I programmi di screening colorettale della Regione Toscana: situazione attuale e prospettive future

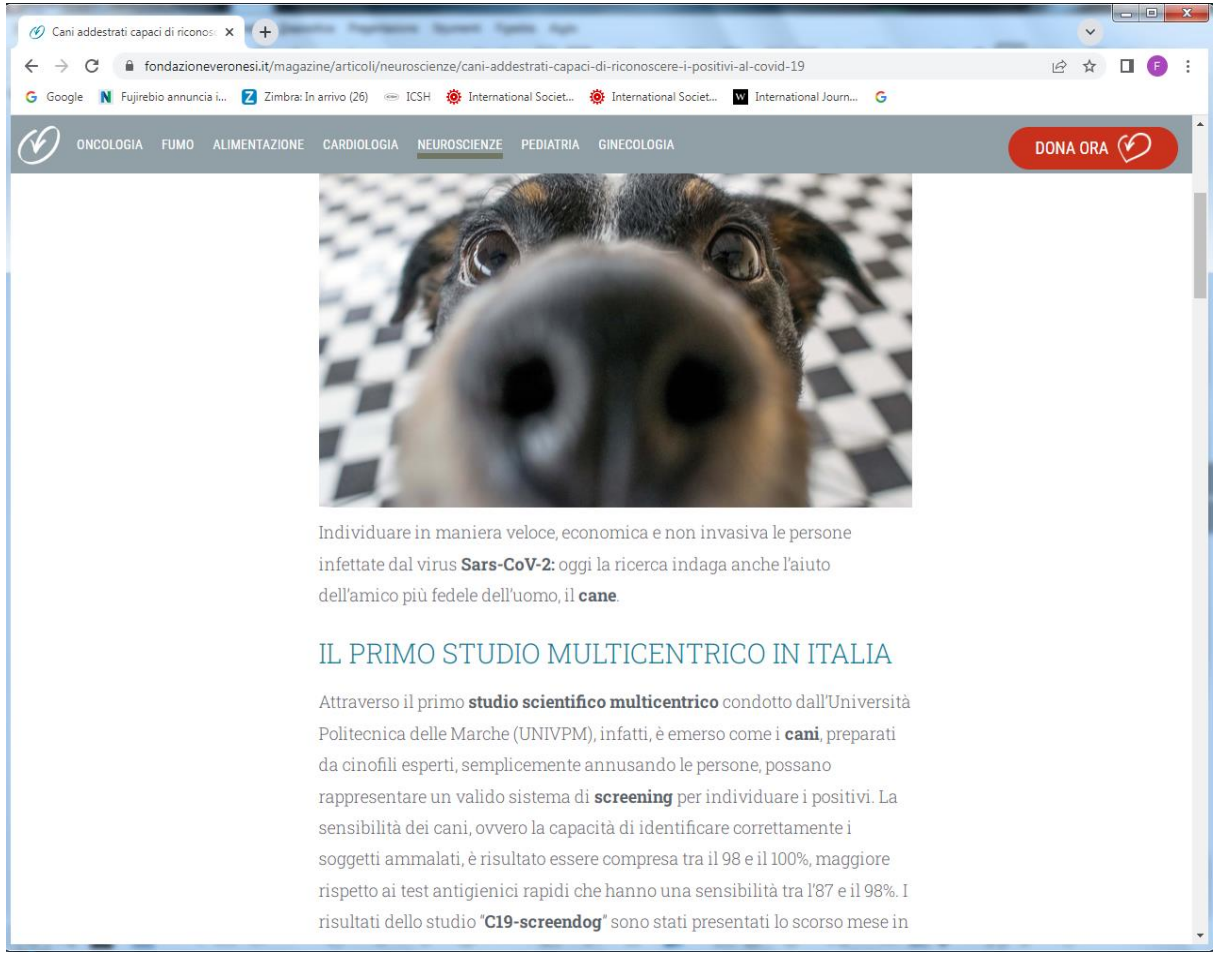
Il ruolo dei composti organici volatili nella diagnosi precoce del tumore del colonretto

Stefano Rapi. Azienda USL Toscana Nord Ovest.
Coordinatore GdL I livello Gruppo Italiano Screening Colorettale

Il sottoscritto
Stefano Rapi
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,
Dichiara:

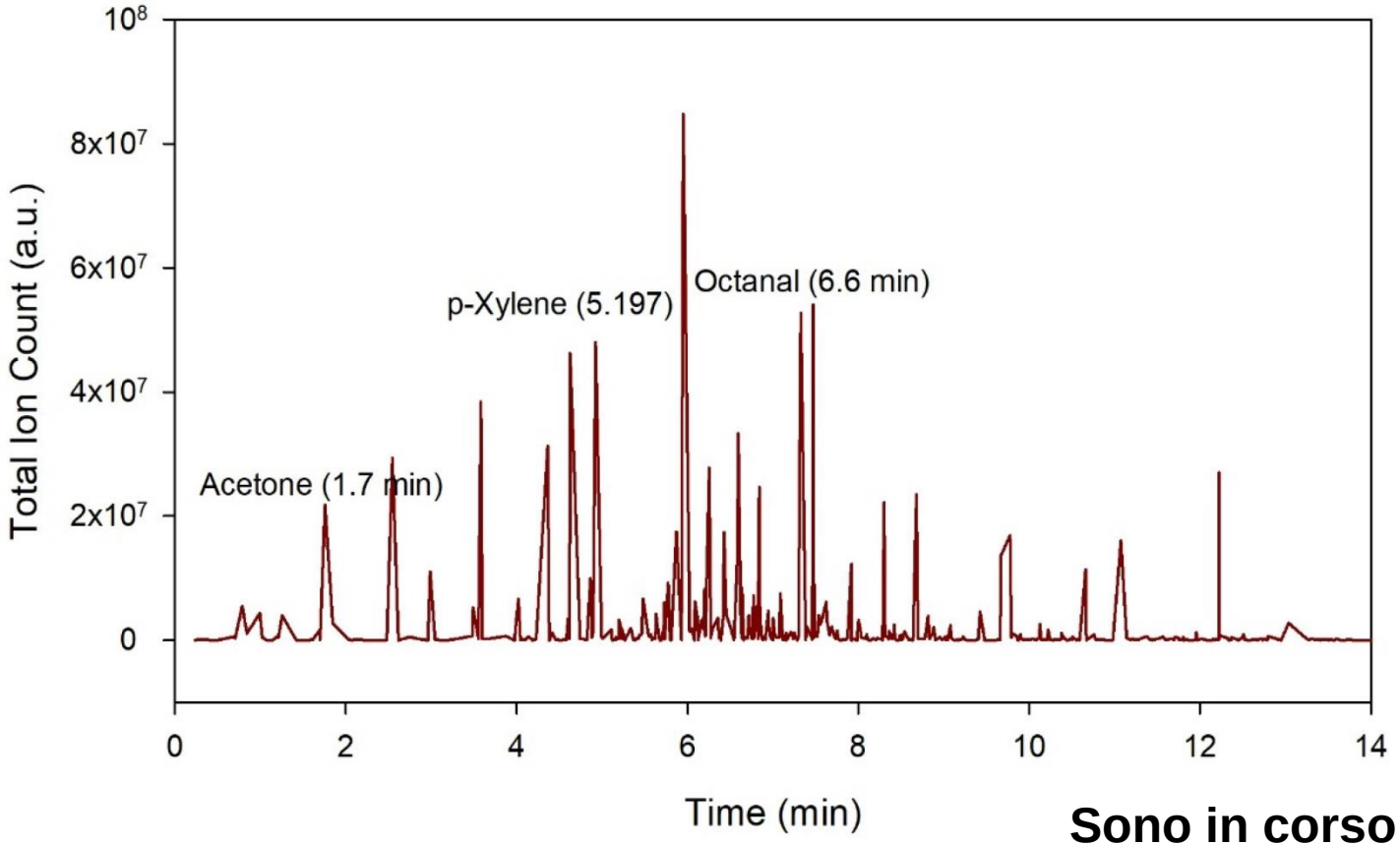
X *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:*

- Classe di composti organici caratterizzati da alta tensione di vapore a temperatura ambiente (volatilità)
- Volatilità: alta tensione di vapore e basso punto di ebollizione.
- I VOCs sono responsabili sia di odori che di inquinamento.



- Composti gassosi derivanti dal metabolismo (animale, vegetale) e dall'ambiente
- Presenti in tutti i compartimenti dell'organismo (respiro / sangue / urine / feci).
- Cambiano in situazioni patologiche (metaboliche, virali, neoplastiche..)

Composti Organici Volatili



- **Lo studio dei COV è cominciato con l'uso della GC-MS**
- **Si sta sviluppando con nuove tecnologie basate su biosensori (identificano classi di composti)**

Sono in corso numerosi studi focalizzati su:

1. **Materiale più idoneo urine / sangue / espirato /feci**
2. **Tipo di analisi più efficiente**
3. **Calibrazione sistemi**
4. **Standardizzazione risposte**

VOC nei Tumori del Colon Retto.
..possibile marcatore ?

frontiers in Oncology

SYSTEMATIC REVIEW
published: 26 February 2021
doi: 10.3389/fonc.2021.606915

Volatile Organic Compounds in Human Exhaled Breath to Diagnose Gastrointestinal Cancer: A Meta-Analysis

Lijuan Xiang[1,2†], Sihan Wu[1,3†], Qingling Hua[4], Chuyang Bao[2] and Hu Liu[1]*

[1] Department of Tumor Biotherapy (5th Ward of the Department of Oncology), Anhui Provincial Cancer Hospital, West District of The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China, [2] Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [3] Department of Oncology, Affiliated Provincial Hospital of Anhui Medical University, Hefei, China, [4] Department of Oncology, Yijishan Hospital, Wannan Medical College, Wuhu, China

OPEN ACCESS

Edited by:
Stephen J. Pandol,
Cedars Sinai Medical Center,
United States

Original article

BJS Open 2020; 4: 1189–1199 BJS Open Open Access

Chemical signature of colorectal cancer: case–control study for profiling the breath print

D. F. Altomare[1,4], A. Picciariello[1], M. T. Rotelli[1], M. De Fazio[1], A. Aresta[3], C. G. Zambonin[3], L. Vincenti[5], P. Trerotoli[2] and N. De Vietro[3]

Techniques in Coloproctology (2019) 23:343–351
https://doi.org/10.1007/s10151-019-01963-6

ORIGINAL ARTICLE

Colorectal cancer and adenoma screening using urinary volatile organic compound (VOC) detection: early results from a single-centre bowel screening population (UK BCSP)

E. Mozdiak[1] · A. N. Wicaksono[2] · J. A. Covington[2] · R. P. Arasaradnam[1]

Received: 1 September 2018 / Accepted: 8 March 2019 / Published online: 15 April 2019

PLOS ONE

RESEARCH ARTICLE

Use of the Analysis of the Volatile Faecal Metabolome in Screening for Colorectal Cancer

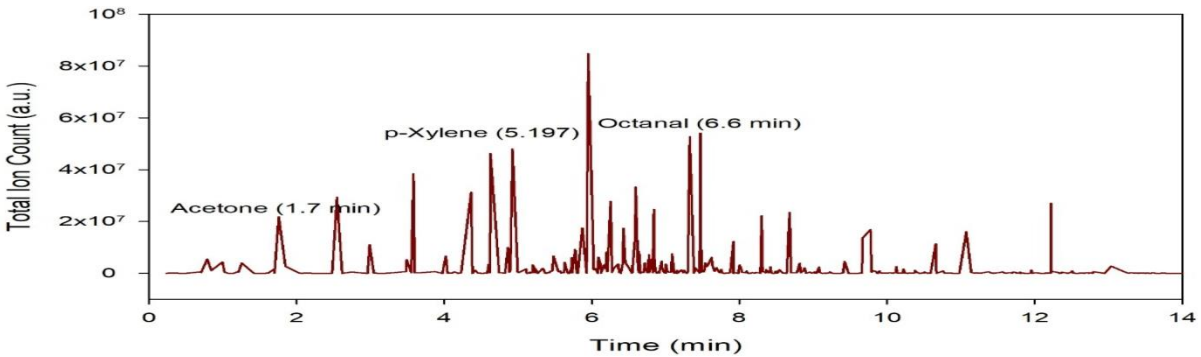
Claire A Batty[1☯], Michael Cauchi[2☯], Célia Lourenço[1☯], John O Hunter[3☯], Claire Turner[1☯*]

PLOS ONE | DOI:10.1371/journal.pone.0130301 June 18, 2015 1 / 14

VOC nell'espirato in GC-MC

Table 3 Multivariable logistic regression analysis of model A: colorectal cancer versus no cancer diagnosis Cut-off value* Regression coefficient (β) s.e. P BJS Open 2020; 4: 1189–1199

Cut-off value*	Regr. s.e.	P	coeffi. (β)	
Age class (years)	>65 versus≤65	0·7294	0·1959	<0·001
Tetradecane	≤0·39 versus>0·39	0·6398	0·2025	0·002
Ethylbenzene	≤0·35 versus>0·35	0·8162	0·2006	<0·001
Methylbenzene	>1·94 versus≤1·94	0·593	0·1989	0·003
5,9-Undecadien-2-one, 6,10-dimethyl (E)	≤0·41 versus>0·41	0·7661	0·2028	<0·001
Benzaldehyde	≤4·06 versus>4·06	0·6440	0·2114	0·002
Decane	≤0·77 versus>0·77	0·5872	0·2060	0·004
Benzoic acid	>0·94 versus≤0·94	0·5423	0·2332	0·020
1,3-Bis(1-methylethenyl) benzene	>0·52 versus≤0·52	0·6035	0·2541	0·018
Decanal	≤5·99 versus>5·99	−1·7920	0·6677	0·007
Unidentified compound	>0·26 versus≤0·26	1·9308	0·6931	0·005
2-Ethyl-1-hexanol	>2·51 versus≤2·51	−0·9643	0·4826	0·046
Dodecane	>3·51 versus≤3·51	1·6296	0·5247	0·002
Ethanone, 1[4-(1-methylethenyl)phenyl]	≤0·39 versus>0·39	1·3405	0·5494	0·015
Acetic acid	>0·41 versus≤0·41	3·0856	0·9442	0·001



Diversa Concentrazione sani/CRC

CRC. Analisi VOC espirato

Original article: **Chemical signature of colorectal cancer: case–control study for profiling the breath print.** BJS Open 2020; 4: 1189–1199

Background: Effective screening for colorectal cancer can reduce mortality by early detection of tumours and colonic polyps. An altered pattern of volatile organic compounds (VOCs) in exhaled breath has been proposed as a potential non-invasive diagnostic tool for detection of cancer. The aim of this study was to evaluate the reliability of breath-testing for colorectal cancer screening and early diagnosis using an advanced breath sampler.

Methods: The exhaled breath of patients with colorectal cancer and non-cancer controls with negative findings on colonoscopy was collected using the ReCIVA® Breath Sampler. This portable device is able to capture the alveolar breath fraction without environmental contamination. VOCs were desorbed thermally and analysed by gas chromatography–mass spectrometry. The discriminatory ability of VOCs in detecting colorectal cancer was evaluated by receiver operating characteristic (ROC) curve analysis for each VOC, followed by cross-validation by the leave-one-out method, and by applying stepwise logistic regression analysis.

Results: The study included 83 patients with colorectal cancer and 90 non-cancer controls. **Fourteen VOCs** were found to have significant discriminatory ability in detecting patients with colorectal cancer. The model with the diagnosis of cancer versus no cancer resulted in **a statistically significant likelihood of discrimination of 173·45 (P < 0·001), with an area under the ROC curve of 0·979. Cross-validation of the model resulted in a true predictive value for colorectal cancer of 93 per cent overall. Reliability of the breath analysis was maintained irrespective of cancer stage.**

Conclusion: This study demonstrated that analysis **of exhaled VOCs can discriminate patients with colorectal cancer from those without**. This finding may eventually lead to the creation of a smart online sensory device, capable of providing a binary answer (cancer/no cancer) and directing to further screening

Table 6 Cross-validation of colorectal cancer discrimination (Model A all patients).

	True condition					
	CRC	No cancer	Total			
Cancer	74	6	80			
No cancer	8	81	89			
Total	82	87		Pred value 93%	Sens 90%	Spec 93%

Analisi in GC-MS

CRC. Esiste un impronta nel respiro e può essere utilizzata

VOC test triage dopo FIT

Open access Protocol

BMJ Open REducing Colonoscopies in patients without significant bowEl DiseasE: the RECEDE Study - protocol for a prospective diagnostic accuracy study

ABSTRACT

Introduction Demand for colonoscopies and CT colonography (CTC) is exceeding capacity in National Health Service Trusts. In many patients colonoscopies and CTCs show no significant bowel disease (SBD). Faecal Immunochemical Testing (FIT) is being introduced to prioritise patients for colonoscopies but is insufficient to identify non-SBD patients meaning colonoscopy and CTC demand remains high. The REducing Colonoscopies in patients without significant bowEl DiseasE (RECEDE) study aims to test urine volatile organic compound (VOC) analysis alongside FIT to improve detection of SBD and to reduce the number of colonoscopies and CTCs.

Risk stratification of symptomatic patients suspected of colorectal cancer using faecal and urinary markers tract

Aim: Faecal markers, such as the faecal immunochemical test for haemoglobin (FIT) and faecal calprotectin (FCP), have been increasingly used to exclude colorectal cancer (CRC) and colonic inflammation. However, in those with lower gastrointestinal symptoms there are considerable numbers who have cancer but have a negative FIT test (i.e. false negative), which has impeded its use in clinical practice. We undertook a study of diagnostic accuracy CRC using FIT, FCP and urinary volatile organic compounds (VOCs) in patients with lower gastrointestinal symptoms.
Method: One thousand and sixteen symptomatic patients with suspected CRC referred by family physicians were recruited prospectively in accordance with national referring protocol. A total of 562 patients who completed colonic investigations, in addition to providing stool for FIT and FCP as well as urine samples for urinary VOC measurements, were included in the final outcome measures.
Results: The sensitivity and specificity for CRC using FIT was 0.80 [95% confidence interval (CI) 0.66-0.93] and 0.93 (CI 0.91-0.95), respectively. For urinary VOCs, the sensitivity and specificity for CRC was 0.63 (CI 0.46-0.79) and 0.63 (CI 0.59-0.67), respectively.
However, for those who were FIT-negative CRC (i.e. false negatives), the addition of urinary VOCs resulted in a sensitivity of 0.97 (CI 0.90-1.0) and specificity of 0.72 (CI 0.68-0.76).
Conclusions: When applied to the FIT-negative group, urinary VOCs improve CRC detection (sensitivity rises from 0.80 to 0.97), thus showing promise as a second-stage test to complement FIT in the detection of CRC.
Clinical Trial Colorectal Dis (2018 Dec;20(12):O335-O342)

In uso in GB

second-stage per implementare FIT nel rilevamento dei CRC.

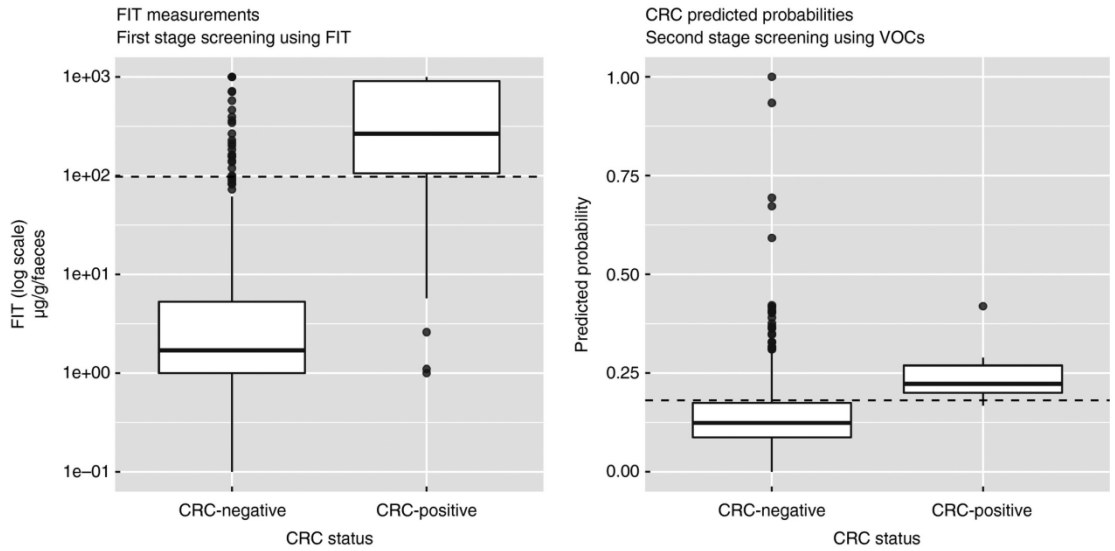
sensibilità dal 0.80 (FIT-Hb) a 0.97 FIT-Hb+VOC

Mt-fDNA & VOC test triage dopo FIT

Table 4. Diagnostic performance of biomarker combination for CRC and high-risk/advanced adenoma.
Biomedicines 2022, 10, 255

Disease Group	Biomarker(s)	Sens (%)	Spec (%	PPV (%)	NPV (%)	Ref.
CRC (n = 65)	FIT (20 µg);	73.8				
Cologuard®		92.3	94.9			N. Engl. J. Med. 2014
HRA (n = 757)	FIT (20 µg);	42.2	86.6			
Cologuard®		23.8				
CRC (n = 35)	FIT (3 µg);	80	93	44	99	Colorectal Dis. 2018
VOCs	(FIT –)	97	72		100	

Triage sui test negativi



Sensibilità FIT

Bowel cancer screening

OPEN ACCESS

Original research

Faecal immunochemical test is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: a diagnostic accuracy study

Nigel D'Souza ,[1,2,3] Theo Georgiou Delisle,[1,3] Michelle Chen,[4] Sally Benton,[5] Muti Abulafi ,[1] The NICE FIT Steering Group

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-321956).

[1]Colorectal Surgery, Croydon University Hospital, Croydon, UK
[2]Colorectal Surgery, Basingstoke and North Hampshire Hospital, Basingstoke, UK
[3]Surgery & Cancer, Imperial College London, London, UK
[4]Research & Development, RM Partners, London, UK
[5]Clinical Biochemistry, Royal Surrey County Hospital, Guildford, UK
Correspondence to
Mr Muti Abulafi, Colorectal Surgery, Croydon University Hospital, Croydon CR7 7YE, UK; muti.abulafi@nhs.net

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► http://dx.doi.org/10.1136/gutjnl-2020-323118

To cite: D'Souza N, Georgiou Delisle T, Chen M, *et al*. *Gut* 2021;70:1130-1138.

ABSTRACT

Objective To assess whether a faecal immunochemical test (FIT) could be used to select patients with suspected colorectal cancer (CRC) symptoms for urgent investigation.

Design Multicentre, double-blinded diagnostic accuracy study in 50 National Health Service (NHS) hospitals across England between October 2017 and December 2019. Patients referred to secondary care with suspected CRC symptoms meeting NHS England criteria for urgent 2 weeks wait referral and triaged to investigation with colonoscopy were invited to perform a quantitative FIT. The sensitivity of FIT for CRC, and effect of relevant variables on its diagnostic accuracy was assessed.

Results 9822 patients were included in the final analysis. The prevalence of CRC at colonoscopy was 3.3%. The FIT positivity decreased from 37.2% to 19.0% and 7.6%, respectively, at cut-offs of 2, 10 and 150 µg haemoglobin/g faeces (µg/g). The positive predictive values of FIT for CRC at these cut-offs were 8.7% (95% CI, 7.8% to 9.7%), 16.1% (95% CI 14.4% to 17.8%) and 31.1% (95% CI 27.8% to 34.6%), respectively, and the negative predictive values were 99.8% (95% CI 99.7% to 99.9%), 99.6% (95% CI 99.5% to 99.7%) and 98.9% (95% CI 98.7% to 99.1%), respectively. The sensitivity of FIT for CRC decreased at the same cut-offs from 97.0% (95% CI 94.5% to 98.5%) to 90.9% (95% CI 87.2% to 93.8%) and 70.8% (95% CI 65.6% to 75.7%), respectively, while the specificity increased from 64.9% (95% CI 63.9% to 65.8%) to 83.5% (95% CI 82.8% to 84.3%) and 94.6% (95% CI 94.1% to 95.0%), respectively. The area under the receiver operating characteristic curve was 0.93 (95% CI 0.92 to 0.95).

Conclusion FIT sensitivity is maximised to 97.0% at the lowest cut-off (2 µg/g); a negative FIT result at this cut-off can effectively rule out CRC and a positive FIT result is better than symptoms to select patients for urgent investigations.

Trial registration number ISRCTN49676259.

Significance of this study

What is already known on this subject?

- Faecal immunochemical tests (FIT) are already recommended by the National Institute for Heath and Care Excellence to guide referral of patients with low-risk bowel symptoms but has not been recommended for all symptomatic patients due to concerns over the quality and power of previous studies.

What are the new findings?

- FIT sensitivity for colorectal cancer (CRC) is maximised to 97.0% at the limit of detection of 2 µg haemoglobin (Hb)/g faeces (µg/g).
- A faecal Hb concentration (f-Hb) result less than the limit of detection in symptomatic patients indicates that their chances of not having CRC is 99.8%.
- There was no significant variation in the ability of FIT to detect CRC by patient or tumour characteristics, including age, sex, ethnicity, deprivation or iron-deficiency anaemia.

How might it impact on clinical practice in the foreseeable future?

- FIT could be used to rule out CRC in primary care for symptomatic patients meeting 2 weeks wait criteria, with sensitivity equivalent to colonoscopy at a cut-off of 2 µg/g.
- FIT can be used to prioritise patients for investigation, as CRC and other serious bowel disease is more likely at higher f-Hb concentrations.
- The diagnostic accuracy of FIT for CRC is superior to symptoms.

INTRODUCTION

Bowel symptoms are the imprecise basis of referral for urgent investigation in England to rule out cancer.[1 2] Symptoms are non-specific for colorectal cancer (CRC); 96 of 100 patients referred urgently on a 2-week (2WW) wait pathway under National Institute for Health and Care Excellence (NICE) NG12 guidelines will not have CRC.[1] Urgent referrals have increased by 90% over the last 5 years[2]; 45% of UK endoscopy units are failing to meet CRC waiting targets.[3]

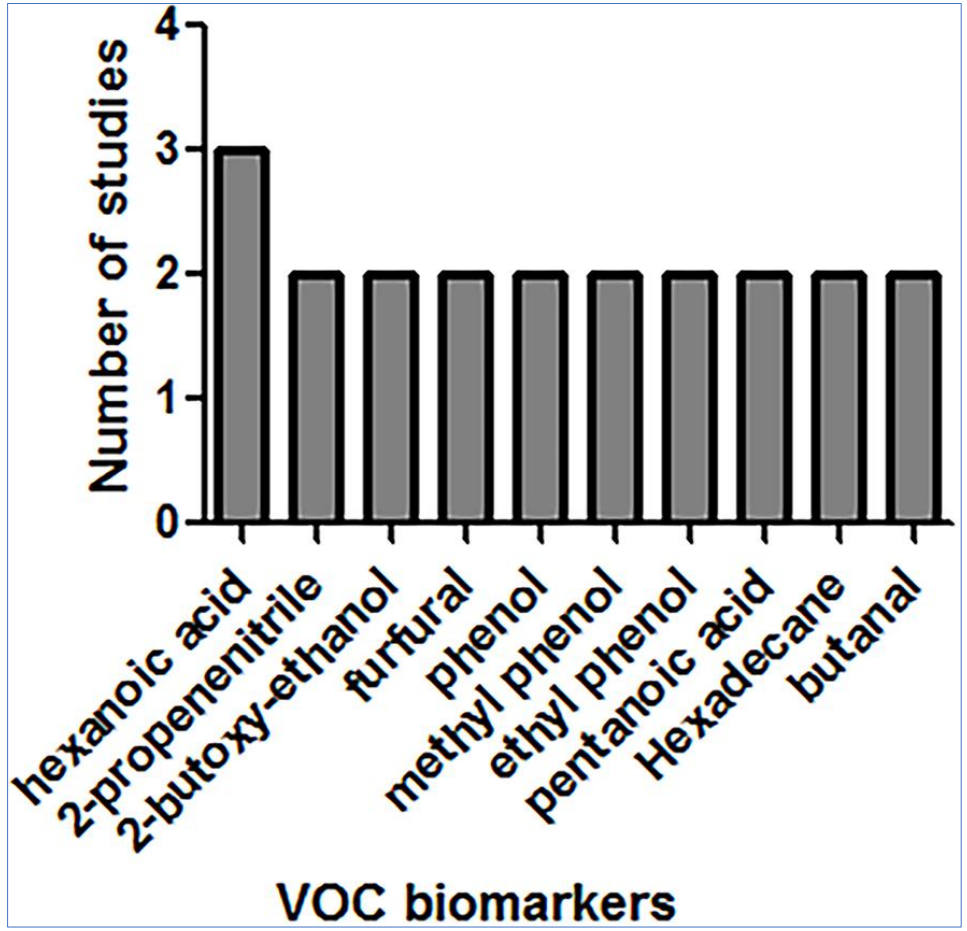
The faecal immunochemical test (FIT) was recommended by NICE (DG30)[4] in 2017 to guide the referral of patients with low-risk symptoms of

Table 4 Diagnostic accuracy of FIT for CRC and SBD at different cut-offs

Risk category	FIT positivity	Cut-off (µg/g)	Sensitivity	Specificity	PPV	NPV
≥2	37.2	CRC	97.0 (94.5 to 98.5)	64.9 (63.9 to 65.8)	8.7 (7.8 to 9.7)	99.8 (99.7 to 99.9)
		HRA	65.8 (61.0 to 70.3)	64.1 (63.1 to 65.0)	7.6 (6.7 to 8.5)	97.7 (97.3 to 98.0)
		IBD	73.1 (68.6 to 77.2)	64.4 (63.4 to 65.4)	8.5 (7.7 to 9.5)	98.1 (97.8 to 98.5)
		SBD	77.1 (74.6 to 79.5)	68.2 (67.2 to 69.2)	24.8 (23.4 to 26.3)	95.6 (95.1 to 96.1)
≥10	19.0	CRC	90.9 (87.2 to 93.8)	83.5 (82.8 to 84.3)	16.1 (14.4 to 17.8)	99.6 (99.5 to 99.7)
		HRA	45.4 (40.5 to 50.3)	82.2 (81.4 to 83.0)	10.3 (8.9 to 11.7)	97.1 (96.7 to 97.5)
		IBD	57.8 (53.0 to 62.6)	82.8 (82.0 to 83.6)	13.3 (11.8 to 14.9)	97.7 (97.4 to 98.1)
		SBD	62.6 (59.8 to 65.4)	87.0 (86.3 to 87.7)	39.6 (37.4 to 41.8)	94.5 (93.9 to 95.0)
≥150	7.6	CRC	70.8 (65.6 to 75.7)	94.6 (94.1 to 95.0)	31.1 (27.8 to 34.6)	98.9 (98.7 to 99.1)
		HRA	22.1 (18.2 to 26.4)	93.0 (92.5 to 93.5)	12.4 (10.1 to 15.0)	96.4 (96.0 to 96.8)
		IBD	36.8 (32.2 to 41.5)	93.7 (93.2 to 94.2)	21.0 (18.1 to 24.1)	97.0 (96.7 to 97.4)
		SBD	41.0 (38.2 to 43.9)	96.9 (96.5 to 97.3)	64.5 (60.9 to 67.9)	92.4 (91.8 to 92.9)

Sintomatici Le performance del FIT restano molto interessanti. ... la presenza di sangue nelle feci è un ottimo indicatore di lesione

Sappiamo che esiste un ‘impronta’ dell’espirato come renderla facilmente accessibile e come utilizzarla?



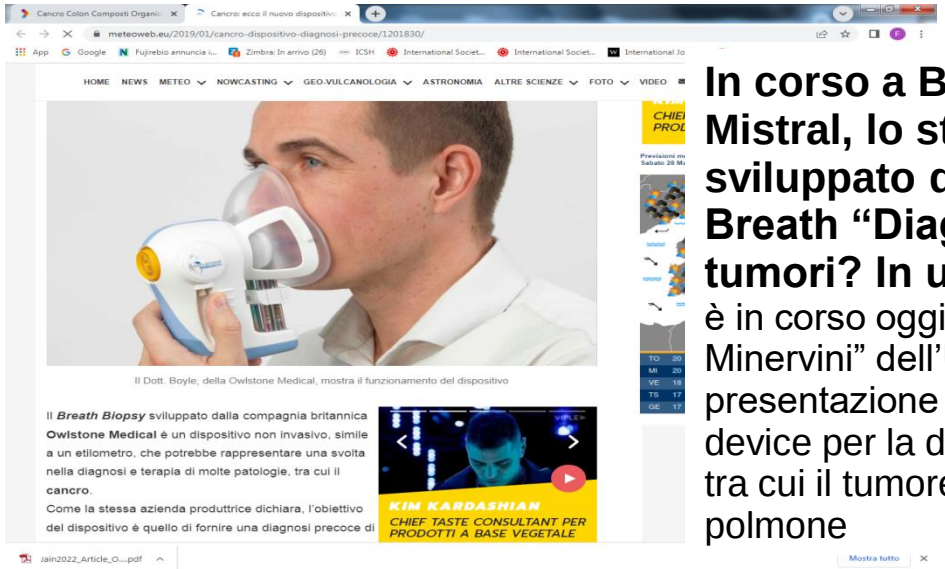
VOCs riportati in 2 o più pubblicazioni

Table 1. All breath test VOCs analyzed in each specific study.

	Colorectal Carcinoma (CRC)
References	**Identified VOCs**
Altomare 2020 [26]	Tetradecane; ethylbenzene; methylbenzene; 5,9-undecadien-2-one + 6,10-dimethyl (E); tridecane; benzaldehyde; dodecane; benzoic acid; 1,3-bis(1-methylethenyl) benzene; decanal; 2-ethyl-hexanol; ethenone + 1[4-(1-methylethenyl) phenyl]; acetic acid; butyl hydroxy toluene; unknown VOC.
Steenhuis 2020 [27]	n.a.
Van Keulen 2020 [23]	n.a.
Markar 2019 [28]	Propanal; ammonia; ethanol; acrolein; propanol; butanol; carbon disulfide.
Altomare 2016 [29]	Methane.
Amal 2016 [30]	Acetone; ethyl acetate; 4-methyl-octane; ethanol.
Altomare 2015 [31]	1,2-pentadiene; 2-methylbutane; 3-ethylpentane; methylcyclo-pentane; cyclohexane; nonanal; methylcyclohexane; 4-methyl-2-pentanone; 1,4-dimethylbenzene; 1,3-dimethylbenzene; decanal.
Wang 2014 [32]	Cyclohexanone; 2,2-dimethyldecane; 4-ethyl-1-octyn-3-ol; ethylaniline; cyclooctylmethanol; trans-2-dodecen-1-ol; 3-hydroxy-2,4,4-trimethylpentyl 2-methylpropanoate; dodecane.
Altomare 2013 [33]	4-methyl-octane; 1,2-pentadiene; 2-methylbutane; cyclohexane; nonanal; methylcyclohexane; 4-methyl-2-pentanone; 1,4-dimethylbenzene; 1,3-dimethylbenzene; 2-methylpentane; 3-methylpentane; 4-methylundecane; trimethyldecane; decanal.
Peng 2010 [34]	1,3-dimethylbenzene; 1,10-(1-butenylidiene) bis-benzene; 1-iodonane; [(1,1-dimethylethyl) thio] acetic acid; 4-(4-propylciclohexyl)-4′-cyano [1,10-biphenyl]-4-yl ester benzoic acid; 2-amino-5-isopropyl-8-methyl-1-azulenecarbonitrile.

naso elettronico?

Sensori in fase avanzata di sperimentazione



In corso a Bari la presentazione di Mistral, lo strumento diagnostico sviluppato dal cluster Inside the Breath "Diagnosi precoce dei tumori? In un soffio!":
è in corso oggi, nell'aula Balab "Guglielmo Minervini" dell'Università di Bari, la presentazione di Mistral, l'innovativo device per la diagnosi di varie patologie, tra cui il tumore del colon-retto e del polmone

In uso in GB

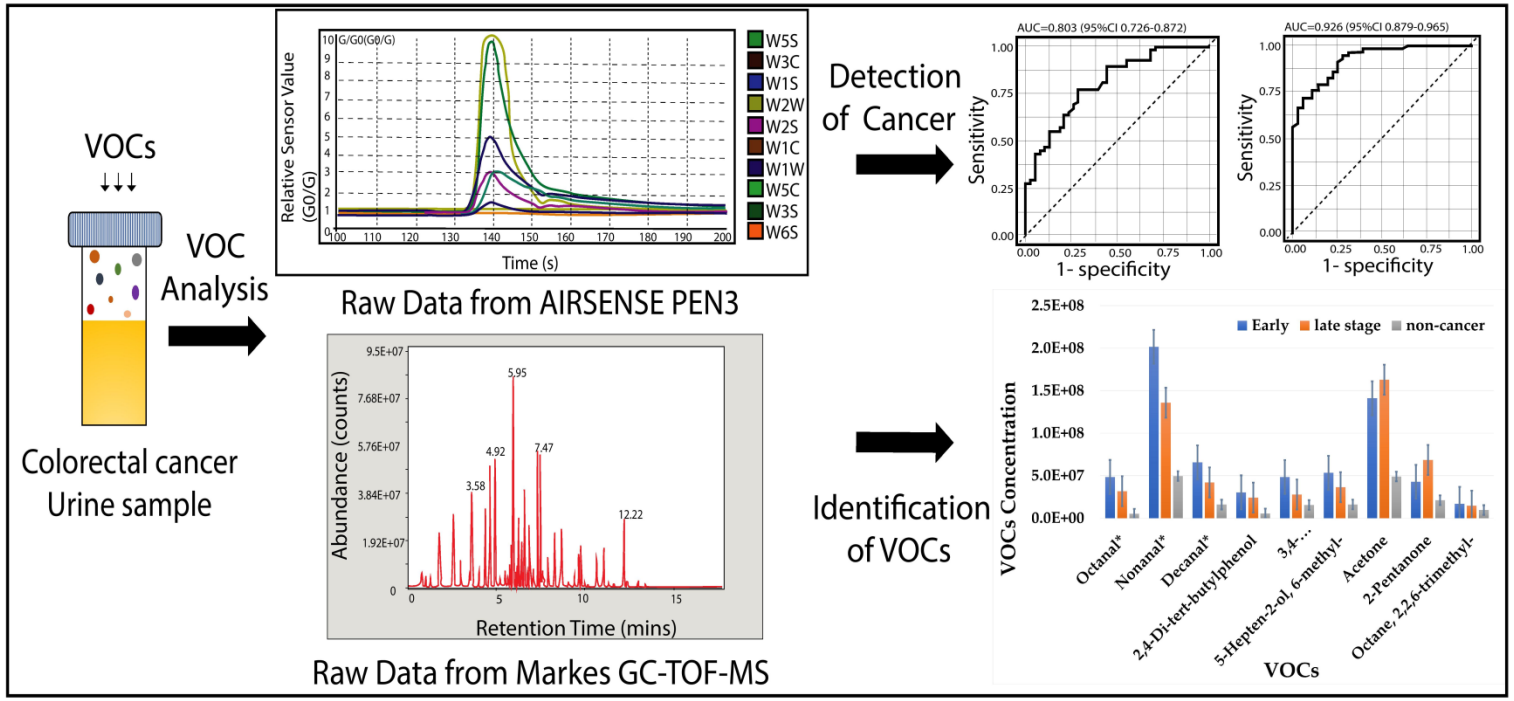
Mistral nasce dalla ricerca del cluster tecnologico pugliese Inside the Breath (composto dalle aziende Predict S.r.l., Wel.Co.Me S.r.l. e Reti Meridiane e da Dipartimento di Biologia e Facoltà di Medicina dell'Università degli Studi Aldo Moro di Bari), che ha evidenziato come la presenza di alcuni composti organici volatili (VOCs) nell'espirato sia indice dell'insorgenza di una determinata patologia.

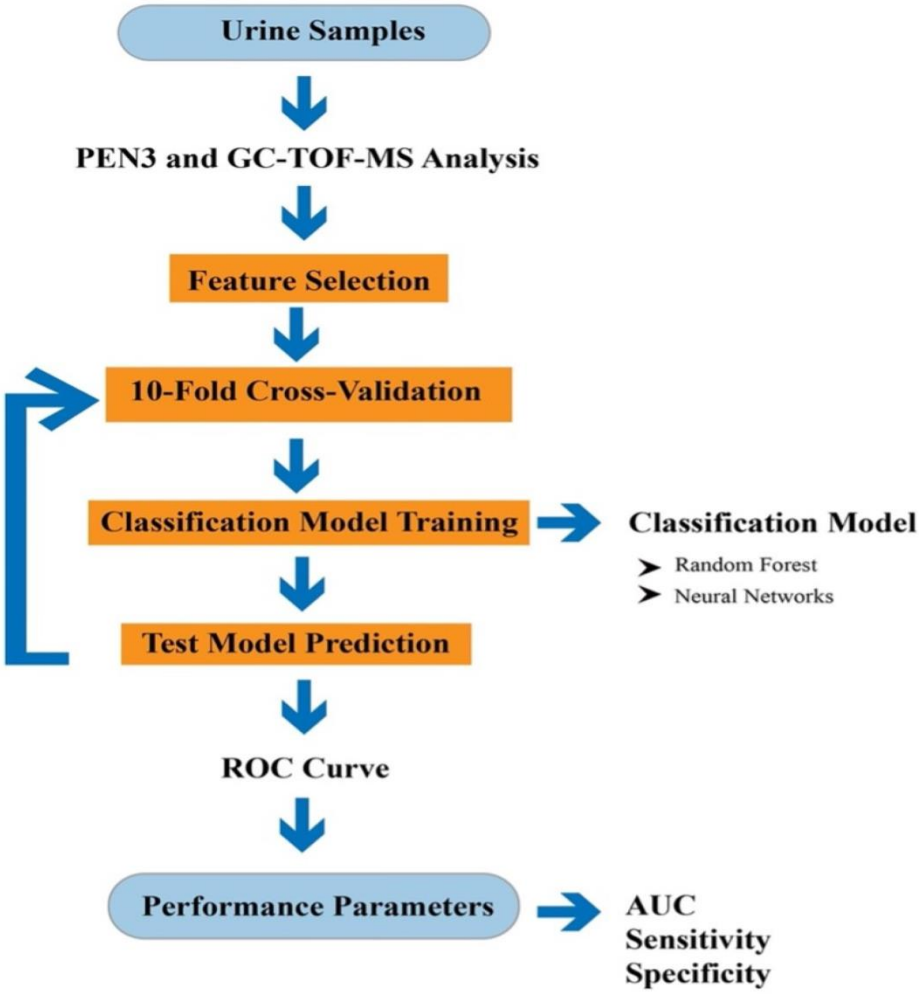
L'incontro di questa mattina, presieduto da Gianluigi De Gennaro (Dipartimento di Biologia, Università degli Studi di Bari) e Donato Altomare (Dipartimento dell'Emergenza e dei Trapianti di organi, Policlinico di Bari), prevede l'intervento di chi ha partecipato attivamente al progetto, e può dunque descrivere le diverse fasi operative.

Dopo i saluti di Antonio Felice Uricchio (rettore Università degli Studi "Aldo Moro" di Bari) e Rocco De Franchi (consigliere per la tutela ambientale, lo sviluppo sostenibile e la decarbonizzazione), l'introduzione di Angelo Gigante (Predict) darà il via ai lavori; alle 10.30, il panel "Breath biopsy per lo screening del cancro colorettale", tenuto da Donato Altomare (Dipartimento dell'Emergenza e dei Trapianti di organi, Policlinico di Bari); alle 11.00, Rosaria Orlandi (Molecular Targeting Unit – I.R.C.S.S. Milano) parlerà di "Sviluppare l'analisi del respiro per una diagnostica oncologica completamente non invasiva"; alle 11.30, il panel "La breath analysis ed il suo possibile ruolo nella diagnostica delle neoplasie del polmone e della pleura" tenuto da Annamaria Catino (Dipartimento di Oncologia Medica – I.R.C.S.S. Bari); alle 12.00, l'intervento di Alessia De Gilio (Dipartimento di Biologia dell'Università degli Studi di Bari); alle 12.30, il panel "Mistral: la diagnosi in un soffio" con Marco Cardanobile (Predict).

Concluderà l'incontro, alle ore 13.00, il Dott. Vito Antonio Delvino (Direttore Generale I.R.C.S.S. Bari).

GC-MS & Strumenti con Sensori





- **Nati per rilevamenti in loco**
- **Utilizzati rilevamenti ambientali, industria,**
- **Rapidi (analisi pochi minuti)**
- **Economici (circa 0,5 Euro determinazione)**
- **Devono essere ‘addestrati’**

Non-Invasive Detection and Staging of Colorectal Cancer Using a Portable Electronic Nose Sensors 2021, 21, 5440

Strumenti a Sensori

- **Identificano Classi di composti**

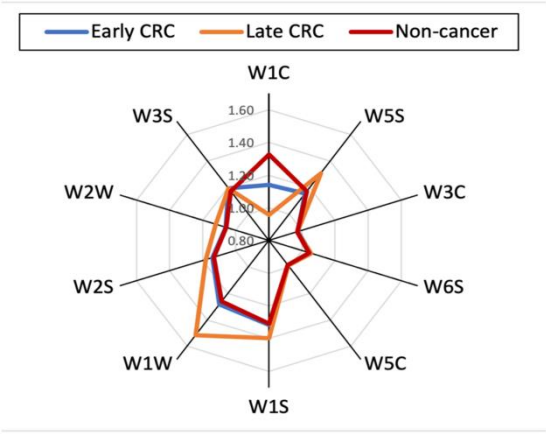
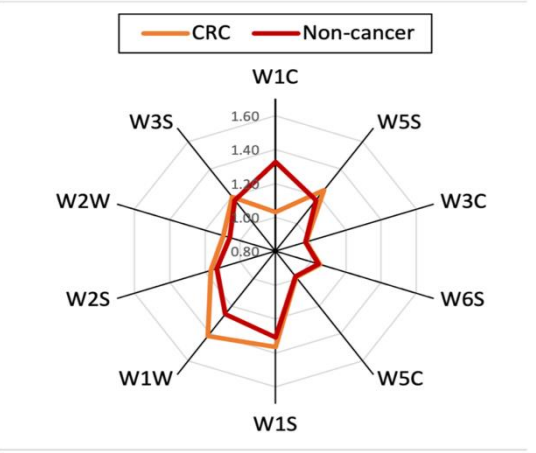


Table 2. Description of the sensors used in PEN3 e-nose provided by Airsense Analytical.

No. Sensors	Substances for Sensing
S1 W1C	Sensitive to aromatic compounds
S2 W5S	Broad range
S3 W3C	Sensitive to aromatic compounds
S4 W6S	Sensitive to hydrogen
S5 W5C	Sensitive to aromatic and aliphatic compounds
S6 W1S	Sensitive to methane in the environment, with broad range
S7 W1W	Sensitive to Sulphur and organic compounds
S8 W2S	Sensitive to alcohol and broad range
S9 W2W	Sensitive to Sulphur compounds
S10 W3S	Sensitive to methane and aliphatic compounds



1. **Costruiscono un ‘impronta digitale’ specifica per patologia**
2. **Vanno elaborati algoritmi specifici per patologia per sistema**
3. **Calibrazione sistemi per esportare informazione**
4. **Armonizzazione risposte tra metodi diversi**

Non-Invasive Detection and Staging of Colorectal Cancer Using a Portable Electronic Nose Sensors 2021, 21, 5440

Revisione sistematica

Original Investigation | Oncology

Diagnostic Performance of Electronic Noses in Cancer Diagnoses Using Exhaled Breath A Systematic Review and Meta-analysis

Max H. M. C. Scheepers, MD; Zaid Al-Difaie, MD; Lloyd Brandts, PhD; Andrea Peeters, MD, PhD; Bart van Grinsven, PhD; Nicole D. Bouvy, MD, PhD

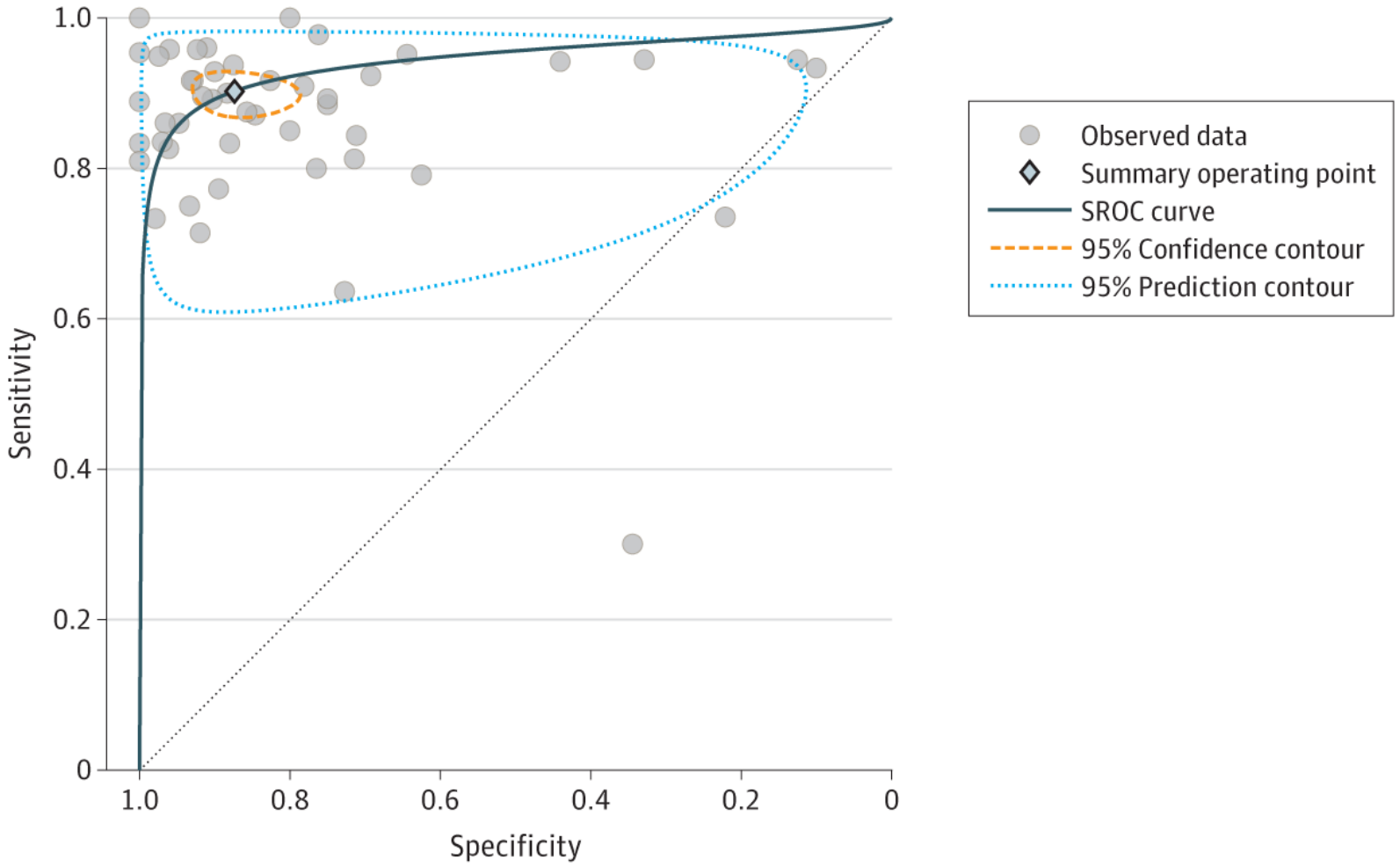
RESULTS

This review identified 52 articles with a total of 3677 patients with cancer. All studies were feasibility studies. The sensitivity of e-noses ranged from 48.3% to 95.8% and the specificity from 10.0% to 100.0%. Pooled analysis resulted in a mean (SE) **area under the receiver operating characteristic curve of 94% (95% CI, 92%-96%),** a **sensitivity of 90% (95% CI, 88%-92%),** and a **specificity of 87% (95% CI, 81%-92%)**.

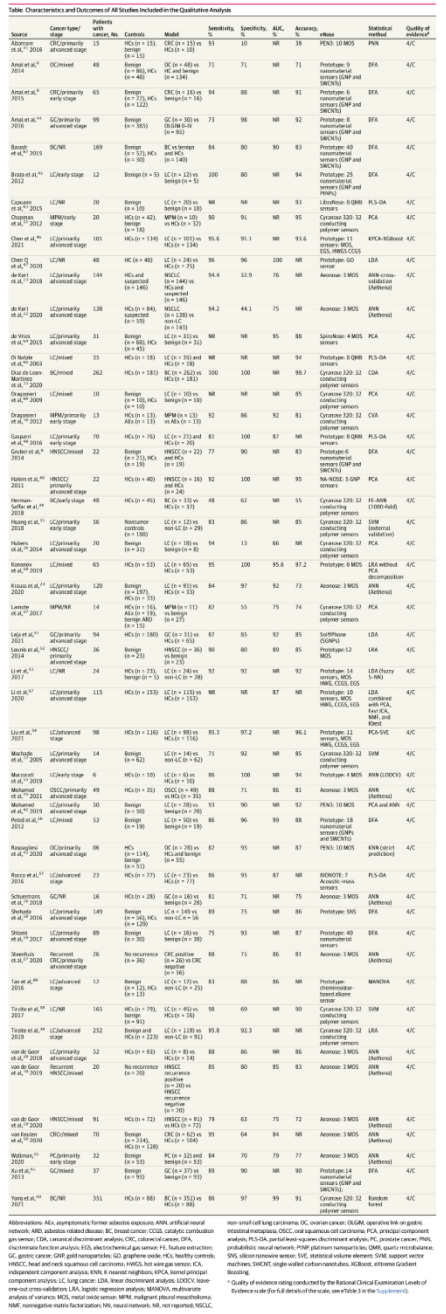
Considerable heterogeneity existed among the studies because of differences in the selection of patients, endogenous and exogenous factors, and collection of exhaled breath.

JAMA Network Open. 2022;5(6):e2219372. doi:10.1001/jamanetworkopen.2022.19372

ROC dei metodi inclusi



Summary Receiver Operating Characteristic (SROC) Curve Analysis of All Electronic NosesFor the summary operating point, sensitivity was 0.90 (95% CI, 0.88-0.92) and specificity was 0.87 (95% CI, 0.81-0.92). For the SROC curve, the area under the curve was 0.94 (95% CI, 0.92-0.95).

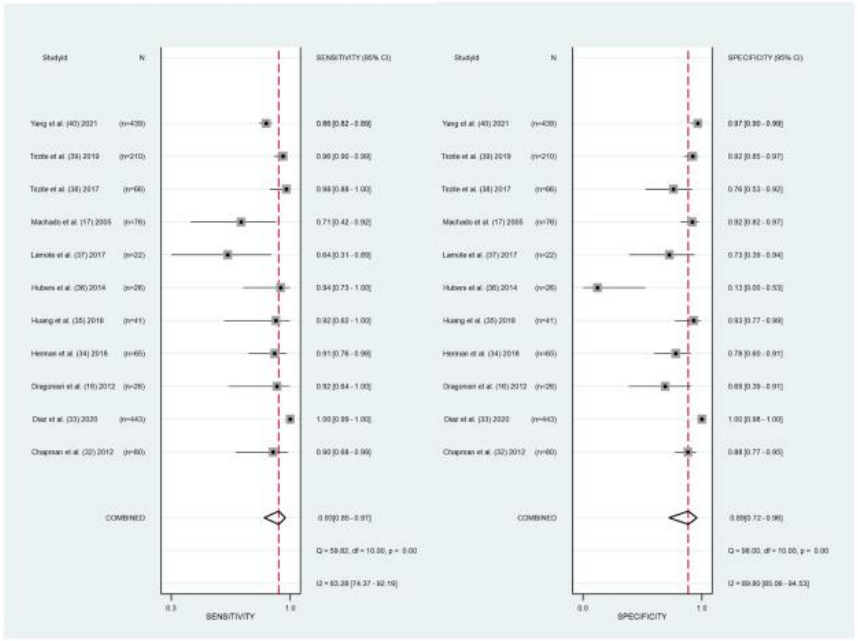


JAMA Network Open. 2022;5(6):e2219372. doi:10.1001/jamanetworkopen.2022.19372

Sensibilità Specificità Cyranose

Tutte neoplasie

eFigure 4: Pooled analysis of all Cyranose320 studies

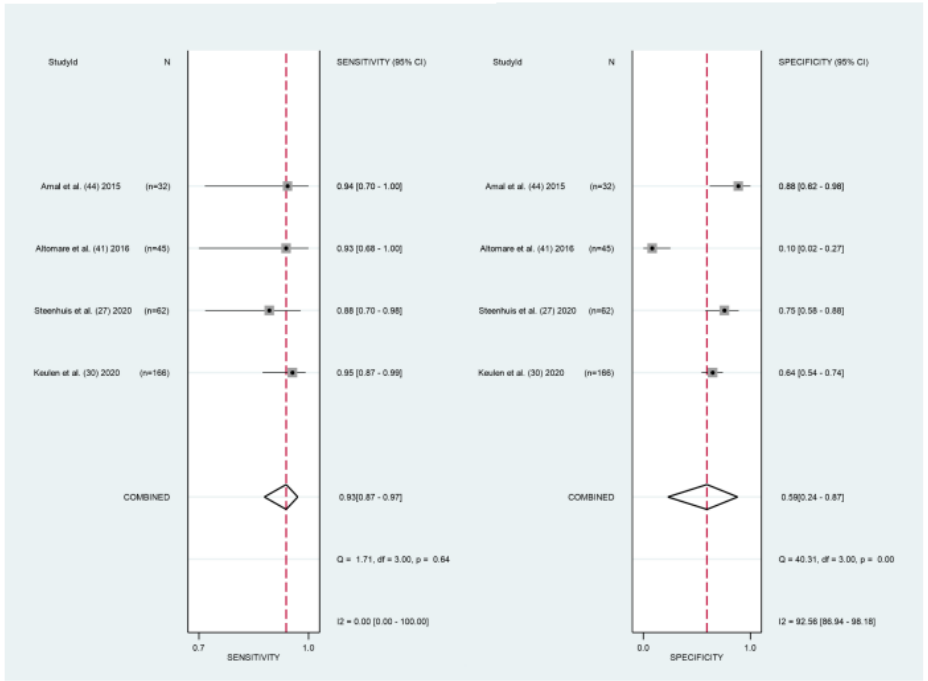


Key Points

Meaning Although e-noses were found to have promising accuracy in detecting cancer**, there is a need for standardized external validation studies that evaluate their diagnostic accuracy so that their role in the diagnostic workup of cancer can be established**

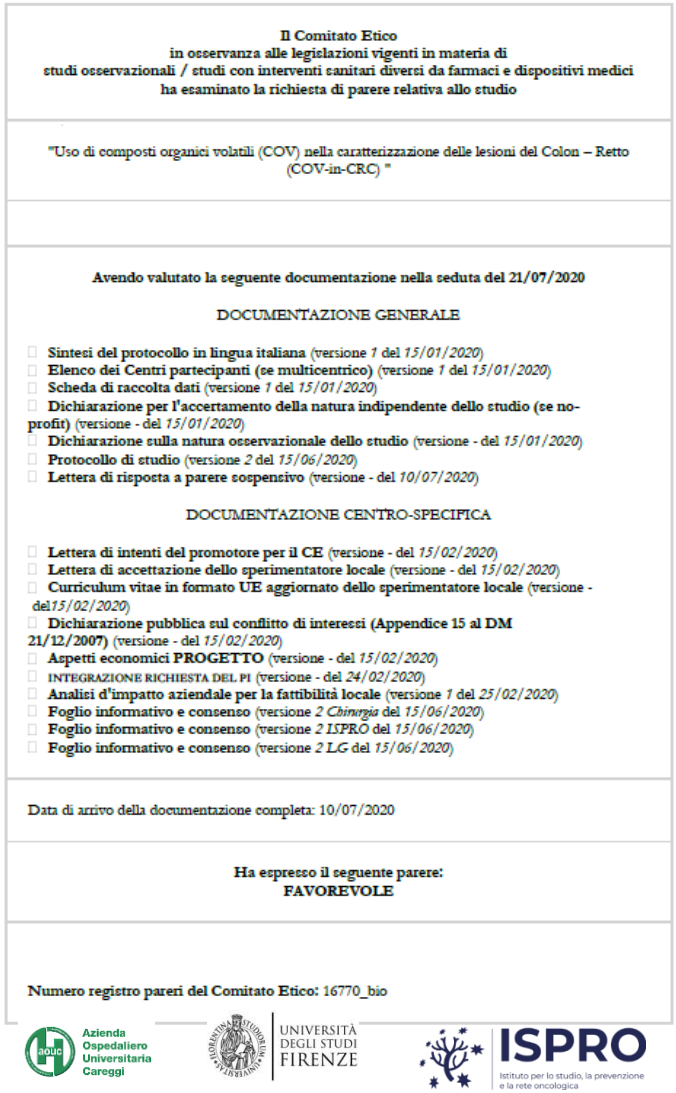
CRC

eFigure 8: Pooled analysis of all colorectal cancer studies



Uno degli studi riporta bassa sensibilità

Studio dei composti organici volatili (COV) per la caratterizzazione delle lesioni del colon-retto (COV in CRC) .



Il Comitato Etico
in osservanza alle legislazioni vigenti in materia di
studi osservazionali / studi con interventi sanitari diversi da farmaci e dispositivi medici
ha esaminato la richiesta di parere relativa allo studio

"Uso di composti organici volatili (COV) nella caratterizzazione delle lesioni del Colon – Retto (COV-in-CRC) "

Avendo valutato la seguente documentazione nella seduta del 21/07/2020

DOCUMENTAZIONE GENERALE

- **Sintesi del protocollo in lingua italiana** (versione *1* del *15/01/2020*)
- **Elenco dei Centri partecipanti (se multicentrico)** (versione *1* del *15/01/2020*)
- **Scheda di raccolta dati** (versione *1* del *15/01/2020*)
- **Dichiarazione per l'accertamento della natura indipendente dello studio (se no-profit)** (versione - del *15/01/2020*)
- **Dichiarazione sulla natura osservazionale dello studio** (versione - del *15/01/2020*)
- **Protocollo di studio** (versione *2* del *15/06/2020*)
- **Lettera di risposta a parere sospensivo** (versione - del *10/07/2020*)

DOCUMENTAZIONE CENTRO-SPECIFICA

- **Lettera di intenti del promotore per il CE** (versione - del *15/02/2020*)
- **Lettera di accettazione dello sperimentatore locale** (versione - del *15/02/2020*)
- **Curriculum vitae in formato UE aggiornato dello sperimentatore locale** (versione - del*15/02/2020*)
- **Dichiarazione pubblica sul conflitto di interessi (Appendice 15 al DM 21/12/2007)** (versione - del *15/02/2020*)
- **Aspetti economici PROGETTO** (versione - del *15/02/2020*)
- **INTEGRAZIONE RICHIESTA DEL PI** (versione - del *24/02/2020*)
- **Analisi d'impatto aziendale per la fattibilità locale** (versione *1* del *25/02/2020*)
- **Foglio informativo e consenso** (versione *2 Chirurgia* del *15/06/2020*)
- **Foglio informativo e consenso** (versione *2 ISPRO* del *15/06/2020*)
- **Foglio informativo e consenso** (versione *2 LG* del *15/06/2020*)

Data di arrivo della documentazione completa: 10/07/2020

Ha espresso il seguente parere:
FAVOREVOLE

Numero registro pareri del Comitato Etico: 16770_bio

Azienda Ospedaliero Universitaria Careggi — Università degli Studi Firenze — ISPRO Istituto per lo studio, la prevenzione e la rete oncologica

Obiettivi: Ottenere una caratterizzazione "*Smell Print*" dei soggetti affetti da CRC, con diversa stadiazione, tramite analisi dell'espirato.

Metodi: La sperimentazione è basata sull'analisi dei composti organici volatili contenuti nell'espirato.

I campioni sono stati analizzati in spettrometria di massa e con un naso elettronico commerciale.

Lo studio ha visto l'arruolamento di soggetti con diversi livelli di rischio.

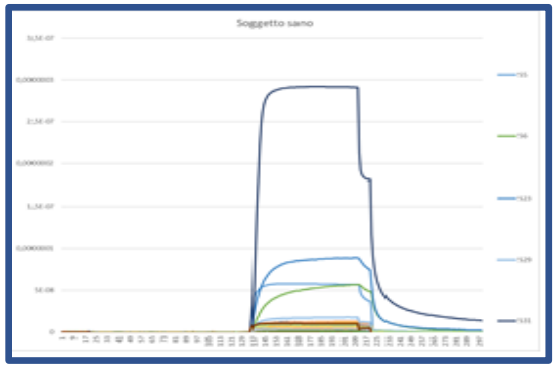
a) Normali: negativi alla ricerca del sangue occulto fecale (Fit-);

b) Positivi: soggetti con intervento chirurgico programmato (CRC);

c) FIT + con raccolta del materiale al momento della gastroscopia.

Capacità dei VOC di fornire indirizzare gli approfondimenti diagnostici ed anticipare le riprese di malattia

Disegno studio

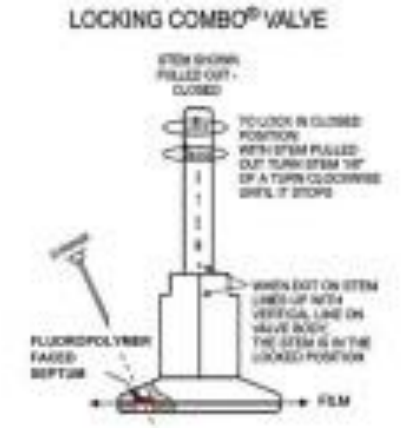


naso elettronico («Cyranose 320»)

Gas Cromatografo-Spettrometro di Massa (GC-MS)

Il campionamento diretto ipotizzato in un primo momento si è rivelato impraticabile in periodo COVID; lo studio è cominciato ‘producendo’ i raccordi necessari.

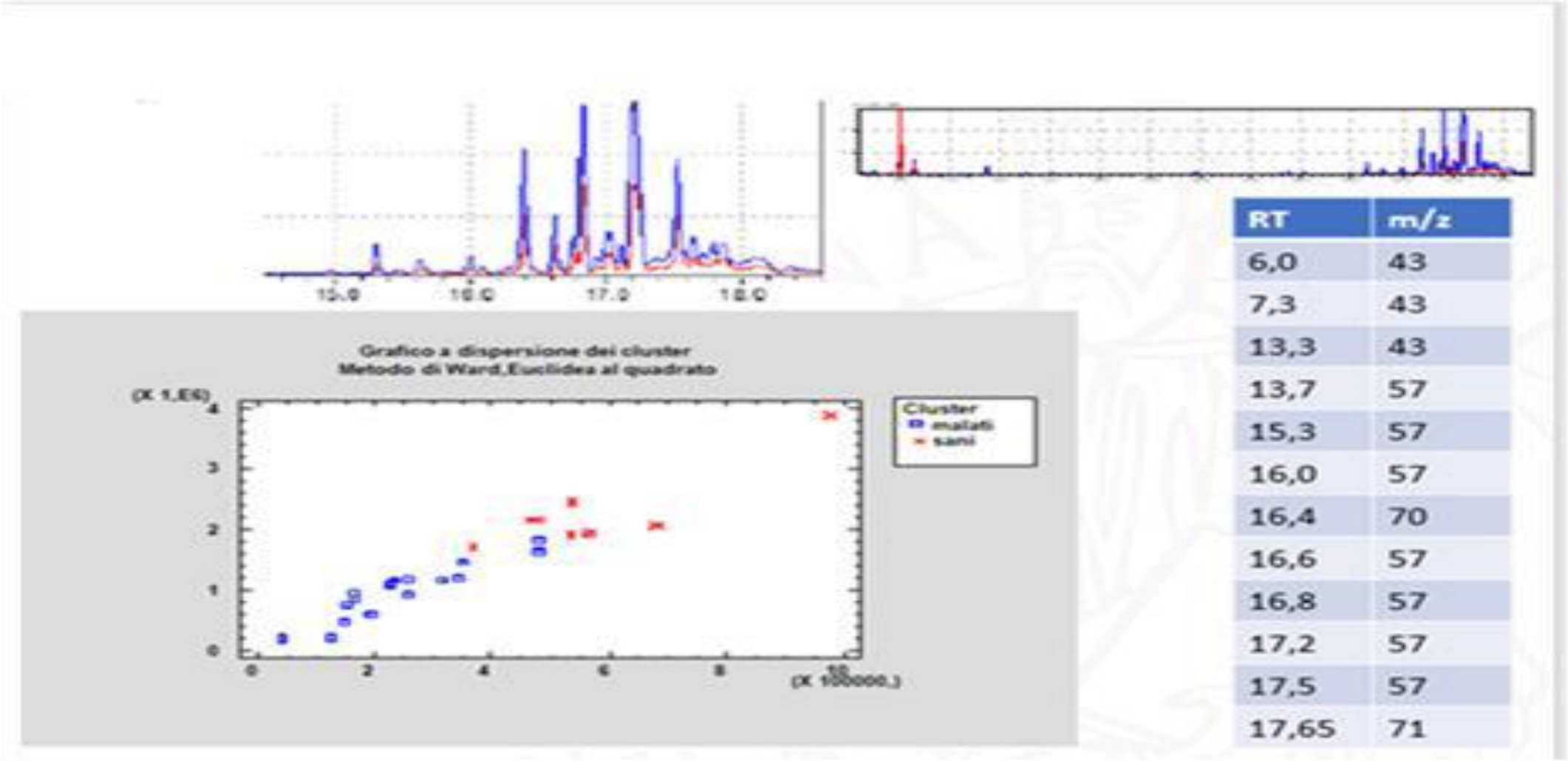
Raccolta del Campione



Dopo alcuni cicli di preparazione (allontanamento composti ambientali) l'espirato viene raccolto, all'interno di sacche multistrato (3 espirazioni) con setto disegnato per consentire una microestrazione in fase solida (fibra SPME) ed analizzati in GC-MS.

Ai fini di eventuale uso nei percorsi di screening la tollerabilità della strategia di prelievo è fondamentale sia per l'adesione che per la 'ripetibilità delle metodiche'.
Nel corso dello studio il campionamento è sembrato ben tollerato dai partecipanti ma l'aspetto andrà valutato in dettaglio.

Risposta Strumentale Spettro GC-MS



RT	m/z
6,0	43
7,3	43
13,3	43
13,7	57
15,3	57
16,0	57
16,4	70
16,6	57
16,8	57
17,2	57
17,5	57
17,65	71

Picchi con differenze significative tra sani e malati

Perché naso elettronico

Requisiti che li rendono particolarmente interessanti

- Semplici (nati per rilevamenti in loco)
- Versatili (rilevamenti ambiente, industria, medicina)
- Rapidi (analisi pochi minuti)
- Economici

Prima dell'utilizzo

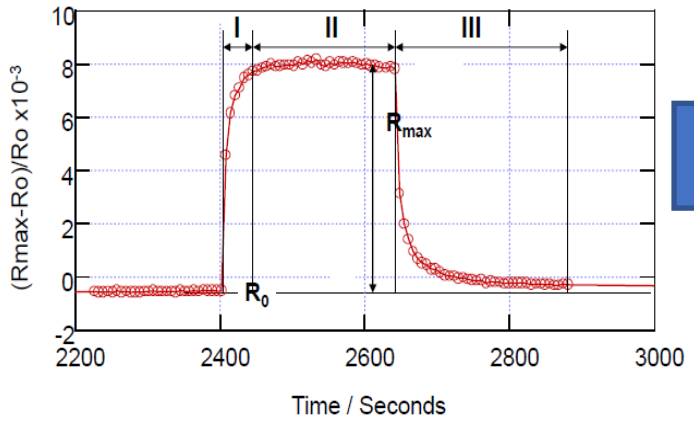
1. Calibrazione sistemi
2. Standardizzazione risposte

Non possono essere tarati ed addestrati ad ogni utilizzo

Risposta Strumentale naso elettronico

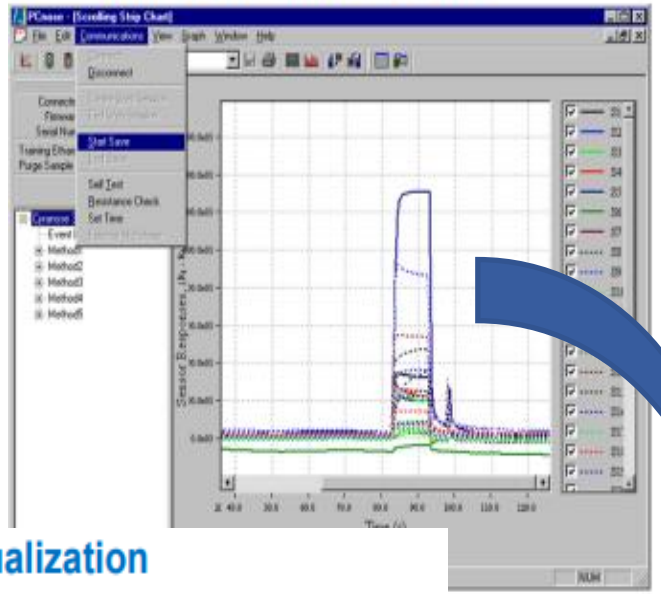
Il naso elettronico ha un software di analisi che va **“addrestrato ”**

Calculation of Sensor Response

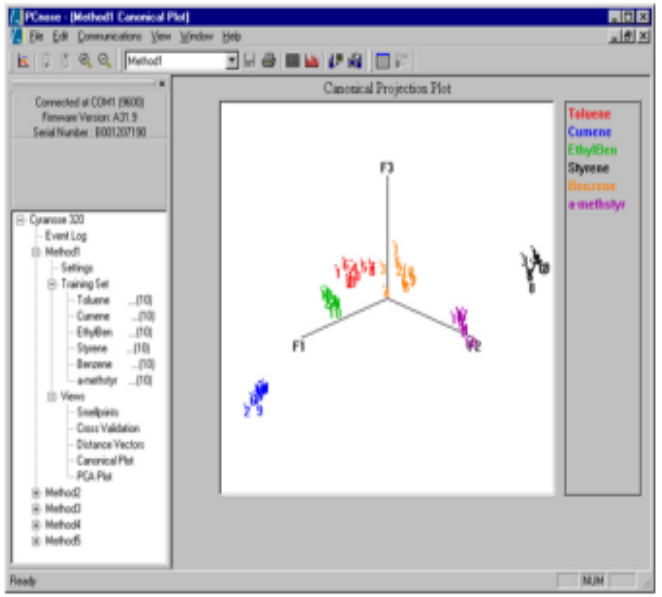


I = dynamic region II= steady-state region III = recovery region

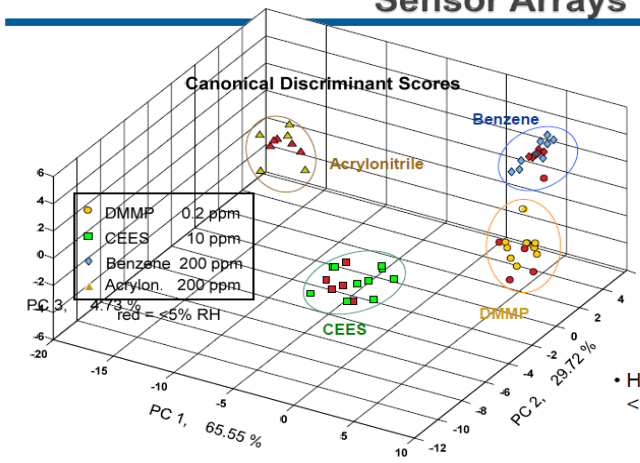
Real-Time Sensor Response



Results Visualization

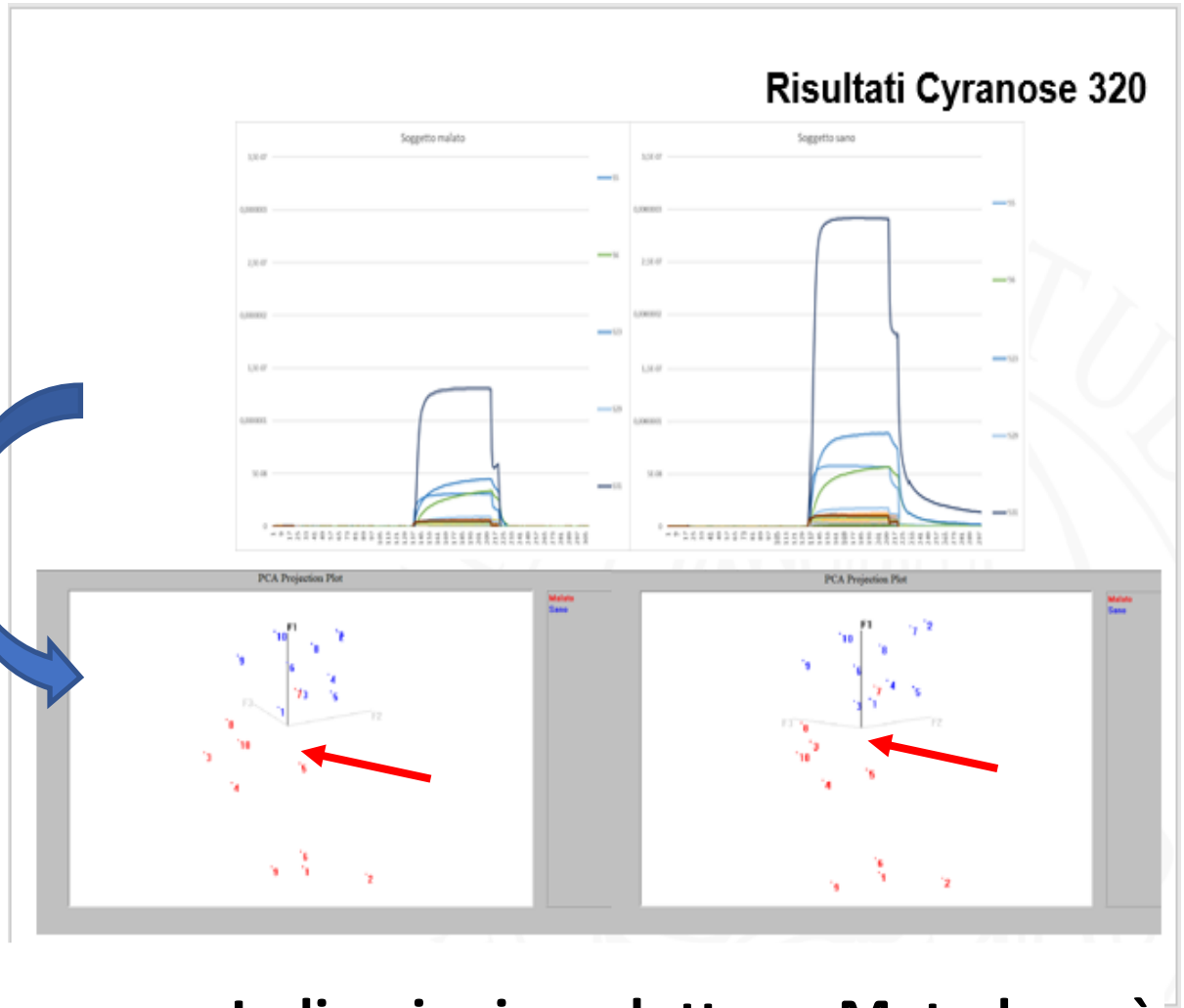


Chemical Identification with Sensor Arrays



- Sensor response pattern is robust with matrix variation
- Humidity levels: <5, 60, 72% RH

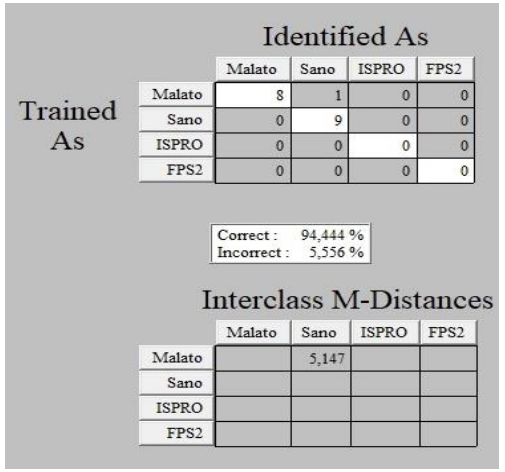
“impronta espirato” Sani Vs CRC



CANONICAL PLOT

Rosso CRC

Blu Sani



Identified As

Trained As	Malato	Sano	ISPRO	FPS2
Malato	8	1	0	0
Sano	0	9	0	0
ISPRO	0	0	0	0
FPS2	0	0	0	0

Correct : 94,444 %
Incorrect : 5,556 %

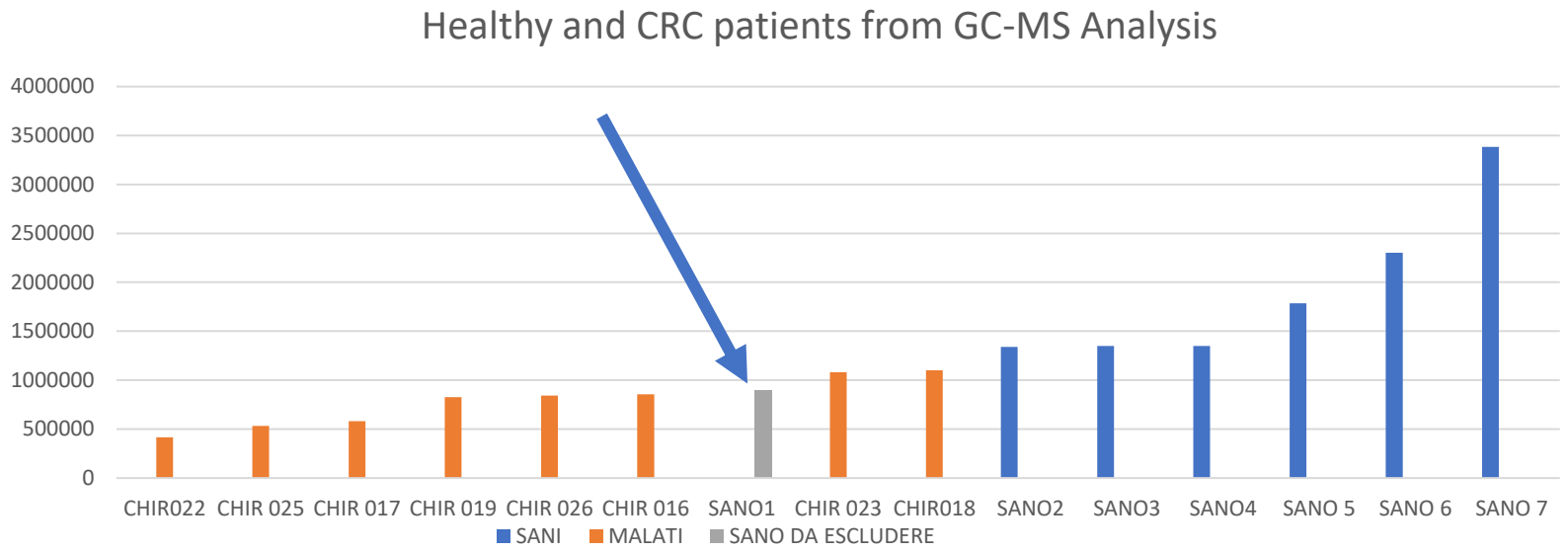
Interclass M-Distances

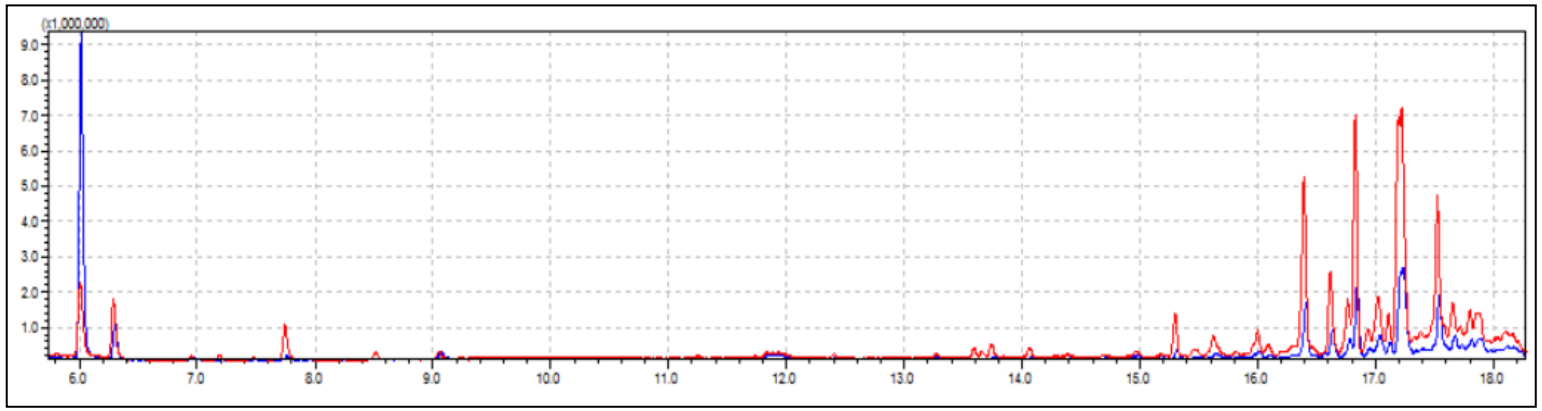
	Malato	Sano	ISPRO	FPS2
Malato		5,147		
Sano				
ISPRO				
FPS2				

Cross validation

Indicazioni produttore. Metodo può essere accettato per:
Cross-validation > 90%
Distanza Euclidea tra I gruppi >/= 5.0 (manufacturer).

Confronto GC-MS vs Naso elettronico





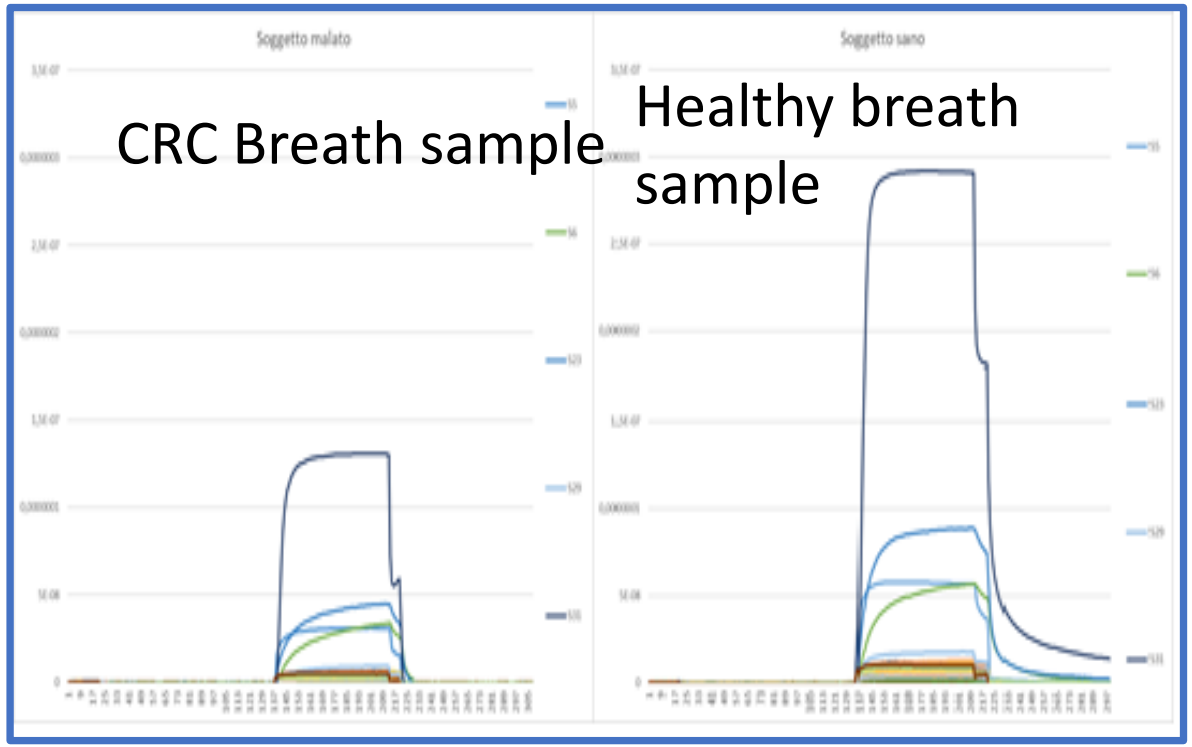
In grafico il confronto delle Medie ottenute dagli 11 picchi più significativi dei gruppi sani e malati

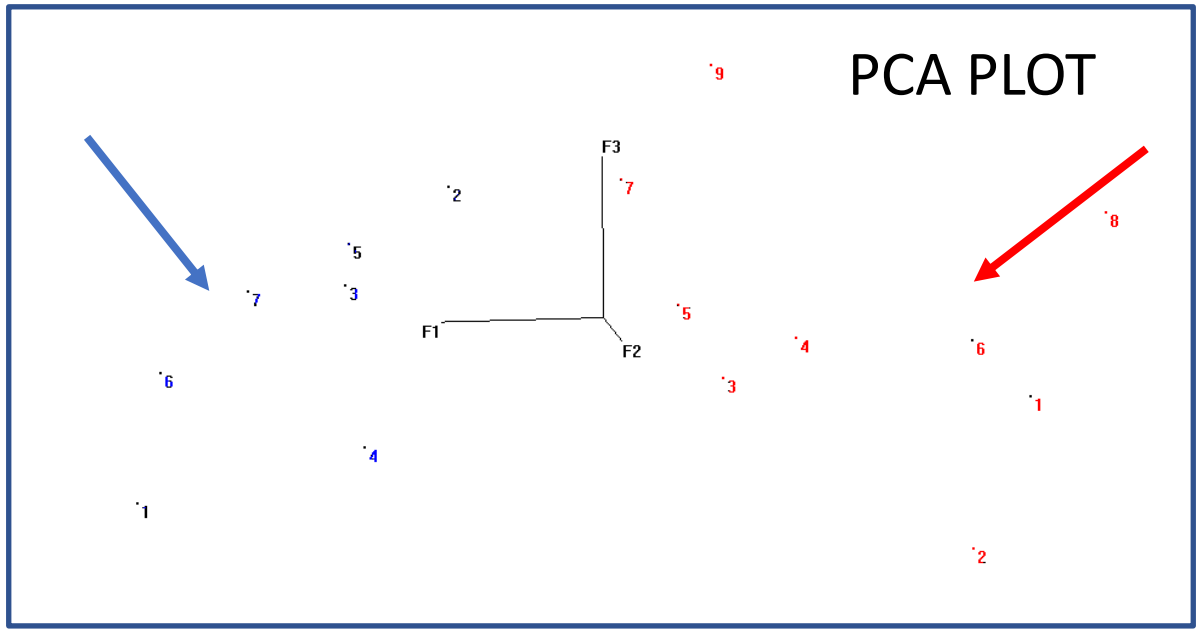
Confrontando le risposte con quelle in GC-MS è stato individuato 1 soggetto 'aberrante'.

L'esclusione dal gruppo di riferimento migliora la risposte dell'algoritmo di classificazione

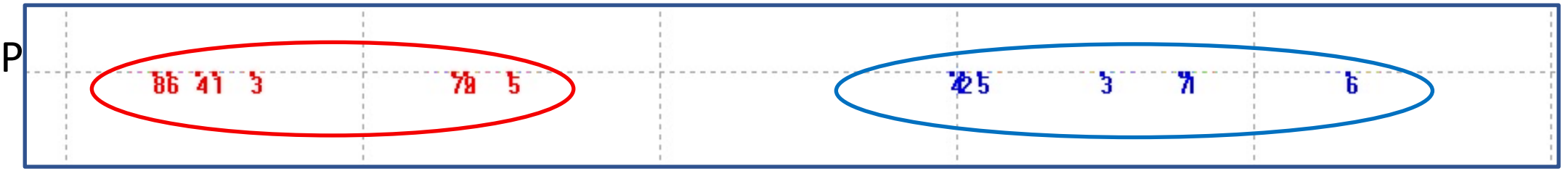
Relazione tra spettro GC-MS e Naso elettronico

Analisi Dati naso elettronico. Sani Vs CRC





CANONICAL P

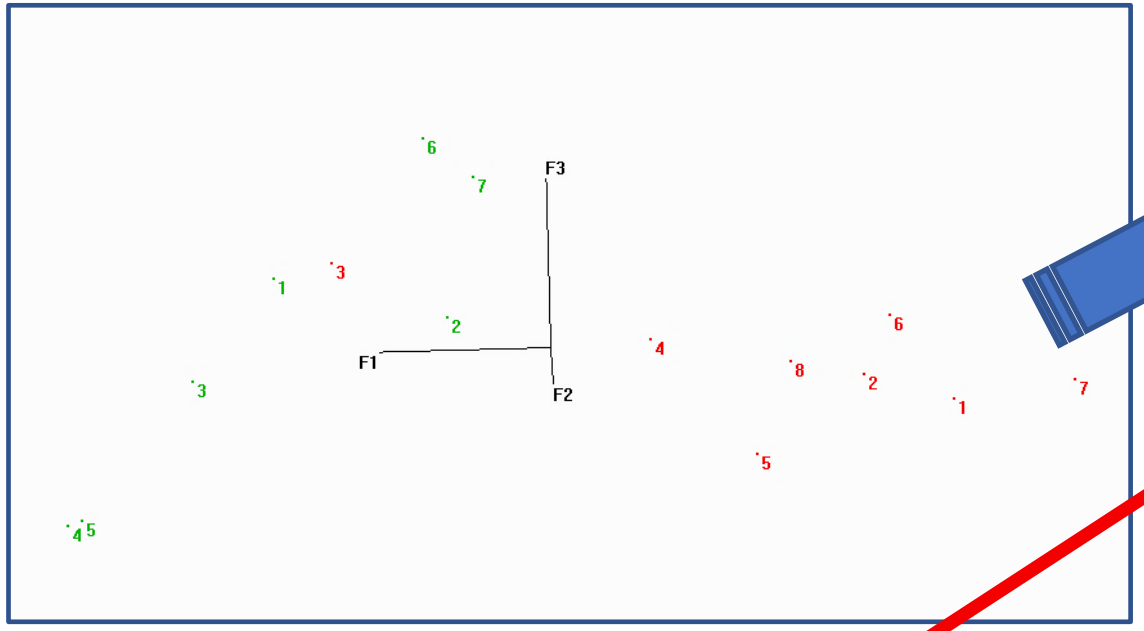


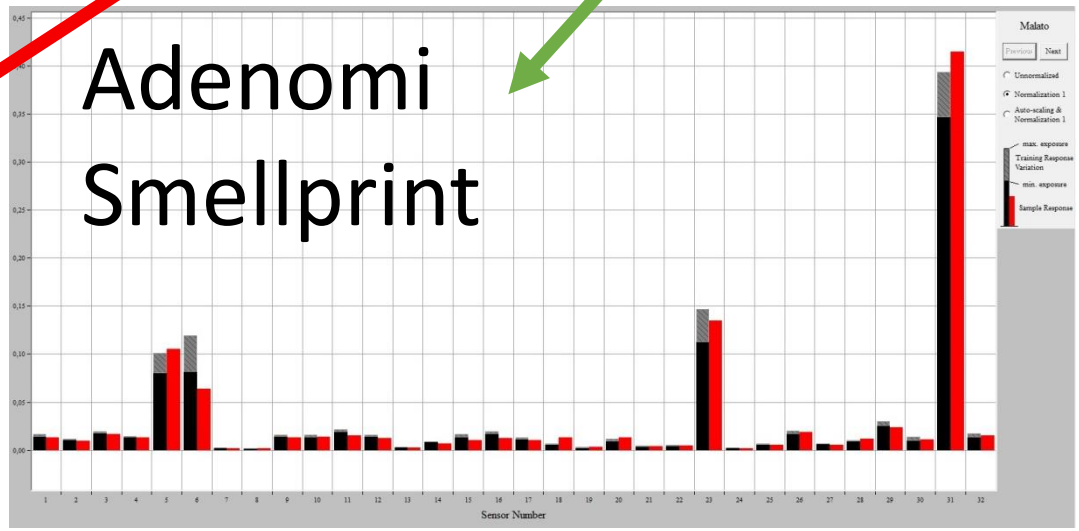
Indicazioni produttore- Metodo può essere accettato per:

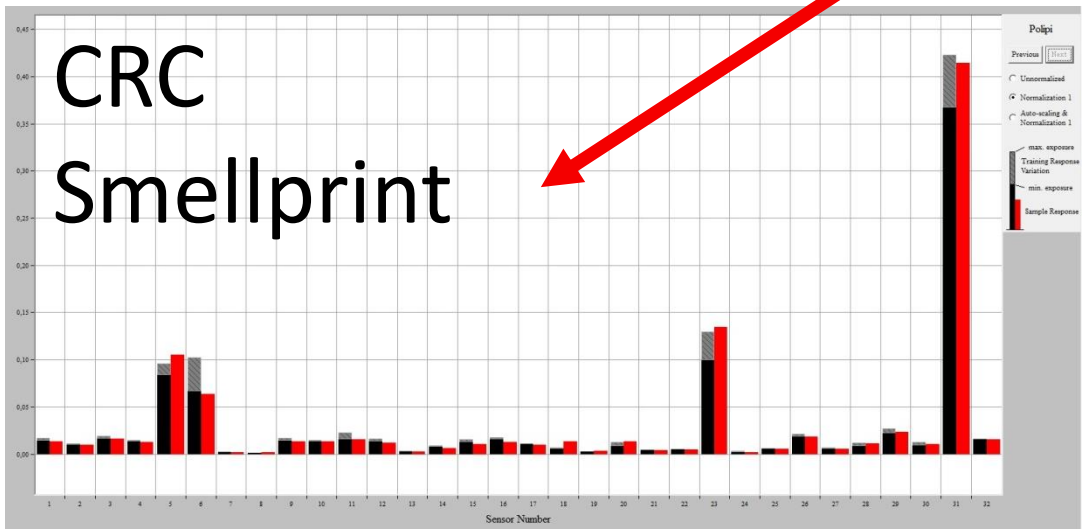
Cross-validation > 90%

Distanza Euclidea tra I gruppi >/= 5.0 (manufacturer).

Analisi dati: Adenomi Vs CRC



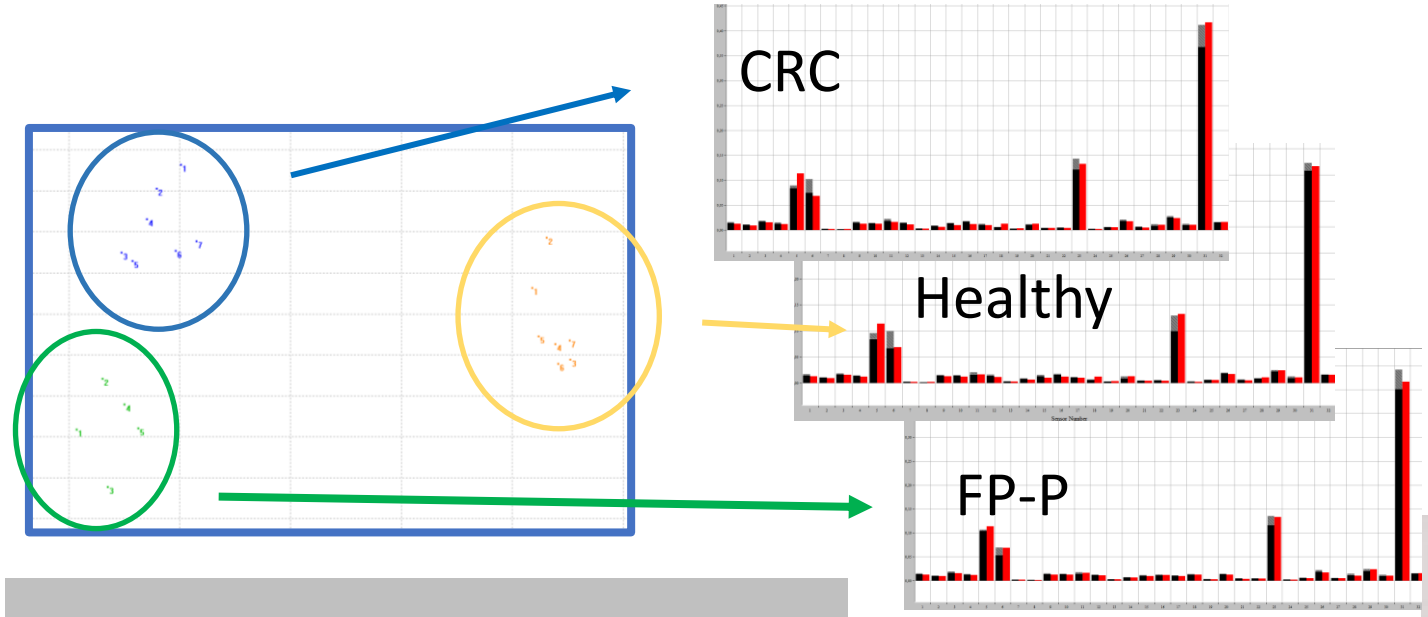




Cross-validation 100%

Distanza tra gruppi 7.65

Sani Vs Adenomi Vs CRC



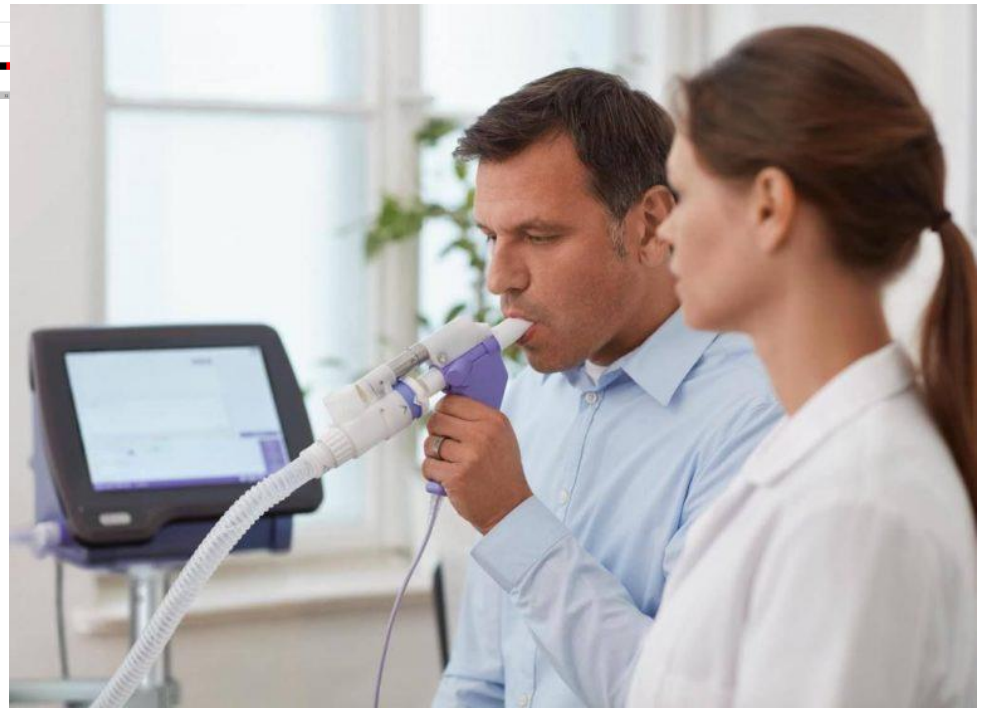
Cross-validation reliability of 100% between classes. Near the clinical setting

Identified As

Trained As	Sano	FPS-P	MalPre
Sano	7	0	0
FPS-P	0	5	0
MalPre	0	0	7

Interclass M-Distances

	Sano	FPS-P	MalPre
Sano		5,352	17,957
FPS-P			20,142
MalPre			



Analisi Dati naso elettronico. Sani / AA / CRC

I dati raccolti confermanto l'ipotesi di partenza. L'espirato di soggetti normali, affetti da adenomi e da neoplasia possono essere caratterizzati dall'analisi dei composti volatili contenuti nell'espirato.
Possono essere analizzati di routine ricorrendo ai Nasi elettronici

sani	64
LRA	14
HRA	14
CRC	32
Tot	124

	M1	M2		M3
CROSS VALIDATION	100%	100%		100%
Dist S-AD	5,91	6,282	CRC-FPSS	6,855
Dist S-CRC			CRC-FPP	4,645
			FPS-FPP	6,25
Sensori esclusi	(2;3;5;7;9;14;20)	(1;3-5;7;9;13-14;16-20;22-23;26-30)		(5;9;13;14;16;25;26;27;29)

Lo studio è stato prolungato come studio prospettico per completare la valutazione degli algoritmi ottenuti sul primo gruppo di soggetti

GRAZIE
DELL'ATTENZIONE