citrullinated peptide (ACPA). Also, specific lab results, namely C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were incorporated in the CRF. Furthermore, the Disease Acitivity Score (DAS)28, an objective instrument to monitor the disease activity in RA, of patients was collected. Participant-perceived discomfort was obtained after breath analysis and was rated on a scale from zero, that indicated no experienced discomfort, to ten, which indicated intolerable discomfort (Appendix D).

Confidentiality was ensured through the participant number that corresponds with data in the digital files. The paper files are kept in a locked cabinet within the research office.

Table 1: Overview of collected data per participant group

Data	Patient	Control
Informed consent	X	X
CRF	X	X
DAS28	X	
Breath sample	X	X
Discomfort	X	X

CRF: case report form, DAS: disease activity score

Breath analysis

Breath analysis was conducted through the Aeonose, an electronic, handheld device containing three metal-oxide sensors (Figure 1 and 2). Through these sensors runs a current that periodically increases their temperature. Once the breath is drawn through the electronic nose, it passes a carbon filter and a High Efficiency Particulate Air (HEPA) filter (3M GSU075). The HEPA filter is electrostatic and inhibits bacteria and smaller particles such as viruses to enter the system with over 99% efficiency. As a result, filtered air enters the lungs of the participant, where gas exchange takes place. Exhaled breath enters the electronic nose through the mouth piece and enters the sample chamber where it passes the earlier mentioned sensors. One way valves prevent the breath from returning to the participant. A nose clip prevents unfiltered air from affecting the measurement.

VOCs in the exhaled breath interact through redox reactions with the surface of the sensors resulting in absorption of the VOCs. After five minutes the sensors are saturated and a signal indicates that the participant has completed their task. The following 10 minutes are used for the desorption of the VOCs. Since redox reactions are temperature dependent, they terminate as a result of increased temperature. After 10 minutes all reactions are terminated and the change in resistance can be plotted against time and changes in temperature.

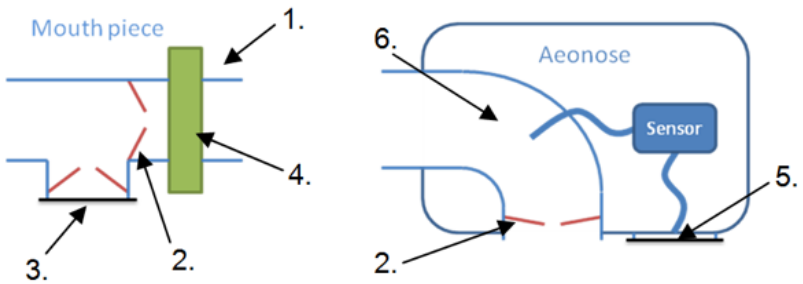

Figure 1: Electronic nose produced by the Enose company. Figure 2: Schematic drawing of the electronic nose. (1) disposable mouth piece, (2) one way valves, (3, 5) carbon filter, (4) HEPA filter, (6) sample chamber

Statistical analysis

The eNose company analyzed breath sample data through a proprietary software package called Aethena. First, data was compressed through a Tucker3 algorithm which translated the data to a vector for each possible sensor combination without compromising accuracy. [28] This compression was performed since each observation results in thousands of data points, which does not allow classification. Afterwards, the generated vectors were submitted to an artificial neural network (ANN). ANN created different models through algorithms that required tweaking for optimal results. Also several other statistic methods for classification, such as random forest, were executed. These different results were compared and these models were internally validated by using leave-10%-out cross-validation. The optimal model was selected by comparing several models in terms of sensitivity, specificity and AUC. Eventually this resulted in a score between -1 and 1 for every observation, where scores closer to 1 indicated a higher chance to test positive for RA.

Demographic and clinical variables were analyzed through mean comparison and descriptive statistics. Subgroup analysis was performed to investigate the confounding impact of the fact whether a participant ate less than three hours prior to breath analysis. Correlation between breath sample classification and the DAS28 category was examined through a Pearson correlation analysis.

A receiver operator characteristic (ROC) curve was derived from the Aeonose score that was received from the eNose company. Additional prediction value of demographic and clinical variables, which differed between patients and controls, was investigated through multivariate logistic regression. Backward elimination ($p < 0.10$) was applied to determine which characteristics needed to be considered.

Results

Baseline characteristics

Screening consultation hours resulted in 98 willing RA patients that were eligible (Figure 3). Five of these 98 were not able to complete the measurement. In two cases, a defective device was the cause, whereas three patients could not complete the measurement. Of the 93 complete observations 10 got lost since the server did not receive them. Therefore, the patient group includes 83 observations. In the control group, 52 respondents were eligible. One participant did not complete the measurement as a result of safety concerns regarding COVID-19. Three of the 51 complete observations got lost in sending and receiving the observation resulting in 48 observations in the control group.

During the analysis it was discovered that one control was misclassified as a patient. Removal of this participant led to 83 patients and 47 controls and an RA prevalence of 64% in the study population.

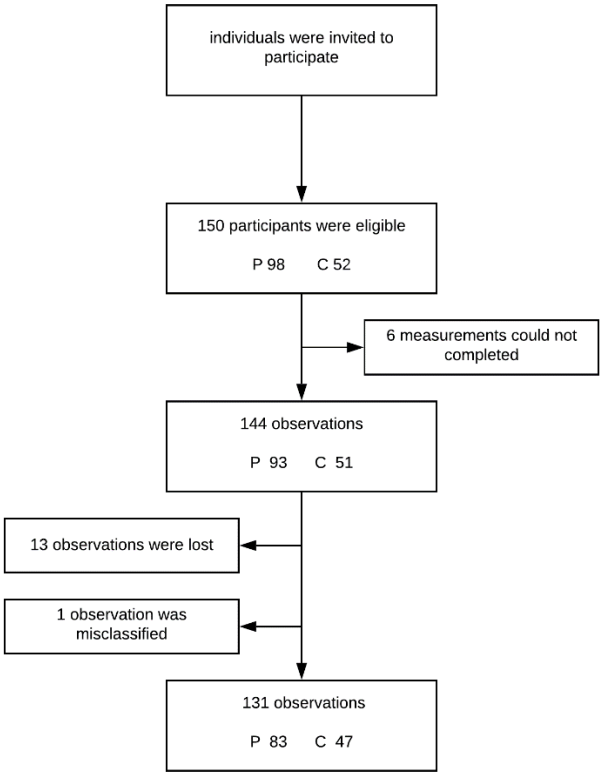

Figure 3: Inclusion process of the observations

The characteristics of all participants are displayed in Table 2. Patients and controls differed significantly in terms of age (p=0.001), smoking (p<0.001) and whether they ate less than three hours prior to measurement (p=0.019). No significant difference was observed in mean BMI score. However, when displayed in categories, BMI classification differed significantly (p=0.003). Of the RA patients 19 (23.2%) had a normal weight whereas 25 (53.2%) of the controls had a normal weight.

Furthermore, whether a participant ate less than three hours prior to measurement showed a significant difference (p=0.019) between the two groups. Since this likely reflects a logistical difference between patients and controls rather than a clinical variable associated with RA, it is a potential confounder instead of a possible predictor of RA.

Patients scored an average of 2.7 for discomfort. Here, the patients that could not endure the measurement were included. They were attributed a 10, which equals the worst possible

discomfort. Even with this adjustment, the groups showed no significant difference (p=0.418) considering an average score of 2.4 in the control group.

Table 2: Baseline characteristics of the total study cohort (n=130)

	RA patients (n=83)	**Controls** (n=47)	**p value**
Age in years mean (SD)	63.6 (11.4)	56.5 (11.1)	0.001
Gender n (%)			0.077
Female	55 (66.3)	38 (80.9)	
Male	28 (33.7)	9 (19.2)	
BMI mean (SD)	26.6 (4.1)	25.5 (3.9)	0.161
BMI category n (%)			0.003*
Underweight	9 (10.8)	1 (2.1)	
Normal	19 (23.2)	25 (53.2)	
Overweight	39 (47.6)	13 (27.7)	
Obese	15 (18.3)	8 (17.0)	
Smoking n (%)			<0.001*
Current smoker	21 (25.3)	4 (8.5)	
Former smoker	38 (45.8)	11 (23.4)	
Never smoker	24 (28.9)	32 (68.1)	
Comorbidity n (%)**			0.279
Yes	17 (20.5)	5 (12.5)	
No	66 (79.5)	35 (87.5)	
Ate < 3 hours prior to measurement n (%)			0.019
Yes	47 (58.8)	35 (79.6)	
No	33 (41.3)	9 (20.5)	
Discomfort mean (SD)	2.7 (2.6)	2.4 (2.1)	0.418

**The p value was determined through Fisher's exact test instead of Pearson's Chi-square test*

*** Specified in Appendix C*

RA specific characteristics

Overall, RA characteristics appeared representative for the general RA population (Table 3). The DAS28 resulted in an average of 3.1. When the DAS28 scores were classified in categories, 23 (33.3%) of the patients are in a remissive state. 16 (23.2%) patients experience low disease activity, 23 (33.3%) of them experience moderate disease activity and seven (10.1%) patients experience a high disease activity.

In total 134 RA-specific drugs were prescribed. 91 (67.9%) of these drugs were csDMARDS. bDMARDS were prescribed in 39 (29.1%) cases and tsDMARDs in 2 (1.5%) cases.

Table 3: Characteristics of the RA group (n=83)

	RA patients
Rheumatoid factor n (%)	
Positive	52 (68.4)
Negative	24 (31.6)
ACPA n (%)	
Positive	46 (63.9)
Negative	26 (36.1)
Erosive n (%)	
Yes	22 (28.6)
No	55 (71.4)
CRP mean (SD)	7.7 (12.7)
BSE mean (SD)	19.6 (19.5)
DAS28 mean (SD)	3.1 (1.5)

DAS28 category n (%)	
Remission	23 (33.3)
Low	16 (23.2)
Moderate	23 (33.3)
High	7 (10.1)
Medication use n (%)	
csDMARDS	91 (67.9)
Methotrexate	56 (41.8)
Sulfasalazine	8 (6.0)
Leflunomide	4 (3.0)
Hydroxychloroquine	23 (17.2)
bDMARDS	39 (29.1)
Abatacept	2 (1.5)
Rituximab	1 (0.8)
TNF-inhibitor	18 (13.4)
Adalimumab	6 (4.5)
Certolizumab pegol	2 (1.5)
Etanercept	9 (6.7)
Golimumab	1 (1.2)
tsDMARDS	2 (1.5)
IL6-inhibitor	2 (1.5)
Tocilizumab	2 (1.5)

Breath analysis

The VOC composition in exhaled breath differed between RA patients and the control group with an initial AUC of 0.80 (95% CI 0.72 – 0.88) (Figure 4). Corresponding sensitivity was 0.75 (95% CI 0.64 – 0.83) with a negative predictive value (NPV) of 0.60 (95% CI 0.47 – 0.72) and a specificity of 0.68 (95% CI 0.54 – 0.80) with a positive predictive value (PPV) of 0.81 (95% CI 0.70 – 0.88) at a threshold of 0.00. Subgroup analysis of RA patients and controls that ate less than three hours prior to the measurement was performed to investigate the confounding potential of the last food consuming moment. This resulted in a slightly changed outcomes, such as an AUC of 0.83 (95% CI 0.74 – 0.92). Sensitivity of 0.78 (95% CI 0.64 – 0.87) with a NPV of 0.69 (95% CI 0.52 – 0.81) and a specificity of 0.73 (95% CI 0.56 – 0.85) and a PPV of 0.81 (95% CI 0.68 – 0.90) were detected.

Correlation between breath sample classification and the DAS28 category was examined through a Pearson correlation analysis. This revealed negligible correlation with a coefficient of -0.27 (p=0.025).

In order to obtain a higher PPV, the threshold for the Aeonose score was, after examination of the scatterplot, set to 0.25 (Figure 5). This resulted in a sensitivity of 0.51 (95% CI 0.40 – 0.61) with a NPV of 0.51 (95% CI 0.40 – 0.61) and a specificity of 0.89 (95% CI 0.77 – 0.95) with a PPV of 0.89 (95% CI 0.77 – 0.95). ACC was 0.65 (95% CI 0.56 – 0.72). In pursuit of a higher sensitivity, the threshold was set to -0.27. This resulted in a sensitivity of 0.89 (95% CI 0.81 – 0.94) with a NPV of 0.76 (95% CI 0.60 – 0.87) and a specificity of 0.60 (95% CI 0.45 – 0.72) with a PPV of 0.80 (95% CI 0.70 – 0.87). The ACC was 0.78 (95% CI 0.71 – 0.85).

In an attempt to further improve the discriminating ability of the test, multivariate logistic regression with backward elimination was performed. Whether a participant ate less than three hours prior to the measurement was here not taken into account due to its logistical and confounding properties. The addition of clinical variables showed that besides breath analysis, age and smoking history significantly predicted group membership (Table 4).

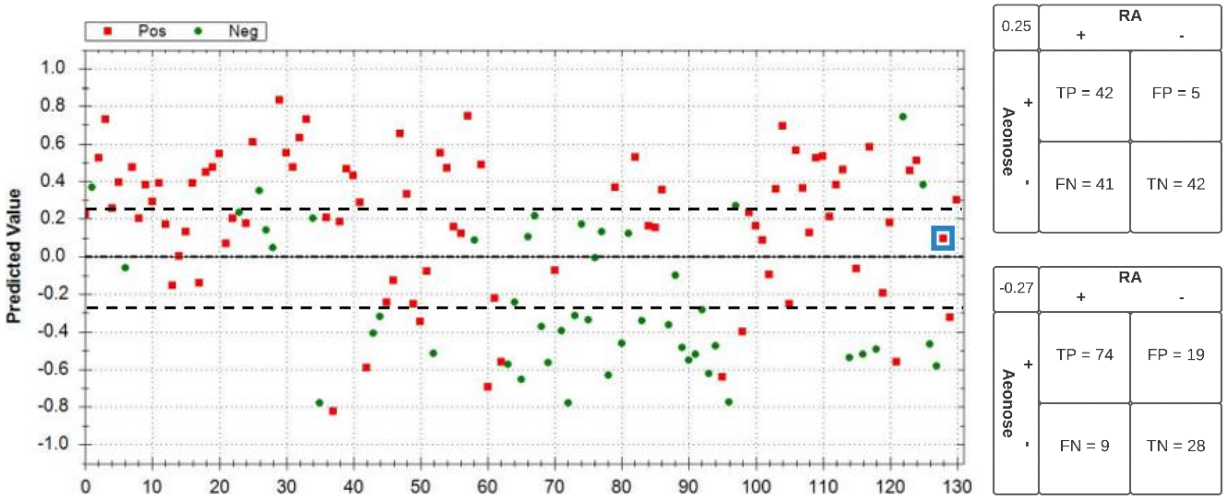

Figure 4: Scatterplot of the predicted value per observation. The blue square indicates the misclassified observation. Figure 5: Tables with diagnostic values per threshold (left upper corner). TP: true positive, FP: false positive, FN: false negative and TN: true negative.

Table 4: Results of the multivariate logistic regression analysis through backward elimination

Variable	Odds ratio (95% CI)	B	p value
Breath value	12.94 (3.79 – 44.20)	2.56	< 0.001
Age	1.046 (1.00 – 1.10)	0.05	0.074
Smoking history			
Never smoker	1		
Former smoker	3.81 (1.32 – 10.99)	1.34	0.013
Current smoker	5.55 (1.40 – 21.93)	1.71	0.015

Data are presented as odds ratio (95% confidence interval). Cut-off point: 0.10, constant: -2.67, R^2: 2.34. B: regression coefficient.

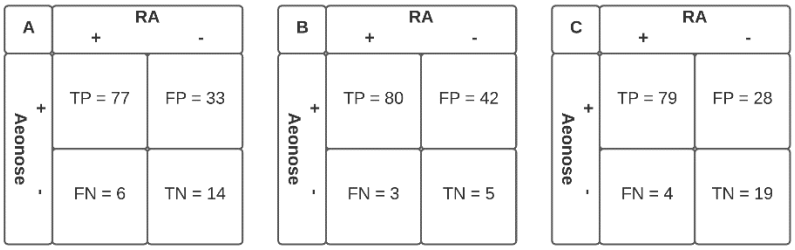

Figure 6: Tables with diagnostic values per model (left upper corner). Threshold: 0.30. TP: true positive, FP: false positive, FN: false negative and TN: true negative.

Three logistic regression models were composed where a probability of RA ≥ 30% was regarded as a positive test result (Figures 6 and 7) in order to be discriminating and diagnostically relevant. Model A consisted solely of the breath analysis and had an AUC of 0.80 (95% CI 0.72 – 0.88). Sensitivity was 0.93 (95% CI 0.85 – 0.97) with a NPV of 0.70 (95% CI 0.48 – 0.85) and a specificity of 0.30 (95% CI 0.19 – 0.44) with a PPV of 0.70 (95% CI 0.61 – 0.78) was observed. ACC was 0.70 (95% CI 0.62 – 0.77).

Model B included only the relevant clinical variables as determined by backward elimination and showed an AUC of 0.77 (95% CI 0.68 – 0.85). Corresponding sensitivity was 0.96 (95% CI 0.90 – 0.99) with a NPV of 0.63 (95% CI 0.31 – 0.86) and a specificity of 0.11 (95% CI 0.05 – 0.23) with a PPV of 0.66 (95% CI 0.57 – 0.73) was observed. ACC was 0.65 (95% CI 0.57 – 0.73).

Model C combined both models A and B and displayed an AUC of 0.85 (95% CI 0.79 – 0.92). Sensitivity was 0.95 (95% CI 0.88 – 0.98) with a NPV of 0.83 (95% CI 0.63 – 0.93) and a specificity of

0.40 (95% CI 0.28 – 0.55) with a PPV of 0.66 (95% CI 0.57 – 0.73) were detected. The ACC was 0.75 (95% CI 0.67 – 0.82).

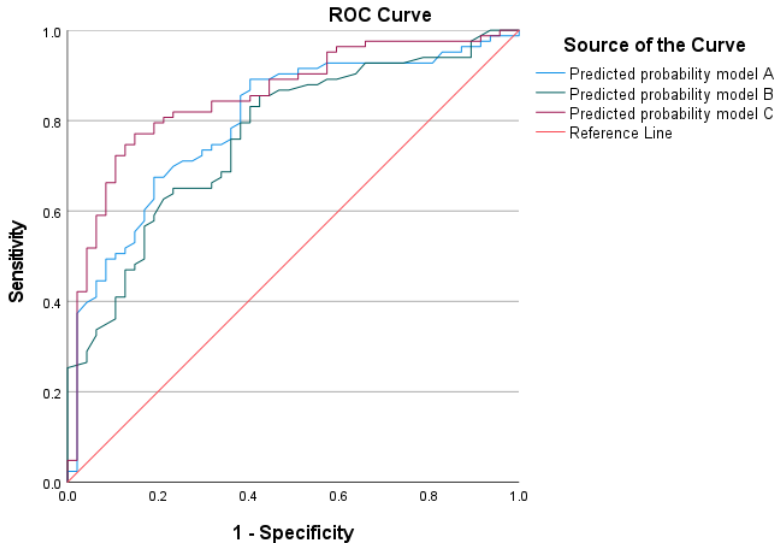

Figure 7: ROC curves for model A, B and C

Discussion

This research investigated the ability of the Aeonose to discriminate between RA patients and controls. An initial sensitivity of 0.93 and NPV of 0.7, based on solely breath analysis, were found at a threshold of 0.30. Addition of clinical variables led to an improved sensitivity and NPV, respectively 0.95 and 0.83. These outcomes indicate possible diagnostic potential for the Aeonose for screening for RA. With NPV values up to 0.83 when adding age and smoking history, the electronic nose might contribute to ruling out the presence of RA in a point-of-care setting.

Choosing a relative threshold depends on the goal of the test. Testing positive at a high threshold, shows a high probability of testing positive for RA. On the other hand, testing negative at a low threshold, indicates the participant probably does not have RA. Practically, a high NPV is probably more desired considering general practitioners already refer their patients when they are in doubt of are fairly sure of RA presence. Through a high NPV, the models can be used as a pre-screening tool. Also, the conclusion of a rheumatologist is hard to replace by a model with a high PPV.

Several studies regarding discriminating abilities of the electronic nose have been published including one study that addresses discrimination between RA patients, psoriatic arthritis (PsA) patients and controls. [27] However, this is the first RA related discriminating study that utilized machine learning and had a relatively large sample size. Overall, studies use different types of electronic noses, but the discriminating ability is similar. For example, healthy individuals could be discriminated from COPD patients with sensitivities and specificities that varied from 0.85 up to 0.91. [22]

An important strength is that this is the first study that also measured the patient reported discomfort of the Aeonose procedure. This resulted in two recommended adaptations to the measurement procedure in order to reduce the experienced discomfort during future measurements. Firstly, an alternative for holding the device is desired. Patients repeatedly stated that it was hard for them to hold the device due to the dexterity restriction caused by RA. Secondly, participants of both research groups mentioned the self-consciousness which complicated the measurement. They indicated it would be easier to endure the measurement if they had a visual distraction to focus on rather than their breathing.

Another strength is the fact that all measurements were completed in a controlled environment. All measurements took place on the same device in the same lab and were prepared and guided by trained staff. For example, they ensured the participants wore gloves and a nose clip during the measurements to counter the potential confounding effect of rubbing alcohol and breathing in unfiltered air. However, participants were still able to breathe alongside the mouthpiece instead of fully through the mouthpiece. For this reason, participants were precisely instructed to cover the mouthpiece entirely.

This study also has some limitations. Several differences in baseline characteristics were observed, which can be partly explained by regulations following the COVID-19 pandemic. For example, patients were obligated to visit the hospital on their own. As a result, only scheduled patients and employees, who are generally younger and more vital, could be compared. In the future, it is advised to recruit peers or relatives of patients as controls due to similarities in sociodemographic characteristics, genetics and/or lifestyle. However, literature shows differences in age have no significant effect on the composition of the exhaled VOCs. [29]

Also, unlike in the study of Brekelmans, controls did not provide blood samples to ensure negative serological factors. Although these provide information about the presence of relevant antibodies in the controls, this seemed too excessive considering the invasiveness relative to the

added value for the study. Besides, RA patients might test negative and healthy individuals might test positive for RF. [30]

Further research is recommended to acquire further insight in the diagnostic performance of the electronic nose. Although distinction was possible between patients and controls, it is unsure whether the actual pathological expression of RA or something else characteristic of RA is captured by the Aeonose. Since the majority of the patients was on medication, it is possible that the effect of variables such as medication caused the measured difference. Also, this research included patients that were treated by a specialist and might be an RA patient for a longer period of time.

Another factor that needs to be taken into account is the fact that the models were based solely on training data. The only performed statistical validation, cross-validation, led to elimination of a number of models. However, this does not guarantee the models are free of overfitting.

Therefore, external validation with larger sample sizes is desired. Also, further subgroup analysis regarding variables such as RF, ACCP, medication and comorbidities can be conducted to investigate whether these variables affect the discrimination possibilities. Here, it is advised to incorporate the duration of the illness in order to investigate the discriminating potential in early RA.

Extension into other inflammatory conditions such as SpA or gout is also an option, since the promising results of this study sparked interest in exploring their discrimination options**.**

In conclusion, the Aeonose shows promising ability to discriminate between RA patients and controls and could possibly contribute in the future RA diagnosis process. However, external validation is desired in order to confirm these findings.

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Appendices

Appendix A: Informed consent

INFORMATIE OVER DEELNAME AAN EEN WETENSCHAPPELIJK ONDERZOEK

TITEL: Het opsporen van inflammatoire reumatische ziekten met een elektronische neus.
ONDERZOEKERS: dr. H.E. Vonkeman, mw. dr. M. Ghiti Moghadam
CENTRUM: Medisch Spectrum Twente

Inleiding
U wordt gevraagd om deel te nemen aan een medisch-wetenschappelijk onderzoek (zie titel). In dit onderzoek wordt onderzocht of stoffen in de uitgeademde lucht kunnen helpen bij het stellen van de diagnose.
U beslist zelf of u mee wilt doen. Voordat u een beslissing neemt, is het belangrijk dat u over de benodigde informatie beschikt om te kunnen beslissen of u wilt deelnemen. Een arts of één van de onderzoekers zal het onderzoek met u bespreken en al uw vragen beantwoorden. U mag ook met familie en vrienden over uw beslissing praten. Neem alstublieft voldoende tijd om te beslissen.
Dit onderzoek zal uw aandoening niet verbeteren, maar andere patiënten kunnen mogelijk in de toekomst voordeel halen uit de informatie die in dit onderzoek wordt verzameld. Hebt u na het lezen van deze informatie nog vragen? Dan kunt u terecht bij de onderzoeker. Op bladzijde 2 vindt u de contactgegevens.

Doel van het onderzoek
Het doel van dit onderzoek is om te onderzoeken of door met een elektronische neus te ruiken aan uitademingslucht op een minder belastende en snellere manier inflammatoire reumatische ziekten aangetoond of uitgesloten kan worden. Deze methode wordt vergeleken met de huidige onderzoeksmethodes.

Onderzoeksprocedure
Als u deelneemt aan dit wetenschappelijk onderzoek wordt bij u naast de geplande onderzoeken een ademanalyse test gedaan, die niet belastend is.
Op dezelfde dag dat bij u op de polikliniek komt, zal u gevraagd worden om maximaal 5 minuten op uw gewone tempo via de mond in een apparaat te ademen, een elektronische neus. De meting vindt plaats bij het afnamelaboratorium in het ziekenhuis. U hoeft dus geen extra bezoek te brengen aan het ziekenhuis.

Voor- en nadelen van deelname
U heeft zelf geen voordeel van meedoen aan dit onderzoek.
Het onderzoek bestaat enkel uit het opvangen van uitgeademde lucht via een niet belastend apparaat, er worden geen medicijnen toegediend. Er zijn dan ook geen risico's verbonden aan deelname aan dit onderzoek.

Vertrouwelijkheid
Naast bovengenoemde metingen zullen wij mogelijk een aantal andere gegevens van u gebruiken: leeftijd, geslacht, of u rookt of niet, de eventuele aanwezigheid van andere ziekten die invloed kunnen hebben op uw adem, laboratoriumuitslagen, medicijngebruik en de diagnose. Uw persoonlijke gegevens worden enkel in gecodeerde vorm (om ervoor te zorgen dat uw identiteit vertrouwelijk blijft) opgeslagen. Volgens wettelijke bepalingen zullen uw gegevens 15 jaar bewaard worden.

Vrijwillige deelname
Uw deelname aan dit onderzoek is geheel vrijwillig. Als u besluit niet mee te doen, hoeft u verder niets te doen. Indien u wel mee wilt doen, kunt u op elk moment stoppen zonder dat dit gevolgen heeft voor uw verdere behandeling.

Toestemming
Hierbij verklaar ik dat men mij uitgebreid uitleg gegeven heeft over dit onderzoek. Ik heb dit toestemmingsformulier gelezen en begrepen. Al mijn vragen zijn naar tevredenheid beantwoord. Ik stem vrijwillig in met deelname aan dit onderzoek en verzameling van relevante medische informatie. Ik weet dat ik te allen tijde mag stoppen met dit onderzoek en dat dit geen verdere gevolgen voor mij heeft. Ik ontvang een getekend en gedateerd exemplaar van dit toestemmingsformulier.

Ik wil meedoen aan dit onderzoek.

Naam proefpersoon:

Handtekening: Datum : __ / __ / __

Ik verklaar hierbij dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam onderzoeker (of diens vertegenwoordiger):

Handtekening: Datum: __ / __ / __

Bijlage A: Contactgegevens voor Medisch Spectrum Twente

Onderzoekscentrum: Medisch Spectrum Twente

Koningsplein 1

7512 KZ Enschede

Hoofdonderzoekers:

dr. H.E. Vonkeman en mw. dr. M. Ghiti Moghadam.

Bereikbaar tijdens kantooruren op 053-4872450. Voor spoedgevallen buiten kantooruren kunt u contact opnemen met het algemene telefoonnummer 053-4872000 en vragen naar de dienstdoende reumatoloog.

Persoonsgegevens:

Voor meer informatie over de naleving van uw rechten bij de verwerking van uw persoonsgegevens kunt u contact opnemen met de Functionaris voor de Gegevensbescherming van MST, mw. P. van Paridon, telefoon: 06-31751387.

Diagnosing inflammatory rheumatic diseases using an electronic Nose

Patiënten sticker

Studienummer …….

Datum inclusie …….

Contactgegevens:

Mirjam Hegeman
Research coördinator Reumatologie
tel. +31 53 487 24 50
m.hegeman@mst.nl

CRF <u>PATIENTEN</u>

In- en exclusie criteria (in te vullen door reumatologie):

1. Wil patiënt meedoen aan de ademtesten?
   - ☐ Ja
   - ☐ Nee, omdat
     - ☐ Logistieke reden/tijd
     - ☐ Angst voor benauwdheid
     - ☐ Angst voor pijn/ongemak
     - ☐ Angst voor ademtest ('enge stoffen')
     - ☐ Anders, namelijk……..

Inclusiecriteria	Exclusiecriteria
☐ ≥ 18 jaar en getekend informed consent	☐ Reden om aan te nemen dat patiënt geen blaastest kan uitvoeren
☐ Diagnose RA	☐ Nederlandse taal onvoldoende machtig
☐ Reumafactor positief	☐ Maligniteit in heden of in afgelopen 5 jaar, uitgezonderd basaalcelcarcinoom
☐ Erosief	
☐ Gebruik DMARD en/of biololgical	

2. Is de patiënt geschikt om mee te doen?
   - ☐ Ja
   - ☐ Nee (vink de reden voor exclusie aan in bovenstaande tabel) --> einde studie

Gegevens patiënt (in te vullen door reumatologie):

3. Demografische gegevens:

   Leeftijd ……jaar

   Geslacht

   - ☐ Man
   - ☐ Vrouw

   Lengte ……cm

   Gewicht ……kg

4. Rookt u of heeft u gerookt?
   - ☐ Ja, aantal jaar: …… aantal sigaretten per dag: ……..
   - ☐ Gestopt, jaartal (benadering):.....

☐ Nee

Behandelgegevens patiënt (in te vullen door onderzoeker):

5. Bloedtest:

   ☐ Anti-CCP antistoffen pos/neg

   ☐ CRP waarde + datum …….

   ☐ BSE waarde + datum ……..

6. Co-morbiditeit(en):

   …….

   …….

   …….

7. Reumamedicatie

   ☐ Methotrexaat

   ☐ Sulfasalazine

   ☐ Leflunomide

   ☐ Hydroxychloroquine

   ☐ TNFi:…….

   ☐ IL6-remmer:……

   ☐ Abatacept

   ☐ Rituximab

   ☐ JAK-remmer:…….

   ☐ Overig:……

CRF <u>HEALTHY CONTROLS</u>

In- en exclusie criteria (in te vullen door reumatologie):

1. Wil proefpersoon meedoen aan de ademtesten?
   - ☐ Ja
   - ☐ Nee, omdat
     - ☐ Logistieke reden/tijd
     - ☐ Angst voor benauwdheid
     - ☐ Angst voor pijn/ongemak
     - ☐ Angst voor ademtest ('enge stoffen')
     - ☐ Anders, namelijk……..

Inclusiecriteria	Exclusiecriteria
☐ ≥ 18 jaar en getekend informed consent	☐ Reden om aan te nemen dat proefpersoon geen blaastest kan uitvoeren
	☐ Nederlandse taal onvoldoende machtig
	☐ Maligniteit in heden of in afgelopen 5 jaar, uitgezonderd basaalcelcarcinoom
	☐ Diagnose RA

2. Is de proefpersoon geschikt om mee te doen?
   - ☐ Ja
   - ☐ Nee (vink de reden voor exclusie aan in bovenstaande tabel) --> einde studie

Gegevens healthy control (in te vullen door reumatologie):

3. Demografische gegevens:

   Leeftijd ……jaar

   Geslacht

   - ☐ Man
   - ☐ Vrouw

   Lengte ……cm

   Gewicht ……kg

4. Rookt u of heeft u gerookt?
   - ☐ Ja, aantal jaar: …… aantal sigaretten per dag: ……..
   - ☐ Gestopt, jaartal (benadering):.....
   - ☐ Nee

Behandelgegevens healthy control (in te vullen door onderzoeker):

5. Co-morbiditeit(en):

   ……

   ……

   ……

6. Medicatie:

   ……

   ……

   ……

   ……

Appendix C: Comorbidities and their frequencies

DBC codes comorbiditeit

Specialisme		DiagnoseCode	
Chronische longziekte			
0313	Inwendige geneeskunde	601	Astma, COPD, emfyseem
0322	Longgeneeskunde	1201	Astma
0322	Longgeneeskunde	1241	COPD
0322	Longgeneeskunde	1601	Interstitiële aandoeningen
Myocard infarct			
0313	Inwendige geneeskunde	102	Instabiele AP, myocardinfarct
0320	Cardiologie	204	ST elevatie hartinfarct
0320	Cardiologie	205	Non ST elevatie hartinfarct
Hartfalen			
0313	Inwendige geneeskunde	107	Decompensatio cordis
0320	Cardiologie	301	acuut hartfalen
0320	Cardiologie	302	chronisch hartfalen
Hypertensie			
0313	Inwendige geneeskunde	311	Hypertensie
0318	Maag-, Darm-, en Leverziekten	901	Hypertensie
0320	Cardiologie	902	Hypertensie
Cerebrovasculair Accident			
0330	Neurologie	1102	Intracerebrale bloeding
0330	Neurologie	1111	Onbloedige beroerte
Fractuur			
0303	Heelkunde	203	Wervelkolom
0303	Heelkunde	204	Wervelkolom met ruggenmerglaesie
0303	Heelkunde	207	Humerus proximaal en schacht
0303	Heelkunde	208	Distale humerus / (epi)condyl(en)
0303	Heelkunde	212	Pols
0303	Heelkunde	213	Carpus
0303	Heelkunde	218	Femur, proximaal (+ collum)
0303	Heelkunde	219	Femur overig
Diabetes mellitus			
0313	Inwendige geneeskunde	221	Diabetes mellitus zonder secundaire complicaties
0313	Inwendige geneeskunde	222	Diabetes mellitus met secundaire complicaties
0313	Inwendige geneeskunde	223	Diabetes mellitus chronisch pomptherapie
Maagulcer / Maagprobleem			
0313	Inwendige geneeskunde	913	Benigne ulcus ventriculi
0313	Inwendige geneeskunde	915	Ongecompliceerd ulcus duodeni
0313	Inwendige geneeskunde	916	Erosieve gastritis en duodenitis
0318	Maag-, Darm-, en Leverziekten	301	Gastro-oesofageale refluxziekte/oesofagitis
0318	Maag-, Darm-, en Leverziekten	401	Gastritis diversen
0318	Maag-, Darm-, en Leverziekten	402	(benigne)Peptisch ulcus
Maligniteit			
0303	Heelkunde	313	Neoplasma bronchus, long
0303	Heelkunde	318	Maligne neoplasma mamma

0303	Heelkunde	333	Maligne neoplasma colon (exclusief sigmoïd / rectum)
0303	Heelkunde	334	Maligne neoplasma recto-sigmoïd overgang
0303	Heelkunde	335	Maligne neoplasma rectum
0303	Heelkunde	350	Maligne melanoom van huid
0303	Heelkunde	353	Ziekte van Hodgkin, non-Hodgkin
0306	Urologie	040	Prostaatcarcinoom
0306	Urologie	048	Prostaatcarcinoom (orchidectomie)
0307	Gynaecologie	M13	Maligniteit cervix
0307	Gynaecologie	M16	Maligniteit ovarium / tuba
0310	Dermatologie	14	Maligne dermatosen
0313	Inwendige geneeskunde	751	Hodgkin lymfoom
0313	Inwendige geneeskunde	752	Non Hodgkinlymfoom (NHL) laaggradig
0313	Inwendige geneeskunde	753	Non Hodgkin lymfoom (NHL) intermediair/hooggradig
0313	Inwendige geneeskunde	621	Maligniteit, kleincellig carcinoom bronchus
0313	Inwendige geneeskunde	622	Maligniteit, grootcellig carcinoom bronchus
0313	Inwendige geneeskunde	811	Maligniteit mamma
0313	Inwendige geneeskunde	821	Maligniteit ovarium
0313	Inwendige geneeskunde	822	Maligniteit cervix
0313	Inwendige geneeskunde	832	Maligniteit prostaat
0313	Inwendige geneeskunde	842	Maligniteit huid/melanoom
0313	Inwendige geneeskunde	927	Maligniteit colorectaal
0322	Longgeneeskunde	1303	Tumoren NSCLC
0322	Longgeneeskunde	1304	Tumoren SCLC

DBC	**Condition**	**Frequency**	
		Patient	Control
40	Prostaatcarcinoom	1	
218	Femur, proximaal (+ collum)	1	
221	Diabetes mellitus zonder secundaire complicaties		1
222	Diabetes mellitus met secundaire complicaties	1	
301	Gastro-oesofageale refluxziekte/oesofagitis	1	1
302	Chronisch hartfalen	1	
311	Hypertensie	1	2
318	Maligne neoplasma mamma	2	
350	Maligne melanoom van huid	2	
753	Non Hodgkinlymfoom (NHL) intermediair/hooggradig	1	
811	Maligniteit mamma	2	
902	Hypertensie	1	
1111	Onbloedige beroerte	1	
1201	Astma	1	1
1241	COPD	4	
1601	Interstitiële aandoeningen	2	

TRIAL

Aanvrager: Vonkeman, H.E.
Contact: Inst TRLAB

Patient Study nr.: _____(wordt ingevuld door research)

In te vullen door de Medlon

Aenose nr apparaat:.....

- Wanneer heeft u voor het laatst iets gegeten?
  - ☐ >3 uur geleden
  - ☐ <3 uur geleden
- Zou u bereid zijn om in de toekomst nogmaals een ademtest te ondergaan?
  - ☐ Ja
  - ☐ Nee, vanwege .....
- In welke mate had u tijdens de test last van ongemak (angst, pijn en/of benauwdheid)? Een **0** betekent 'helemaal geen ongemak' en **10** betekent 'ondragelijk ongemak'?
- Verloop ademtest:
  - ☐ Succesvol
  - ☐ Niet succesvol, vanwege .....
- Opmerkingen (bv na 2 minuten gestopt, hoesten enz.):

_____
_____
_____

- Datum blazen: .....
- Tijdstip blazen: .....

Ademanalyse Reuma

Aanvraagscherm : Trials/Projecten
Aanvraag : **Ademanalyse Reuma**