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# Detection of differentiated thyroid carcinoma in exhaled breath with an electronic nose

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## Abstract

This proof-of-principle study investigates the diagnostic performance of the Aeonose in differentiating malignant from benign thyroid diseases based on volatile organic compound analysis in exhaled breath. All patients with a suspicious thyroid nodule planned for surgery, exhaled in the Aeonose. Definitive diagnosis was provided by histopathological determination after surgical resection. Breath samples were analyzed utilizing artificial neural networking. About 133 participants were included, 48 of whom were diagnosed with well-differentiated thyroid cancer. A sensitivity of 0.73 and a negative predictive value (NPV) of 0.82 were found. The sensitivity and NPV improved to 0.94 and 0.95 respectively after adding clinical variables via multivariate logistic regression analysis. This study demonstrates the feasibility of the Aeonose to discriminate between malignant and benign thyroid disease. With a high NPV, low cost, and non-invasive nature, the Aeonose may be a promising diagnostic tool in the detection of thyroid cancer.

## 1. Introduction

Thyroid carcinoma is the most common malignancy of an endocrine organ, accounting for approximately 2% of all diagnosed cancers worldwide [1]. During the past three decades, the incidence of thyroid carcinoma has rapidly increased in developed countries though mortality has remained relatively stable [2]. The use of ultrasound and the introduction of novel diagnostic methods may play a role in this increase in diagnoses of thyroid carcinoma. In the Netherlands, 700 patients are diagnosed with thyroid carcinoma each year. The most common histological forms are well-differentiated papillary and follicular carcinoma, comprising 80%–85% of all thyroid cancers [3]. Well-differentiated thyroid carcinomas have a relatively good prognosis because they tend to grow and metastasize slowly.

These patients typically present with a thyroid nodule, which can be benign or malignant. The diagnostic work-up of a newly discovered thyroid nodule aims to distinguish benign from malignant thyroid nodules. The first step of this work-up is to perform an ultrasound of the neck to confirm the presence of the nodule and to report it according to the thyroid imaging reporting and data system (TI-RADS). This risk-stratification system for thyroid nodules is based on ultrasound features [4]. When indicated based on the TI-RADS score, fine-needle aspiration cytology (FNAC) is performed, resulting in the reporting of the Bethesda classification estimating the risk of malignancy. The FNAC has been considered the gold standard diagnostic test for evaluating thyroid nodules [5]. Unfortunately, both ultrasound and FNAC often result in an inconclusive risk assessment of malignancy, resulting in the need for a diagnostic hemithyroidectomy for a definite diagnosis [6]. About 40%–94% Of the suspected thyroid nodules appear to be benign after resection [7].

As a result, preoperative evaluation of thyroid nodules is associated with invasive and non-accurate diagnostics for patients. Therefore, a quick, non-invasive diagnostic tool to determine the nature of thyroid nodules is of paramount importance. Such a novel test could fasten the diagnostic process for patients with malignancies and reduce the number of unnecessary surgeries for benign conditions.

A promising development in cancer detection is based on volatile organic compounds (VOCs), gaseous degradation products of biochemical processes detectable in exhaled breath. During pathophysiological processes related to tumor growth, alterations in cell metabolism lead to a shift in the production of VOCs [8]. A study by Guo *et al* using gas chromatography - ion mobility spectrometry (GC-IMS) found seven characteristic VOCs in exhaled breath in patients with thyroid cancer that differed from healthy controls [9]. More than 850 individual VOCs have already been detected in exhaled breath [10]. In recent years, several techniques have been developed to assess these VOCs. A relatively new technique is the electronic nose (e-nose). This is a portable, handheld device that sensors incorporated on which VOCs in exhaled breath react and generate patterns. The detection of VOC patterns by an e-nose is possible due to binding of VOCs to sensors within the e-nose. An electrical response is generated upon binding of VOCs to the sensors. This electrical response can then be measured. The diagnostic accuracy of this technique has already been extensively investigated in the detection of several other malignancies [10–20].

In this proof-of-principle study, we investigate the diagnostic performance of an e-nose in detecting thyroid carcinoma in exhaled breath of patients with a suspicious thyroid nodule by comparing the VOC patterns with the definitive diagnosis by histopathological determination as the reference standard. This study aims to prove a high diagnostic accuracy of the e-nose in discriminating benign from malignant thyroid nodules. Moreover, data from exhaled breath are combined with clinical parameters to investigate whether this can further improve diagnostic accuracy.

## 2. Materials and methods

### 2.1. Study population

This prospective proof-of-principle study was conducted at the Maastricht University Medical Center (MUMC+) from October 2016 to March 2021. Patients with a suspicious thyroid nodule, planned for a diagnostic procedure including an ultrasound of the neck followed by FNAC, were recruited via the outpatient clinic of the Department of Surgery or the Department of Endocrinology. Only if a diagnostic (hemi-)thyroidectomy for obtaining the definitive pathology of the thyroid nodule was indicated, patients were eligible for inclusion. Exclusion criteria were the evidence of other invasive cancer in the past five years or the inability to understand the study information.

After the post-operative definitive pathology was obtained, the included patients were divided into two groups: the ‘malignant group’ consisting of well-differentiated thyroid carcinomas (both papillary or follicular), or the ‘benign group’ consisting of benign thyroid abnormalities (benign nodule or multinodular goiter).

The study was approved by the medical ethical committee of the MUMC+ and was conducted according to the Declaration of Helsinki. Oral and written information was given by all patients eligible for the study. Written informed consent was obtained before breath analysis.

### 2.2. Study design

Measurements were performed at the outpatient clinic of the Department of Surgery or in a measuring room specially equipped for the e-nose, with stable humidity and room temperature and without disinfecting alcohol in the vicinity of the device. Inclusion took place before the patient underwent the (hemi-)thyroidectomy or any other therapeutic intervention and at least three days after the FNAC to limit the effects of this procedure on the VOCs pattern. The patients were allowed to eat and drink before the measurement. Trained physicians guided the breath collection.

Information including gender, age, body mass index (BMI), current smoking status, Bethesda classification, post-operative histopathological diagnosis, and the location where the measurement took place was collected for all patients. The postoperative histopathological diagnosis was linked to each breathing pattern. Double-checking of histopathological diagnosis was performed by two researchers to avoid mistakes.

### 2.3. Materials

For this study, the Aeonose was used. This is an electronic device manufactured by The eNose Company, located in Zutphen, the Netherlands. The Aeonose consists of three micro hotplate metal-oxide sensors: carbon monoxide (AS-MLC), nitrogen dioxide (AS-MLN), and VOC (AS-MLX) sensors. During each measurement, the metal-oxide sensors go through a sinusoidal temperature cycle between 260 °C and 340 °C. These sensors react via a redox reaction with the VOCs in the exhaled air, inducing changes in the conductivity of the sensors and generating numeric patterns. These numeric data are exported to and stored in a data center, to be analyzed afterward.

During a measurement, patients breathed through a disposable mouthpiece containing a carbon filter and a high-efficiency particulate air filter to prevent contamination of the internal tubing of the Aeonose. To prevent rebreathing, the device contains one tube with silicon valves (a one-way system). A disposable nose clip was placed on the nose of each patient to avoid entry of non-filtered air. Patients were asked to close their lips over the mouthpiece during the entire measurement. Before each measurement, the Aeonose was flushed with environmental room air. Only one device was used during this study.

A single full measurement required 15 min, of which the patient breathed the first five consecutive minutes in the device. During the first two minutes, a washout period took place for clearing the lungs from ambient, possibly polluted air to eliminate exogenous VOCs. This was followed by a three-minute guiding of exhaled breath over the three metal-oxide sensors. During the remaining ten minutes, regeneration of the device takes place during which the sensors are flushed with fresh air. Thereafter, the device was ready for re-use.

### 2.4. Statistical analysis

Differences in baseline characteristics between the malignant- and benign groups were analyzed with an independent sample t-test when normality of the data was visually confirmed, or Fisher's exact test, or Pearson's Chi-square test, as appropriate.

During a single breath analysis, the Aeonose measures every 20 s a total of 64 values per sensor. Each breath analysis contains 36 of these measuring cycles. The obtained numerical data were then preprocessed and compressed, resulting in a single vector of limited size per participant. Together with the patients' histopathological diagnosis, the vectors were entered in a Random Forest. The analysis package Aethena (The eNose Company) was used to optimize results by combining several pre-processing techniques and vector lengths. A 'leave-10%-out' cross-validation was applied to prevent the fitting of the data on artifacts instead of breath profile characteristics. The results were presented in a scatter plot and a receiver operating characteristic curve (ROC curve). Extensive details on analysis via the Aeonose have already been published [12]. Besides the analysis by the Aethena package, two multivariate regression analyses were performed to investigate whether the predictive value of having a thyroid malignancy could be further improved. For the first analysis, only patients with a clinically relevant Bethesda classification ($\geqslant$Bethesda II) were selected. For the second, post-hoc analysis, all patients were selected, including the inconclusive Bethesda (Bethesda 1) classification and the patients where no FNAC was performed (no Bethesda). Clinical variables that were different between the malignant and benign groups and the value (between $-1$ and $+1$) obtained from the Aeonose were added to the regression analysis. An independent epidemiologist (JvdP) supported the data analysis.

## 3. Results

First, the diagnostic performance of the Aeonose in discriminating benign from malignant thyroid nodules in exhaled breath using histopathological determination as the reference standard was investigated. A total of 134 patients were included in this analysis, 49 of whom were diagnosed with well-differentiated thyroid carcinoma (malignant group) and 85 were diagnosed with benign thyroid disease (benign group). All patients were able to finish the breath test; no adverse effects were observed. One patient in the malignant group was excluded due to technical difficulties during sample collection.

The distribution over the malignant and benign groups as well as the clinical characteristics of the patients are listed in table 1. The mean age and BMI were comparable between both groups. There were proportionally more males in the malignant group and interestingly, there were more smokers in the benign group, although this was not a statistically significant difference.

The prevalence of well-differentiated thyroid carcinoma in our study population was 36%. The composition of the exhaled air differed significantly between the malignant and benign groups, with an area under the curve (AUC) of 0.76. A threshold of $-0.07$ resulted in a sensitivity of 0.73 (95% CI 0.59–0.84) and a negative predictive value (NPV) of 0.82 (95% CI 0.72–0.90). The specificity and positive predictive value (PPV) were 0.69 (95% CI 0.59–0.79) and 0.57 (95% CI 0.45–0.69) respectively. The overall accuracy was 0.71. Figure 1 illustrates the ROC curve, figure 2 illustrates the scatterplot.

Additionally, a multivariate logistic regression analysis was performed in which age, smoking status, and the Bethesda classification were added to the value obtained from the Aeonose (range $-1$ to $+1$). For this additional analysis, only the data of 87 patients with a clinically relevant Bethesda classification were used; data of patients that had not undergone an FNAC and therefore had no Bethesda classification ($n = 30$) and patients with an inconclusive result (Bethesda I, $n = 16$) were left out of this analysis. This resulted in a model listed in table 2, with an AUC of 0.95. When the probability of a malignancy was set to $\geqslant$30%, this resulted in a sensitivity and NPV of 0.94 (95% CI 0.83–0.99) and 0.95 (95% CI 0.85–0.99) respectively. The specificity was 0.76 (95% CI 0.63–0.87) and the PPV was 0.76 (95% CI 0.60–0.85).

Post-hoc, a second analysis, including the data of patients that had not undergone a FNAC and therefore had no Bethesda classification ($n = 30$)

**Table 1.** Baseline characteristics of the study cohort ($n = 133$).

| | Malignant ($n = 48$) | Benign ($n = 85$) | $P$-value |
|---|---|---|---|
| Type of thyroid disorder | | | |
| Follicular carcinoma, n (%) | 16 (33.3) | | — |
| Papillary carcinoma, n (%) | 32 (66.7) | | — |
| Benign nodule, n (%) | | 50 (58.8) | — |
| Multinodular goiter, n (%) | | 35 (41.1) | — |
| Characteristics | | | |
| Male gender, n (%) | 17 (35.4) | 18 (21.2) | 0.073 |
| Age (years), mean ± SD | 54.3 ± 16.9 | 57.9 ± 14.0 | 0.188 |
| BMI (kg m$^2$), mean ± SD | 26.6 ± 4.9 | 27.2 ± 5.7 | 0.542 |
| Smoker, n (%) | 4 (8.3) | 18 (21.2) | 0.056 |
| Bethesda classification | | | |
| None, n (%) | 8 (16.7) | 22 (25.9) | |
| 1, n (%) | 4 (8.3) | 12 (14.1) | |
| 2, n (%) | 2 (4.2) | 25 (29.4) | |
| 3, n (%) | 5 (10.4) | 10 (11.8) | |
| 4, n (%) | 11 (22.9) | 15 (17.6) | |
| 5, n (%) | 13 (27.1) | 0 (0) | |
| 6, n (%) | 5 (10.4) | 1 (1.2) | |

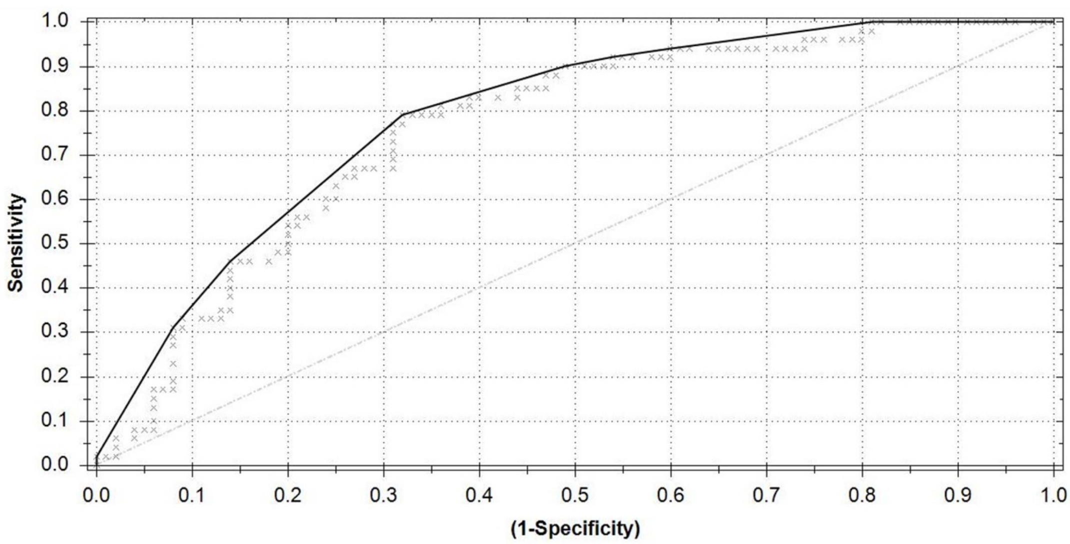


**Figure 1.** The receiver operating characteristic (ROC) curve illustrates the diagnostic performance of the Aeonose. The area under the curve is 0.76.

and patients with an inconclusive result (Bethesda I, $n = 16$) was performed. This resulted in the model listed in table 3, with an AUC of 0.89. When the probability of a malignancy was set to ⩾30%, this resulted in a sensitivity and NPV of 0.90 (95% CI 0.81–0.98) and 0.93 (95% CI 0.86–0.99) respectively. The specificity was 0.74 (95% CI 0.65–0.83) and the PPV was 0.66 (95% CI 0.55–0.78).

## 4. Discussion

Accurately assessing the risk of malignancy of thyroid nodules still poses a challenge to clinicians. The current diagnostic work-up of suspicious thyroid nodules is invasive, patient unfriendly, and inaccurate. Consequently, patients with a suspected thyroid nodule are frequently exposed to unnecessary surgery with potential complications. Therefore, a new and accurate diagnostic tool is needed. In this proof-of-principle study, we investigated the diagnostic accuracy of the Aeonose in the discrimination of benign from malignant thyroid nodules based on VOC patterns in exhaled breath. The results of this pilot study suggest that the Aeonose may have the potential to become an accurate, quick, and non-invasive diagnostic tool in the detection of thyroid carcinoma. The Aeonose was able to discriminate malignant from benign thyroid nodules with an NPV of 82% and a sensitivity of 73%. By adding clinical variables, including age, current smoking status,

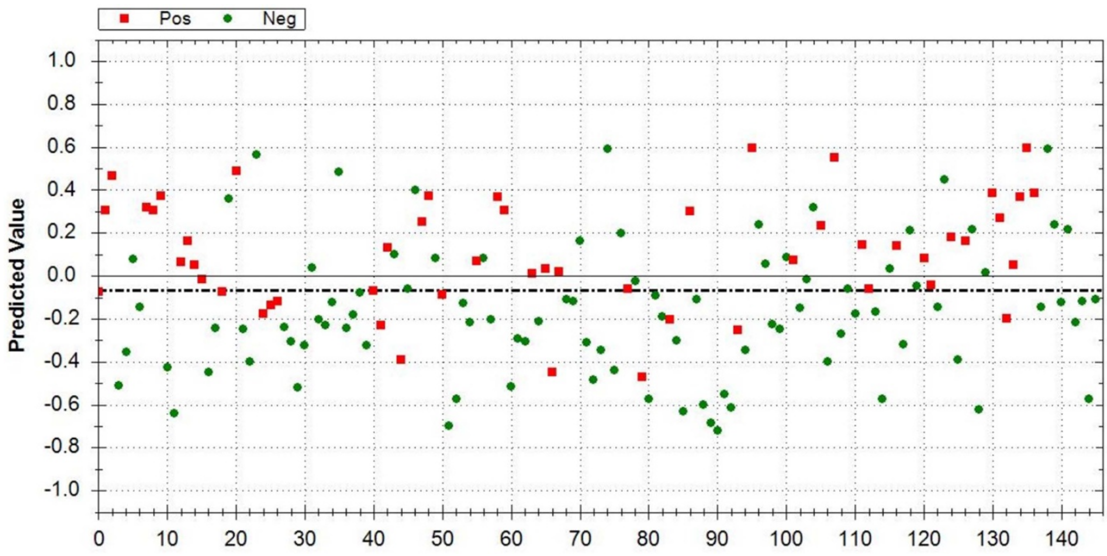


**Figure 2.** Scatterplot of individual predictive values of each patient. A green dot represents a patient from the benign group and a red dot from the malignant group. Values >−0.07 are scored as malignant.

**Table 2.** Results of the multivariate logistic regression analysis with addition of clinical variables.

| Variable | Odds ratio (95% CI) | B |
|---|---|---|
| Current smoker | 9.0 (0.96–84.5) | 2.2 |
| Bethesda II | 1 (reference category) | |
| Bethesda III and IV | 18.6 (1.7–200) | 2.9 |
| Bethesda V and VI | 1031 (30.2–35 181) | 6.9 |
| Age | 0.97 (0.92–1.02) | −0.03 |
| Machine learning classifier | 492 (14.2–17 060) | 6.2 |

Data are presented as odds ratio (95% confidence interval). Constant is −3.559. B: regression coefficient.

**Table 3.** Results of the multivariate logistic regression analysis with addition of clinical variables for all patients.

| Variable | Odds ratio (95% CI) | B |
|---|---|---|
| Current smoker | 3.52 (0.71–17.4) | 1.26 |
| Bethesda 1/not performed | 1 (reference category) | |
| Bethesda II | 0.26 (0.04–1.6) | −1.3 |
| Bethesda III and IV | 2.87 (0.97–8.47) | 1.1 |
| Bethesda V and VI | 82.8 (8.18–838.5) | 4.4 |
| Age | 0.99 (0.95–1.02) | −0.2 |
| Machine learning classifier | 48.5 (7.05–333) | 3.9 |

Data are presented as odds ratio (95% confidence interval). Constant is −3.559. B: regression coefficient.

and the clinically relevant Bethesda classification to the value obtained from the Aeonose in a regression analysis, the NPV and sensitivity improved to 95% and 94% respectively. These results suggest that the Aeonose has the potential to aid clinicians in choosing the optimal therapeutic or diagnostic strategy for patients with potential malignant thyroid nodules, based on ultrasound or FNAC. A separate, post-hoc, regression analysis, including all patients, showed a reduction in the diagnostic accuracy of the Aeonose, with an AUC, sensitivity, and NPV of 0.89, 0.90 and 0.93 respectively. This reduction in diagnostic accuracy is likely due to the introduction of uncertainty in the regression model because of the inclusion of patients with a Bethesda 1 and patients that had not undergone an FNAC (no Bethesda).

In concordance with our findings, several studies have demonstrated the diagnostic potential of VOC pattern analysis by the use of an e-nose. This has been demonstrated for several indications including lung cancer, colorectal cancer, breast cancer, and pre-malignant indications such as Barrett esophagus [13–16]. To date, only one study has analyzed the use of VOCs as a potential biomarker in the detection of thyroid cancer [9]. Using a different method of VOC analysis, Guo *et al* analyzed VOCs in exhaled breath from patients with papillary thyroid carcinoma (PTC), patients with nodular goiter, and healthy controls. Utilizing solid-phase micro extraction-gas chromatography and mass spectrometry (GC-MS), significant differences were found in the composition of VOCs between healthy controls and patients with PTC, healthy controls and patients with nodular goiter, and patients with PTC and nodular goiter. Although these findings are in line with our results, the study had a relatively small sample size and was limited to the inclusion of patients with PTC and nodular goiter only.

Our study has several important strengths. This is the first study using VOC pattern analysis in the differentiation of benign and malignant thyroid nodules with an e-nose. In comparison to GC-MS, the use of VOC pattern recognition using an e-nose may offer several advantages including potentially lower costs, faster diagnosis, ease of use, and portability. In addition, in comparison to other e-noses, the Aeonose offers the ability to transfer individual calibration models to other devices, thus allowing large-scale application [17]. Another strength is in the design of our study. FNAC, the current golden standard in the diagnostic work-up of thyroid nodules, often results in an inconclusive diagnosis [6]. Therefore, this would not have been a suitable reference standard. Hence, in comparing the VOC patterns in benign and malignant thyroid nodules, we chose to only include patients scheduled for surgery to obtain a definitive diagnosis by histopathology.

This study also had several limitations that need to be addressed. An inherent limitation of e-nose pattern recognition technology is the inability to identify specific individual VOCs. Therefore, it is not possible to know that the measured VOC patterns are unique for this disease. In this study, to limit exogenous contaminants such as alcohol, we conducted the breath sample collection in two dedicated rooms without any disinfecting alcohol in the vicinity. In this study, patients were not refrained from smoking prior to breath sampling. In the field of e-nose research, there has been conflicting evidence on the influence of smoking on the accuracy of e-noses [18–20]. Future research should further investigate the influence of smoking on e-nose accuracy for each specific indication. In this study, patients were not refrained from eating certain foods or drinking (alcoholic) beverages prior to breath sampling. It has been shown that certain pungent food such as garlic and leek, and the consumption of alcohol and coffee may alter the composition of VOCs in exhaled breath [11]. Further potential endo- and exogenous confounders, including medication use and comorbidities need to be considered and evaluated in further e-nose studies.

In line with our study, a general lack of standardization is found in e-nose studies in all phases of VOC collection and analysis. Future studies should aim to construct a framework to standardize the optimization of sensor systems, sample collection protocols, and data analysis for technical, physiological, and pathophysiological confounders.

The findings of this study suggest that the Aeonose may have the potential to be implemented in the diagnostic workup of patients with a suspected thyroid nodule. This may result in a reduction of unnecessary surgery and consequent complications. With a false negative rate of 6%, there would be a need for careful follow-up to detect any missed malignant nodules. Despite these promising results, future research is needed to externally validate these results. Therefore, a large prospective multi-center external validation study is currently in preparation.

In conclusion, this proof-of-principle study indicates that the Aeonose can discriminate between the VOC profiles in exhaled breath of patients with malignant and benign thyroid disease. The Aeonose, in combination with clinical variables including the Bethesda classification, was able to accurately exclude malignancies in patients with potential malignant thyroid nodules. With a high NPV, low cost, non-invasive nature, and the ability to provide a rapid diagnosis, the Aeonose may be a promising diagnostic triage tool in the exclusion of thyroid malignancy and may reduce unnecessary surgery for diagnostic purposes. Further validation of these results on a blinded sample set is needed to assess the reproducibility and robustness of the developed model.

## Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

## Funding

There was no funding for this study.

## Conflict of interest

Anne G W E Wintjens, Max H M C Scheepers, Zaid J J Al-Difaie, Sanne M E Engelen, Bas Havekes, Tim Lubbers, Marielle M E Coolsen, Job van der Palen, Tessa M van Ginhoven and Menno Vriens: no conflict of interest. Nicole D Bouvy: a first-line relative is an investment manager and small (<5%) shareholder of an investment fund, which holds a (<25%) minority stake in eNose B V.

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