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Canine scent detection in the diagnosis of lung cancer: Revisiting a puzzling phenomenon

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Abbreviations

COPD	**chronic obstructive pulmonary disease**
FEV1	**forced expiratory volume in one second**
LC	**lung cancer**
n	**number**
n.s.	**not significant**
RV	**residual (lung) volume**
SCLC	**small cell lung cancer**
TLC	**total lung capacity**
VC	**vital capacity**
VOC	**volatile organic compound**

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Abstract

Patient prognosis in lung cancer (LC) largely depends on early diagnosis. Exhaled breath of patients may represent the ideal specimen for future LC screening. However, the clinical applicability of current diagnostic sensor technologies based on signal pattern analysis remains incalculable due to their inability to identify a clear target. To test the robustness of the presence of a so far unknown volatile organic compound in the breath of patients with LC, sniffer dogs were applied.

Exhalation samples of 220 volunteers (healthy individuals, confirmed LC, or COPD) were presented to sniffer dogs following a rigid scientific protocol. Patient history, drug administration and clinicopathological data were analyzed to identify potential bias or confounders.

LC was identified with an overall sensitivity of 71% and a specificity of 93%. LC detection was independent from COPD and the presence of tobacco smoke and food odors. Logistic regression identified two drugs as potential confounders.

It must be assumed, that a robust and specific volatile organic compound (or pattern) is present in the breath of patients with LC. Additional research efforts are required to overcome the current technical limitations of electronic sensor technologies to engineer a clinically applicable screening tool.

Key words

biomarker, breath analysis, chronic obstructive pulmonary disease, diagnosis, lung cancer

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Main Body

Introduction:

Lung cancer (LC) continues to represent the second most frequent cancer form in men and women with 391,000 cases/year in Europe [1]. Moreover, it is the most common cause of death from cancer with estimated 342,000 deaths/year. The prognosis of LC largely depends on disease discovery at an early stage, when the tumor is still localized [2]. Unfortunately, early LC is not associated with symptoms, and detection therefore is often by chance. Clinical practice has shown that the available diagnostic techniques (such as the various imaging technologies or bronchoscopy including interventional biopsy procedures) have limitations in reliably discriminating between cancer patients and healthy subjects [3, 4]. No screening method currently exists to test for LC.

Since 1982, research was conducted to develop sensor arrays and pattern recognition technologies, commonly referred to as "electronic noses" that could detect and recognize odors and flavors [5]. It was hypothesized that these devices may be applicable in identifying volatile organic compounds (VOCs) that are linked to cancers in their early stages and thereby making them potential non-invasive and inexpensive diagnostic tools for the medical community [6, 7]. Over the last three decades "electronic sensing" or "e-sensing" technologies have undergone important developments and are now used to fulfill industrial needs [8]. However, their applicability in a clinical setting is limited due to the fact that patients are required to not smoke and to fast before breath samples can be taken. Other limiting factors are that an optimized sample collection is necessary, that the instruments are very sensitive, the long durations for sample analysis, as well as high risks of signal interference. Interestingly, despite of a large body of experimental work, no LC-specific VOCs or VOC patterns have been identified to date [9].

Every now and then, the medical community's attention is drawn to the phenomenon that dogs may detect cancer in patients [10, 11]. Having in mind the limitations of the "electronic nose", we became interested in this phenomenon. Consequently, we trained 4 family dogs and designed a prospective, blinded clinical trial to obtain reliable data regarding (i) diagnostic accuracy and (ii) discriminability of LC from chronic obstructive pulmonary disease (COPD) as a chronic inflammatory condition, which is often associated with the development of LC. Our findings may contribute to the clinical appraisal of breath analysis as a diagnostic approach to identify LC in patients and raise the bar regarding clinical suitability of "electronic nose" technologies.

Methods:

Study design. Hypotheses were tested in a prospective, blinded clinical trial. The study was approved by the Ethics Committee of the University of Tuebingen (434/2009BO1) and the Medical Association of Baden-Württemberg (B-F-2010-004) and registered at *ClinicalTrials.gov* (NCT01141842).

Study subjects. Breath samples from patients with COPD or suspected LC and healthy individuals were collected from 12/2009 to 04/2010 at the Schillerhoehe Hospital (Gerlingen, Germany) and the medical practice "Ambulante Pneumologie" (Stuttgart, Germany) after signed consent was obtained. No restrictions were made regarding food ingestion (including tea, coffee and alcohol) and smoking behavior (no determined smoke free-interval).

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Additionally, all participants provided their medical history to determine the risk of LC and other cancers and pulmonary disease, their medication record to control for confounders, and underwent lung function testing to determine the presence of COPD. Inclusion criteria were males and females, age 18-80 years, and signed informed consent. Exclusion criteria were suspected or confirmed malignant disease (other than LC), previous thoracic surgery and any medical intervention at the chest or the airways (for instance thoracocentesis, aspiration biopsy or diagnostic bronchoscopy) within the preceding 14 days. The participants were classified into three groups: A) healthy, B) LC, and C) COPD. The breath sample of all potential patients with LC was obtained at the beginning of their hospital stay and retained. The decision whether a particular patient was assigned to the cancer group B (or was excluded from the study) was made on the basis of the histology of a tumor biopsy or the resected tumor, respectively, after meticulous work-up including bronchoscopy and/or surgery (Fig. 1). The histological assessment was made by a trained pathologist and the chief of the department of pathology at the Schillerhoehe Hospital.

Breath sample collection. Cylindrical glass tubes (Gaßner Glastechnik GmbH, Munich, Germany) that could be closed using removable end caps (rubber) were obtained (12 cm length, inner diameter 2.2 cm) (Fig. 2A). The lumen of the glass tube was filled with a polypropylene fleece (Asota Ges.m.b.H., Linz, Austria) that was impregnated with a silicone oil to have either hydrophilic or hydrophobic absorbing properties (CHT R. Beitlich GmbH, Tuebingen, Germany). Two tailored straps of the coated fleece (one hydrophilic and one hydrophobic) were loaded into the lumen of the glass tube. Identical test probes that were prepared by the same persons in a standardized procedure were employed at the 2 collection facilities. Each tube was handled by all individuals involved in the execution of this study to omit unintended "scent labeling". For breath sampling, each participant exhaled 5 times through the tube, holding it in their bare hands (Fig. 2B). The tubes were capped, labeled and stored at room temperature in a light-tight cabinet until testing.

Lung function testing. Body plethysmography (flow plethysmography) was performed according to established guidelines (CareFusion, Hoechberg, Germany) [12]. The testing was performed in a sitting position and the patient's height and weight were recorded to calculate the reference values. The diagnosis COPD was made on the basis of medical history and lung function testing according to established guidelines [13].

Dog training. Dog training and testing was performed in a separate room that was specifically prepared for the study and was not used otherwise. Four family dogs (two German shepherd dogs, one Australian shepherd dog, one Labrador retriever) of both sexes (two females, two males) aged 2.5 to 3 years were provided by local dog owners and trained by a professional dog trainer following a reward-based approach to indicate breath samples of patients with LC [14]. Dogs were trained to indicate a positive test tube by lying on the floor in front of the tube with the muzzle touching the test tube. During the training, and also later in the testing, every test tube containing a human breath sample was used only once to preclude simple memory recognition of participants' unique odor signatures.

Breath testing. Three tests were performed in 05/2010 to investigate whether the sniffer dogs were able to identify LC amongst 4 healthy controls (Test I), to discriminate LC from COPD when tested amongst 4 patients with COPD (Test II), and from 4 representatives of a mixed study population of COPD patients and healthy controls (Test III) (Tab. 1). For testing, the

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probes were positioned in 5 separate retainers on the floor, with the rubber caps removed (Fig. 2 C). Each probe was chosen randomly from the group stack (A, B, C). The observers of the dogs' indication were blinded: Probe drawing and positioning was concealed from the dogs, their dog handlers, and the study observers by an opaque curtain. In each test, only one probe of a patient with confirmed LC (group B) was used. The position of this probe (retainer 1 to 5) was determined by dicing (Fig. 2D) (with "6" requiring dicing again). The remaining retainers were randomly filled with test tubes according to test requirements (Tab. 1). For testing, the person who positioned the test tubes left the room and the curtain was opened and the dogs were commanded to sniff the deployed probes. Two observers documented the dogs' indications and matched them with the probe array after every test round.

Statistical analysis. Statistical analysis was performed with the statistical software package R (version 2.11.0, www.r-project.org) and SPSS (version 15 for windows, SPSS Inc, Chicago, Ill). Fisher's exact test for categorical data was applied to test for homogeneity and compare the relative frequency of events between groups. Groups of continuous data were compared by Wilcoxon's test with continuity correction. The Kruskal-Wallis test was chosen to analyze three groups of continuous data simultaneously. For pairwise comparison of several groups Holm's method was applied to adjust *p* values for multiple testing. Fleiss' Kappa was performed to assess the inter-rater agreement of trained dogs in the experimental setting, with $\kappa=1$ indicating complete rater agreement and $\kappa=0$ indicating agreement only by chance. Mixed effects logistic regression was applied to model the dependence of (i) sample age and (ii) medication on dogs' indication. All *p* values were two-sided, and a *p* value of < 0.05 was considered to indicate statistical significance.

Results:

Composition of training and test groups. Applying the in- and exclusion criteria, 220 participants were enrolled (Tab. 2): 110 healthy individuals (Group A), 60 patients with histologically confirmed LC (Group B) and 50 with COPD (Group C). Differing from our primary inclusion criteria, we had to include patients who had undergone diagnostic bronchoscopy within the last 14 days to facilitate sufficient patient numbers. For dog training, breath samples of 60 healthy volunteers and 35 patients with LC were needed. No training was performed for COPD. To ascertain that breath samples of similar donors were used in dog training and testing, training and test subgroups of Groups A and B were compared. Here, no relevant discrepancies were found. As well, a comparison of the three tested (sub)groups A, B and C revealed no significant statistical difference regarding their constitution. As a consequence of the training strategy (applying breath samples of groups A and B, but not C) the sample age of group C was significantly less.

Lung function in training and test groups. Lung function parameters were surveyed to determine whether study participants had a normal or limited lung function (Tab. 3) and whether there was a difference between training and test groups. In group A, statistical analysis indicated slightly increased values for the relative vital capacity (VC) and forced expiratory lung volume (FEV1) in the training group. In contrast, all lung function parameters in Group C showed explicit obstructive patterns.

Trained and tested tumor stages. A comparison of the underlying tumor stages applied for dog training (n=35) and testing (n=25) showed a shift towards higher tumor stages in the test

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group (Fig. 3A). However, a considerable number of employed breath samples were obtained from patients with early and locally advanced LC disease UICC stage I to IIIa (46% in the training and 36% in the test subgroup). Regarding tumor histology, the majority of tested breath samples in Group B was obtained from patients with adenomatous non-small cell LC (Fig. 3B). Diagnostic work up following breath sampling identified 4 tumors as small cell lung cancers (SCLC).

Lung cancer identification by sniffer dogs. Tests I to III were performed within 2 days with no modifications in the test protocol. Following the search command, each investigational course (for the 5 assembled breathe samples) took less than 15 seconds. Every dog indication had to be definite and hesitation free with the dog lying in front of the test tube. If it was not, the indication was assessed as incorrect. Two blinded study observers recorded the dogs' indications (Tab. 4). There were no disagreements in the two observers' records. The hit ratio for the 4 individual dogs was different throughout the course of experiments ranging from 68 to 84 % (Tab. 5). The accuracy of the dog's indication did not favor advanced tumor stages and was 100% for UICC stage I, 75% for UICC stages IIa and IIb, 94% for UICC stage IIIa, 75% for UICC stage IIIb and 63% for UICC stage IV. The overall sensitivity was 71% and the specificity was 93%, with the positive and negative predictive value being 72% and 93% (Tab. 4). The inter-rater variability of the 4 dogs was moderate ($\kappa = 0{,}436$) (Tab. 5). The best results were obtained in test III ("mixed population"), the worse in test I (LC versus healthy controls). Therefore, we defined the "corporate dog decision", which requires at least 3 dogs making the same decision. The "corporate dog decision" analysis, however, did not ameliorate our test scores, resulting in a sensitivity of 72%, a specificity of 94% and a positive and negative predictive value of 75% and 93%, respectively.

Controlling for confounders. The distribution of active smokers was similar between groups (Tab. 2). The inclusion of patients who had previously undergone diagnostic bronchoscopy did not influence the sample classification by the dogs (p=0.6729, CI 0.1618 – 12.2953, odds ratio 1.4751). To eliminate potential bias and confounders, we obtained a detailed medical history and documented all drugs taken by the study participants. Collectively, we recorded 22 diseases and 112 drugs. In our statistical analysis, an inhomogeneous distribution emerged for 4 diseases and 20 active agents (Online depository, Tab. 6). Subsequent mixed effect logistic regression, however, identified 9 potential confounders (Online depository, Tab. 7). Also, employing logistic regression, we excluded the eventuality that the difference of sample age (at time of testing) and age of participants had an influence on the dogs' sample classification (Online depository, Fig. 4).

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Discussion:

This meticulous characterization of 125 breath samples tested by 4 sniffer dogs confirms the existence of a stable marker (or scent pattern) that is strongly associated with LC and independent from COPD, but can be reliably discriminated from tobacco smoke, food odors and (potential) drug metabolites.

Since their first delineation by Pauling and coworkers in 1971, 3481 different VOCs have been described in the human breath - most of them in picomolar concentrations (10^{-12} mol/l or particles per trillion) [15, 16]. It has been hypothesized that tumors produce VOCs and breath analysis therefore might be a very sensitive and at the same time non-invasive method to screen for or diagnose cancer. In particular, this is interesting for LC due to its site of origin, prevalence in the industrialized societies, and unfavorable prognosis. However, the metabolic origin of tumor associated VOCs remains speculative [17]. Nonetheless, three recent publications demonstrated that breath samples from patients with LC and those from healthy subjects can be distinguished by electronic nose technology [18-20]. Tumor stage did not influence the outcome in any of the studies, implying that exhaled breath profiling has the potential to evolve as a screening test for LC – once specific markers have been identified [6].

COPD often precedes and accompanies LC in smoking patients [21]. COPD is characterized by typical lung function deterioration, chronic systemic and local airway inflammation and structural changes in lung parenchyma. It has been shown that the level of exhaled biomarkers is altered in patients with COPD compared to healthy control subjects [9, 20]. Moreover, since the development of LC is much more frequent in COPD patients than in healthy controls, attention needs to be focused on the subtle differences in exhaled biomarker profiles between LC and COPD [6].

Research on electronic nose technologies continues to advance and optimize its technical capabilities [6, 9]. However, the currently required breath sampling procedures are very complex, and their analysis is interference-prone: Sample analysis requires 10 min at best and the obtained detection rates vary considerably [6]. Therefore, it is currently difficult to predict when a clinically applicable diagnostic device for breath analysis will be available.

In contrast, and virtually on the verge of respectability, sniffer dogs off and on emerge as “detection devices” in the medical literature. Initial interest in dogs being able to detect cancer in humans developed when Williams and Pembroke sent a letter to *The Lancet* in 1989 where they described a case where a woman was encouraged to get a skin lesion examination because of her dog’s inordinate amount of interest in the spot on her skin [10]. The outstanding sensitivity of the canine olfactory system has been acknowledged by using sniffer dogs in military and civilian service for detection of a variety of odors. Moreover, sniffer dogs have been employed in pre-clinical studies for cancer diagnosis [22, 23]. In 2006, McCulloch and coworkers reported a sensitivity and specificity of 99% for sniffer dogs to diagnose LC from patients’ breath samples [14]. However, this study might have been biased by odors related to other diseases, therapies, and smoking. In the present study trained sniffer dogs were able to identify LC in 1 out of 5 probes with an overall sensitivity of 71% and specificity of 93%.

In great contrast to related previous studies, the focus of the present work was to exclude potential confounders and bias. No relevant differences were identified between training and test groups (Tab. 2 and 3). Although the study groups showed an inhomogenous distribution regarding age, gender and breath sample age (Tab. 2), multivariate analysis excluded an association between these characteristics and the dogs’ indication. The lung function parameters were pathological for group C, as was hypothesized by the applied study protocol (Tab. 3). The 6-months training period resulted in a Fleiss-Kappa value of 44%, indicating

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moderate rater variability between dogs. Since an improvement of LC identification capabilities can be identified along the test series (Tab. 5), an ongoing training effect must be assumed, calling for even longer dog training in future studies. In theory, breath sample recovery from the study participants without using gloves might have introduced confounding odors. This leaves open the possibility that cancer associated odors may be emitted through the skin, as well as exhaled during respiration. However, that does not help to explain how the dogs' were able to differentiate between groups A, B and C.

Mixed effect logistic regression analysis identified 9 potential confounders among 112 drugs (Online depository, Tab. 7). Therefore, Methoclopramide, Enoxaparin, Dihydrocodein, Triotropiumbromide, Clopidogrel, Ezetmib, Marcumar, Verapamil and Metoprolol may be potential confounders. Actually, the first three drugs have been administered to inpatients diagnosed for lung cancer and therefore may represent a study bias. In contrast, Metropolol, Verapamil and Tiotropiumbromide were consistently distributed between LC and COPD patients, but not found in healthy volunteers. Marcumar, Clopidogrel and Ezetimib were present exclusively in COPD patients. The tested tumor histologies represent the ordinary clinical distribution, and the included tumor stages reflect the entire spectrum of disease (Fig 3). Although the data indicate that sniffer dogs can identify early stage LC, their foundation is too small to conclude that sniffer dogs reliably may be applicable for LC screening. Interestingly, advanced tumor UICC stage IV may impair the display accuracy of sniffer dogs. Here, the presence of secondary lung tissue reactions (f.i. inflammation, necrosis) may be imputed.

Exhaled breath analysis is a promising approach towards future non-invasive LC screening methods. The final goal of our investigation is the development of a clinically applicable screening test for detection of LC. Using sniffer dogs as "detection device", our results set a benchmark for the identification of LC in the breath sample of patients and the discrimination of LC and underlying COPD. Here, we confirm the presence of a detectable marker in the breath of patients, which is strongly associated with LC, but independent from COPD. However, this marker or pattern, despite being reliably detectable even in the presence of tobacco smoke, food odors and drug metabolites, is still unknown. In order to proceed towards non-invasive LC screening methods, precise identification of compounds observed in exhaled breath of LC patients is desirable. Acknowledging the complexity of this endeavor, the integration of sniffer dogs into research strategies may be useful. In our study, sniffer dogs reliably identified LC, whereas electronic nose technologies detect thousands of scents, of which the majority is, to date, not specifiable. Unfortunately, dogs cannot communicate the biochemistry of the scent of cancer.

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Authors' contributions

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R Ehmann initiated this study. R Ehmann and E Boedeker contributed equally. R Ehmann, E Boedeker and T Walles conceived, designed and oversaw all the studies and collection of results. U Friedrich and J Sagert performed the dog training and collected the results along with E Boedeker. J Dippon performed the biometric calculations and statistical analysis with E Boedeker and T Walles. G Friedel and T Walles drafted the manuscript. All authors had an opportunity to contribute to the interpretation of the results and to the redrafting of the report, and all authors approved the final report.

Conflict of interest

U Friedrich owns the dog obedience school where the dog training was performed. The remaining authors declare no conflict of interests.

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Figure legends

Figure 1. Flow diagram showing the criteria for group assignment and reasons for individuals to be excluded. Left column: Healthy volunteers tested to be included into group A. Middle column: Patients suspected for having lung cancer on the basis of patient history and pathological imaging to be included into group B after confirmation of the diagnosis by histology. Right column: Patients treated for COPD to be included into group C. The flow chart indicates that breath samples were obtained at the beginning of each individual patient evaluation process and were assigned to the respective study groups thereafter.

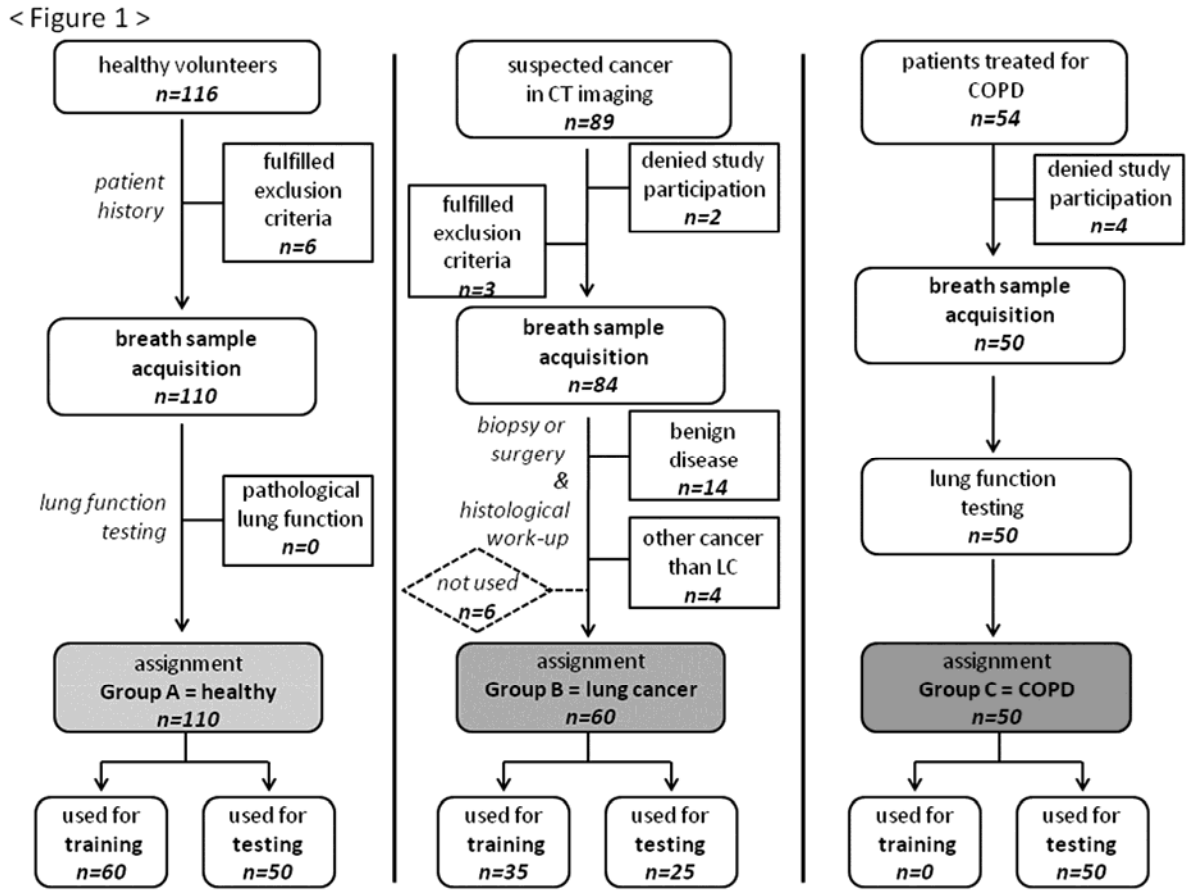

Figure 2. Applied methods for breath sampling and testing. **A** Glass tube used for breath sampling. The lumen is filled with the polypropylene fleece. **B** For breath sampling, study participants exhaled 5 times through the collection device. **C** Test set-up showing the probe retainers. **D** The position of the LC samples was randomized. **E** Sniffer dogs were trained to identify LC in the breath sample of patients. **F** The dogs were trained to indicate a positive test tube by lying on the floor in front of the tube with the muzzle touching the test tube.

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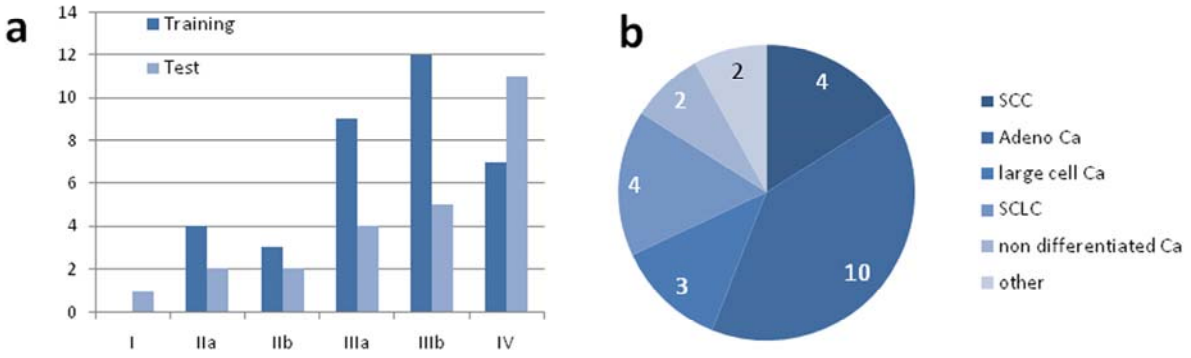
< Figure 2 >

Figure 3. Itemization of trained and tested tumor stages. **A** Early and advanced LC tumor stages were trained and tested. **B** Distribution of tested tumor histologies.

< Figure 3 >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SCLC
non differentiated Ca
other

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Tables

Table 1. Breath sample distribution throughout the study.

	Group A	Group B	Group C
	healthy	**lung cancer**	**COPD**
Training (*n*)	60	35	
Test I (*n*)	40	10	
Test II (*n*)		10	40
Test III (*n*)	10	5	10
total	110	60	50

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Table 2. Composition of training and test groups.

	Group A			*P* training vs test	Group B			*P* training vs test	Group C	*P* test groups A,B,C
	healthy				**lung cancer**				**COPD**	
	all	training	test		all	training	test		test	
n	110	60	50		60	35	25		50	
age (y)	46.2±14.0	45.7±12.5	46.8±15.8		63.6±10.3	65.3±9.8	62.6±11.1		66.7±6.6	
gender (m:f) %	26:74	28:72	24:76		78:22	71:29	88:12		56:44	<0.001
BMI (kg/m^2)	25.3±5.3	25.2±5.4	25.4±5.1		25.4±4.4	24.9±4.7	26.1±4.0		26.5±5.2	
current smoker (n/%)	14 / 12.7	9 / 15	5 / 10.0	n.s.	13 / 21.7	7 / 20.0	6 / 24.0	n.s.	13 / 26.0	n.s.
history of cancer (n/%)	0 / 0	0 / 0	0 / 0		0 / 0	0 / 0	0 / 0		3 / 5	
previous surgery (n/%)	0 / 0	0 / 0	0 / 0		0 / 0	0 / 0	0 / 0		1 / 1.7	
previous intervention (n/%)	0 / 0	0 / 0	0 / 0		34 / 57	18 / 51	16 / 64		0 / 0	<0.001
sample age (d)	23.6±19.0	22.3±21.1	25.2±16.1		38.5±22.4	39.4±22.5	37.3±22.8		8.1±3.8	n.s.

Abbreviations: y = years; m=male; f = female; BMI = body mass index; d = days; n.s. = not significant

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Table 3. Lung function tests in training and test groups.

	Group A			*P* training vs test	Group B			*P* training vs test	Group C	*P* test groups A,B,C
	healthy				**lung cancer**				**COPD**	
	all	training	test		all	training	test		test	
n	110	60	50		60	35	25		50	
VC (l)	4.0±1.0	4.1±1.0	3.8±0.8	n.s.	3.5±1.1	2.9±1.1	3.5±1.1	n.s.	2.8±0.8	<0.001
VC (%)	107±14	111±12	103±16	< 0.01	83±21	79±22	83±21		79±20	
FEV1 (l)	3.3±0.8	3.4±0.8	3.2±0.8	n.s.	2.4±0.8	2.1±1.0	2.4±0.8		1.6±0.6	
FEV1 (%)	109±15	112±13	105±17	<0.05	74±25	73±25	76±25		61±19	
FEV1%VC	81.2±5.9	80.6±5.9	82.0±5.9	n.s.	65±13	65±13	66±12		59±11	
TLC (l)	6.0±1.3	5.9±1.3	6.0±1.3		5.8±1.3	5.9±1.3	5.8±1.3		7.1±1.4	
TLC (%)	105±18	104±13	107±22		92±20	97±21	85±16		120±20	
RV (l)	1.8±1.1	1.6±0.8	2.1±1.3		2.5±1.2	2.7±1.4	2.1±0.7		4.4±1.2	
RV (%)	97±52	87±30	109±69		106±49	118±58	88±25		187±56	
GOLD	0±0.2	0±0.2	0±0.3		1.1±1.3	1.2±1.4	1.1±1.3		1.9±1.0	

Abbreviations: VC = vital capacity; FEV1 = forced expiratory lung volume; TLC = total lung capacity; RV = residual lung volume; n.s. = not significant; GOLD = stage of COPD according to the Global Initiative for Chronic Obstructive Lung Disease.

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Table 4. Cross-tabulation of the dogs' indication and the presence of cancer. Cumulative results.

	breath sample of **volunteer without cancer (groups A+C)**	breath sample of **volunteer with confirmed LC (group B)**	**total**
dogs indicating **presence of LC**	28	71	99
dogs indicating **absence of LC**	372	29	401
total	400	100	500

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Table 5. Hit ratio of sniffer dogs.

	Test I (correct/false)	**Test II** (correct/false)	**Test III** (correct/false)	**overall** (correct/false)	**% correct**	**Inter-raterr variability** (κ)	sensitvity	specifity	positive predictive value	negative predictive value
Dog 1	7 / 3	9 / 1	5 / 0	21 / 4	84	0.436				
Dog 2	4 / 6	8 / 2	5 / 0	17 / 8	68					
Dog 3	6 / 4	7 / 3	4 / 1	17 / 8	68					
Dog 4	5 / 5	8 / 2	5 / 0	18 / 7	72					
"corporate decision" at least 3 dogs alike							0.72 (CI 0.51-0.88)	0.94 (CI 0.87-0.98)	0.75 (CI 0.53-0.91)	0.93 (CI 0.86-0.97)