2012 International Breath Analysis Meeting

Sensor Devices Applied to Breath Diagnostics Research

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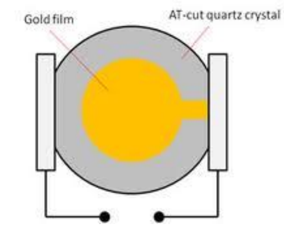
Sensor and Sensor Arrays Devices

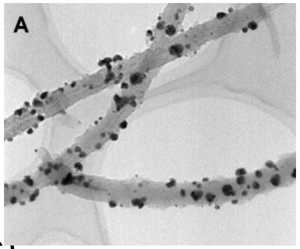


QMB

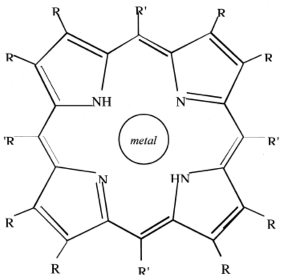
- Transducers – measure changes in a signal property
  - Electrical - resistors, capacitors, transistors (FET)
  - Mass - QMB, SAW, tuning forks (change in frequency or piezoresistance)
  - Optical – fiber optics & optrodes with LED source & photodetector; CCD array, visual


resistor

- Sensing Elements – chemically-sensitive materials often applied as thin films
  - Conductive polymers
  - Redox / acid-base indicators
  - Metalloporphyrins
  - Metallic oxides (SnO_2, WO_3, TiO_2)
  - Metallic nanoparticles (Au, Pt, Pd) and nanowires
  - Composites of polymers and conductors (carbon, metallic particles)
  - Carbon-based semiconductors: carbon nanotubes, graphene



Pd on CNTs



metalloporphyrin

- Sensing Properties - enhanced through chemical modification or formulation
  - Chemically- modified carbon nanotubes
  - Chemically-modified graphene
- Algorithms and Software - interpret the response to provide actionable result
  - Single sensors: Change in resistance, absorbance, wavelength above a set threshold
  - Multi-sensor arrays: Pattern recognition and classification algorithms for array response

    e.g., PCA (unsupervised) and CDA or SVM (supervised)

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Cyranose™ 320 Handheld Instrument

- Fully-Integrated Sensing Instrument
  - sampling system, sensor array, software
- 60 patents for sensors, detectors, applications
- Stable, Robust, Reliable Sensor Manufacturing
  - in production for over 10 yrs
  - many 100's of systems in use worldwide
  - many systems in regular use for 5 to 10 yrs
  - over 80 3rd party industrial research publications
- Medical Research
  - nanocomposite sensors exhibit high sensitivity (ppm to ppb detection limits) for VOCs and semi-volatile compounds in breath
  - over 40 3rd party medical research publications for a variety of conditions

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Select Cyranose Medical Research Publications: 2000 - 2012

Subject	Years	Publications
Lung Cancer	2005 – 2012	7
Other Respiratory Diseases	2007 – 2012	11
Bacterial Infection	2000 – 2011	18
Other Conditions	2005 – 2012	7
Additional Studies in Progress and Planned	2010 – 2014	*several papers submitted and in preparation*

2020 Update:
Now over 200 peer-reviewed clinical research publications using the Cyranose 320

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FDA Approved Breath Tests to 2010

Detected Molecule	Disease/ Condition	Trade Names	Techniques	Manufacturers	Approved
Alcohol	Alcohol intoxication Breath alcohol	AlcoMate, AlcoHawk, AL-5000, Breath Alcohol Check, Bactrack	Semiconductor oxide sensor Electrochemical analyzer Fuel cell sensor	KHN Solutions Q3 Innovations Sentech Korea Akers Biosciences	2004 to 2009
Alkanes (C4-C20)	Grade 3 heart allograft rejection	Heartsbreath	GC-MS	Menssana Research	2004
H_2	Lactose malabsorption	Micro H_2	Electrochemical sensor	Micro Direct	1997, 2004
NO	Asthma, airway inflammation	NIOX, NIOX MINO	Chemiluminescence Electrochemical sensor	Aerocrine AB	2003, 2008
CO	Carbon monoxide poisoning	EC50 ToxCO +	Electrochemical sensor	Bedfont Scientific	2005
^{13}CO2	*H. pylori*	UBiT-IR300, POCone, BreathTek UBiT	Infrared spectrometer	Otsuka Pharmaceutical Meretek Diagnostics	2001 to 2004
CO_2, O_2, N_2O	Respiration	Nier IRMS, Tidal Wave, ABCA-NT	IRMS CF-IRMS	Consolid. Electrod. Corp Novametrix Medical Europa Scientific	1976, 1996 -1997
CO_2, O_2, N_2O, anesthetic agents	Respiration, Ventilation, Anesthetics	M-CAiOVX, M-COVX, M-MINIC, BSM-4100A, AG-920RA, BSM-5130A	Infrared sensors Infrared spectrometer Sensor technology	Datex- Ohmeda GE Healthcare Nihon Kohden	2000 to 2003
$^{13}CO_2$, CO_2	Ventilation, Respiration	C-CO_2, E- MINIC, OLG-2800A, EMMA Capnometer, TG-970P	Colorimetric sensor Infrared sensor Infrared spectrometer Sensor technology	Marquest Medical GE Healthcare Nihon Kohden Phasein AB	2005 to 2009

Table modified (condensed) from: Mashir et al, *Medical Applications of Exhaled Breath Analysis and Testing*, PCCSU, 2011

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FDA Approved Electronic Nose Tests

Detected Molecule	Disease/ Condition	Trade Names	Techniques	Manufacturers	Approved
VOOs, organic acids	Urinary Tract Infection (UTI)	Osmetech Microbial Analyser (OMA – UTI)	Conducting polymer sensor array	Osmetech	2001
VOOs, organic acids	Bacterial Vaginosis (BV)	Osmetech Microbial Analyser (OMA – BV)		Osmetech	2003
		http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K023677			

excerpts from the 510(k) Pre-market Notification for UTI

Clinical Performance Data

"Urine test results with the OMA™-UTI were compared to results using the Standard Culture technique (the "gold standard" for measurement of bacteria in urine) in 1038 urine samples from three Clinical Laboratories (two U.S. and one non-U.S. sites) for assessment of UTI."

"These data indicate that the performance values of the OMA™-UTI compare favorably with the predicate device, Uriscreen TM (K981084), which reported a sensitivity of 95%, specificity of 73%, and accuracy of 80%."

Sensitivity	81.0%	(95% CI 73.7% to 87.0%)
Specificity	83.1%	(95% CI 80.4% to 85.5%)
PPV	44.1%	(95% CI 38.1% to 50.2%)
NPV	96.4%	(95% CI 94.8% to 97.6%)
Accuracy	82.8%	(95% CI 80.3% to 85.0%)

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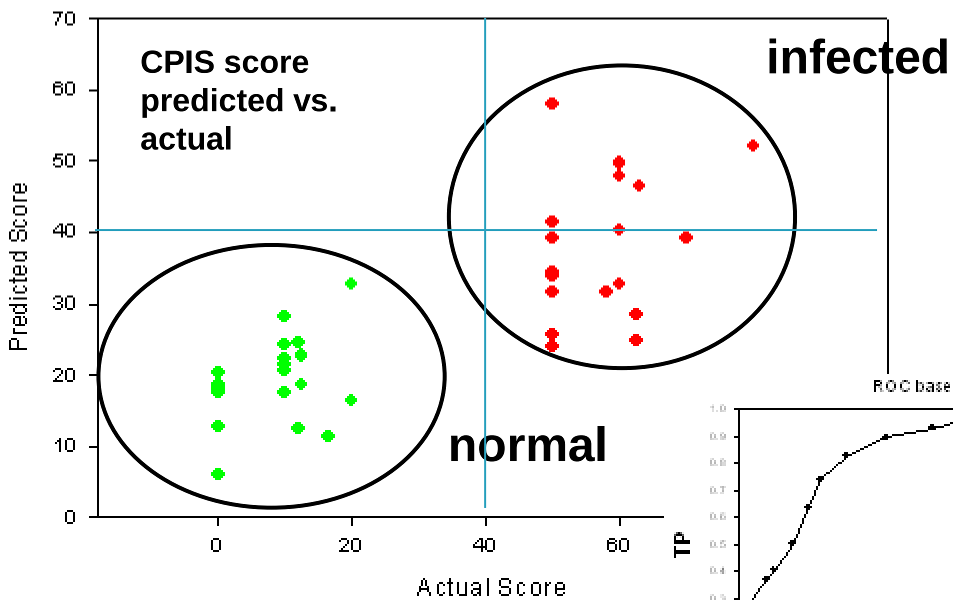
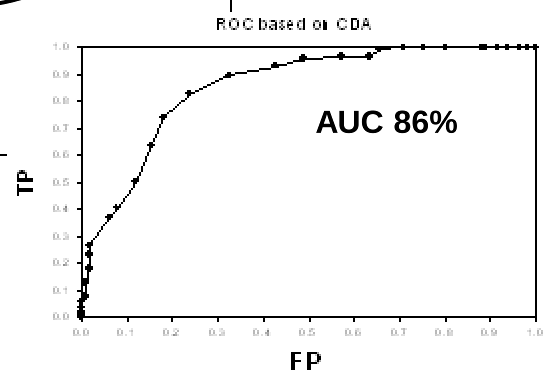
Ventilator Associated Pneumonia (VAP)

Reference: Hanson et al, Amer. Thoracic Society Meeting, 2002
Location: Univ. Pennsylvania Hospital
eNose: Cyranose 320



70% PPV
95% NPV



Result: measurements on exhaled breath compare favorably to the Combined Pulmonary Infection Score (CPIS) used to confirm VAP in the ICU

breath sampled from the expiratory limb of the ventilator circuit

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Acute Rhinosinusitis

Reference: Thaler, et al, *Use of an electronic nose to diagnose bacterial sinusitis.* Amer. Journal of Rhinology, v.20, 170-172, 2006
Location: Univ. Pennsylvania Hospital
eNose: Cyranose 320

sinus samples collected directly from subjects using a nasal breathing cup under normal breathing

	c=100, w=0.5		c=10, w=5	
Model	# correct	% correct	# correct	% correct
SVM	123/123	100	118/123	95.9
SVM+PCA(2)	123/123	100	113/123	91.9
SVM+PCA(3)	123/123	100	121/123	98.4

22 subjects
11 sinusitis
11 controls

samples collected
July – Oct 2003

Other sampling methods tested

Nasal swabs (calgiswab) used to sample mucus from sinus infection “hotspots”

Swabs placed in a vial and the headspace sampled after 2-3 minutes

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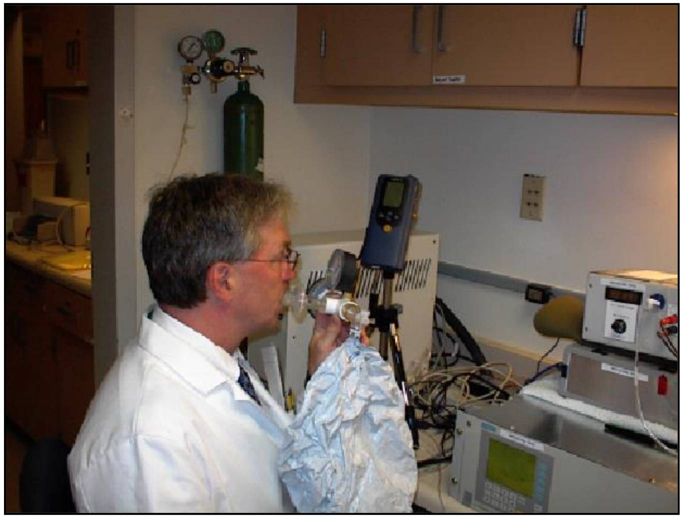
Breath Sample Collection and Measurement for Lung Cancer and Pulmonary Disease Studies

St. Vincent's Hospital, Sydney



Cleveland Clinic, USA

Lung Cancer - Mesothelioma

Reference: Chapman et al, *A breath test for malignant mesothelioma using an electronic nose.* Eur. Respiratory Journal, v.40, 1-7, 2011.

Location: Univ. NSW Medical School, Sydney, Australia

eNose: Cyranose 320

TABLE 1 Subject demographics and lung function data

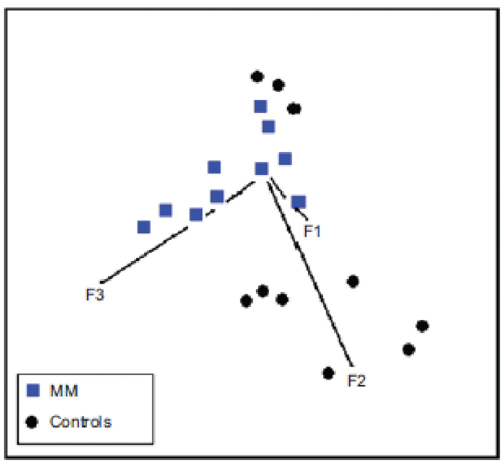
	Controls	Mesothelioma	Asbestosis	Pleural disease
Subjects	42	20	5	13
Age yrs	66.5±14	69±10	70±10.5	70.9±8.2
Male/female	34/8	18/2	5/0	13/0
Nonsmoker/ex-smoker	30/12	8/12	1/4	5/8
FEV_1 % pred	100.1±11.1	ND	72.2±9.4***	90.2±17.5*
FVC % pred	94.4±9.4	ND	78.9±10.4***	82.7±18.6*
FEV_1/FVC % pred	93.4±14.3	ND	76.2±7.8*	80.1±12.7*
IMIG stage 2/stage 1b	NA	19/1	NA	NA

...ume in 1 s; % pred: % predicted; FVC: forced vital capacity; IMIG: International Mesothelioma Interest

...*: $p<0.001$, significant differences between subjects with asbestosis or pleural plaques compared with

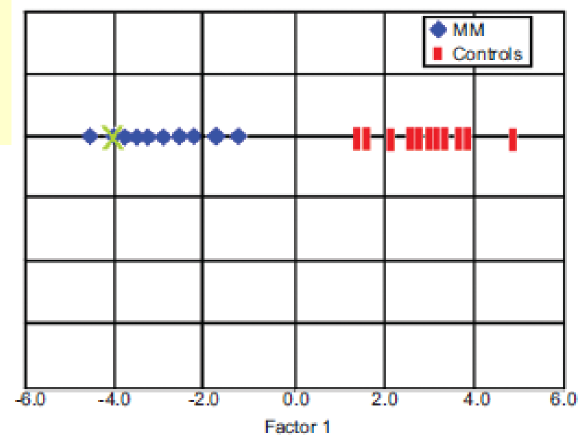
80 subjects
20 mesothelioma
18 non-cancer
42 controls

Breathing unfiltered room air



Training Set
10 mesothelioma
10 controls

PCA scores plot



CDA scores plot

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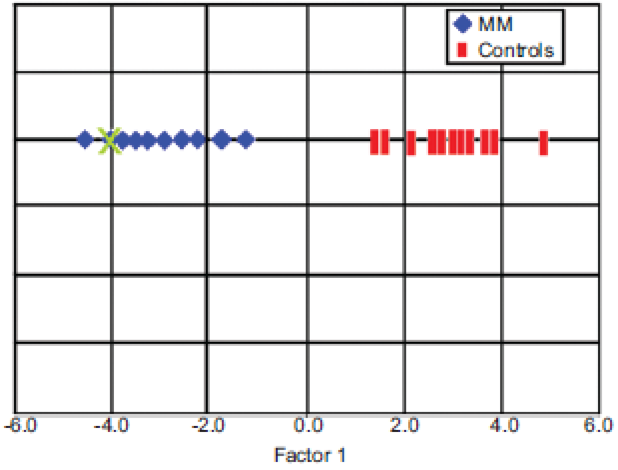
Lung Cancer - Mesothelioma

Reference: Chapman et al, *A breath test for malignant mesothelioma using an electronic nose*. Eur. Respiratory Journal, v.40, 1-7, 2011.
Location: Univ. NSW Medical School, Sydney, Australia
eNose: Cyranose 320

80 subjects total
20 mesothelioma
18 non-cancer
42 controls

Training Set
10 mesothelioma
10 controls



Identification Set #1
10 mesothelioma
18 non-cancer
32 controls

Result:
90% sensitivity
88% specificity

60% PPV
97.8% NPV
relative to histologically proven mesothelioma

Identification Set #2
5 subjects retested after 2, 4 and 6 weeks
2 mesothelioma
3 controls

Result:
86% correct identification over 6 week period

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Lung Cancer – Comparison of 5 Studies 2003 - 2010

Table 6
State of the art of the experiments for lung cancer diagnosis with a gas sensor array.

Reference	Population	Classification	Performance	Markers study	Need for further details
[19]	Cancer: 35 Control: 18	Cancer Control	100% sens. 94% spec.	No	Other lung diseases Markers study Larger study population
[20]	Cancer: 14 Non-cancer: 62 Control: 45	Cancer Non-cancer	71.4% sens. 91.9% spec.	Yes	Classification of the different lung diseases Larger study population
[21]	Cancer: 49 Non-cancer: 73 Control: 21	Cancer Non-cancer Each lung pathol.	73.3% sens. 72.4% spec. 16.7–57.1% sens.	No	Low sensitivity to each lung pathology 3-way classification scheme
[24]	Cancer: 10 COPD: 10 Control: 10	Cancer vs. COPD Cancer vs. control	85% tot. 90% tot.	No	3-way classification scheme Larger study population
[***]	Cancer: 28 Non-cancer: 28 Control: 36	Cancer Non-cancer	79.3% sens. 89.3% spec.		Larger, international study Measurement and analysis optimization

Ref	Yr	Author	Study Location	eNose	Sensor Array	Status
[19]	2003	DiNatale et al	Univ. Rome	ROTV	metalloporhyrin QMB	R&D
[20]	2005	Machado et al	Cleveland Clinic	Cyranose 320	polymer composite	commercial
[21]	2007	Mazzone et al	Cleveland Clinic	Univ. Illinois	colorimetric	R&D
[24]	2009	Dragonieri et al	Univ. Leiden	Cyranose 320	polymer composite	commercial
[***]	2010	D'Amico et al	Univ. Rome	ROTV	metalloporhyrin QMB	R&D

Table 6 and [***] results from: D'Amico et al., *An investigation on electronic nose diagnosis of lung cancer.* Lung Cancer, v.68, 170-176, 2010.

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Asthma and COPD – Internal Validation

Reference: Fens et al, *Exhaled breath profiling enables discrimination of chronic obstructive pulmonary disease and asthma.* Amer. J. Respir. Crit. Care Medicine, v.180, 1076-1082, 2009.

Location: Univ. Amsterdam Medical Center

eNose: Cyranose 320

90 subjects total
30 COPD
20 asthma
20 controls – smoking
20 controls – non-smoking

PCA scores plots

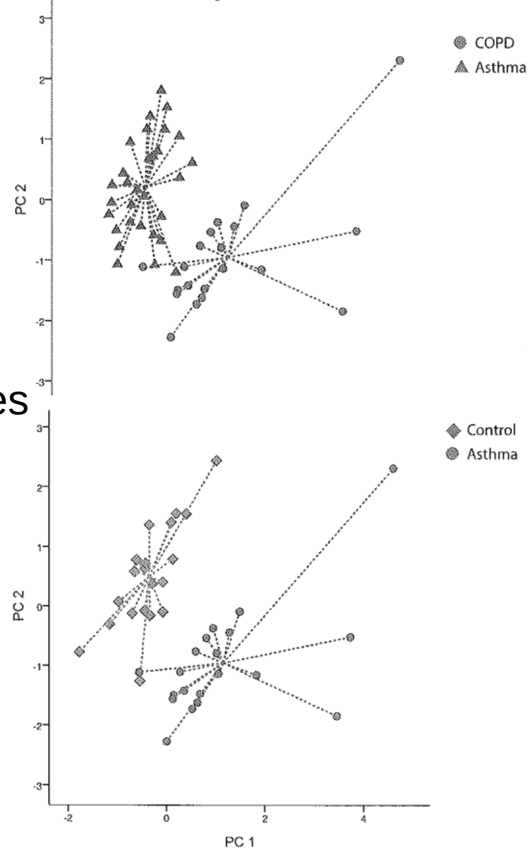

Table 2 Cross-validation values for the discrimination between COPD, asthma and controls.

Analysis	Cross validated accuracy (%)	p-value
Asthma-COPD	**96**	**<0.0001**
- Asthma-COPD smoking	97	<0.0001
- Asthma-COPD ex-smoking	95	<0.0001
- Asthma-COPD ICS	97	<0.0001
- Asthma-COPD no ICS	95	<0.0001
Asthma-Non-smoking controls	**95**	**<0.0001**
COPD-Smoking controls	**66**	**0.006**
- COPD smoking-smoking controls	72	0.018
- COPD ex-smoking-smoking controls	61	0.026
- COPD ICS-Smoking controls	70	0.024
- COPD no ICS-Smoking controls	65	0.047
Controls-Smoking controls	**63**	**0.016**

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Asthma and COPD – External Validation

Reference: Fens et al, *External validation of exhaled breath profiling using an electronic nose in the discrimination of asthma with fixed airways obstruction and chronic obstructive pulmonary disease.* Clinical & Experimental Allergy, v.41, 1371-1378, 2011.

Location: Univ. Amsterdam Medical Center

eNose: Cyranose 320

100 subjects total

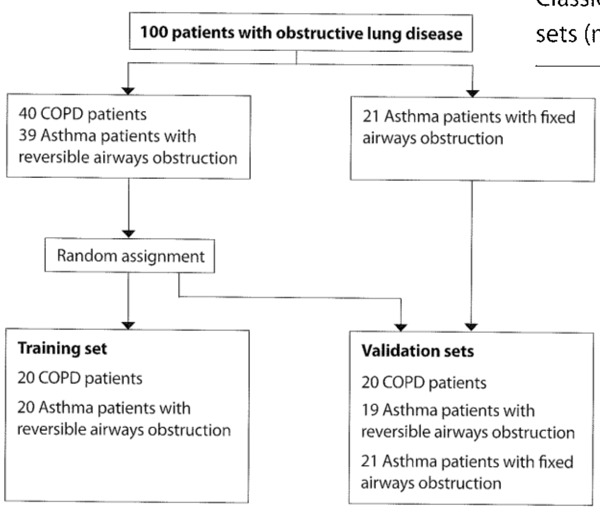
40 COPD

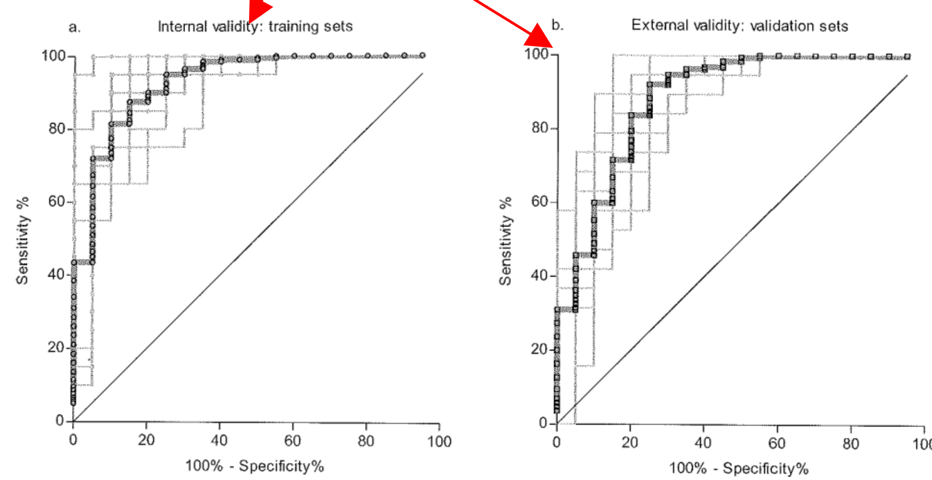
39 asthma – reversible

21 asthma - fixed

Table 3 Validation results of the reproducibility of the diagnostic model for COPD *vs* classic and fixed asthma

Set	Acc	p-value	AUC	95% CI	Sens	Spec	LR+	LR-
Fixed asthma *vs* COPD validation sets (mean)	85 %	<0.001	0.91	0.84-1.00	86 %	80 %	4.3	0.2
Classic asthma *vs* COPD training sets (mean)	85 %	<0.001	0.93	0.85-1.00	88 %	85 %	5.8	0.2
Classic asthma *vs* COPD validation sets (mean)	85 %	<0.001	0.89	0.78-1.00	84 %	80 %	4.2	0.2





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Some Conclusions and Prognostications

Sensor Devices and Senor Array Devices have been approved by FDA for Screening Tests and Diagnostic Tests on breath and urine.

Multi-component signatures of disease can be used for simple and rapid Screening Tests with high NPV.

The number of conditions that can be screened will increase through continuing research. This work may also demonstrate potential for treatment monitoring and other uses.

Research into Breath Tests using Sensors and Sensor Array Devices continues to evolve rapidly:

- Efficacy has been/is being established in pilot and cross-sectional studies for several important conditions including LC, COPD/asthma and bacterial infection
- Independent research groups are finding similar results
- Collaborative studies are showing consistency across larger patient populations
- Results obtained with different Sensor Array Devices, operating on different physical and chemical principles, are yielding similar clinical findings in terms of sensitivity, specificity and predictive value.

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