Exhalon

Pr Stanislas GRASSIN DELYLE

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INSERM U1173 « Infection et inflammation »

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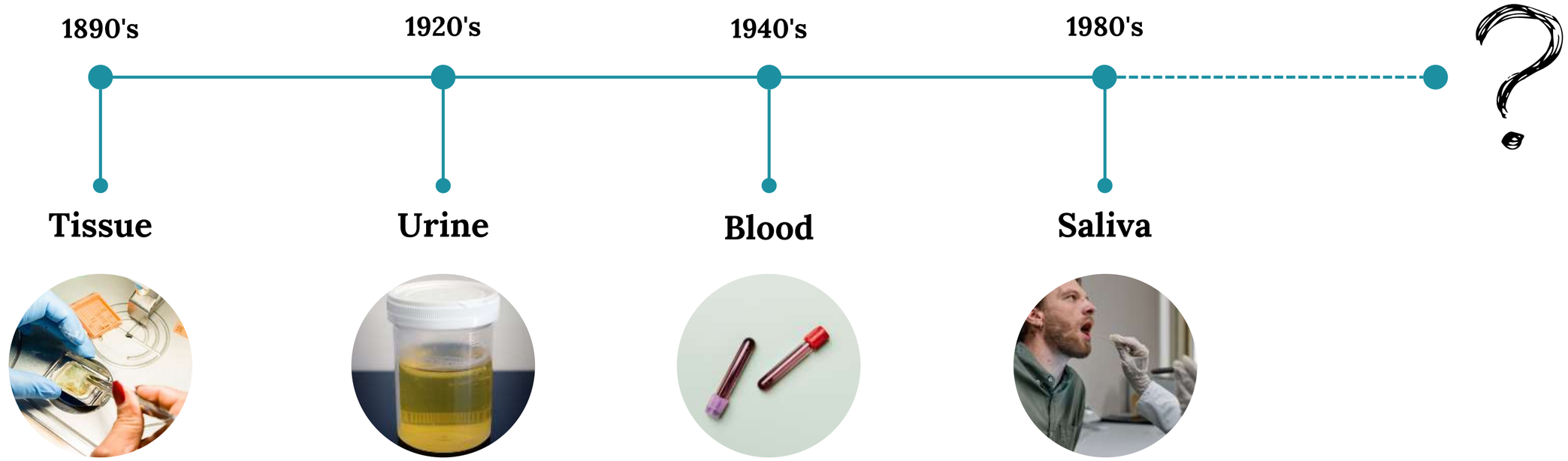
Real-time breath analysis for precision medicine

Advancing healthcare

Throughout history, humanity's drive to advance healthcare has fuelled an obsessive **exploration into novel methods for analysing the human body.**



Each new method has unlocked unprecedented insights, revolutionizing medical diagnostics and treatment strategies. **Is there something left to explore?**

Advancing healthcare

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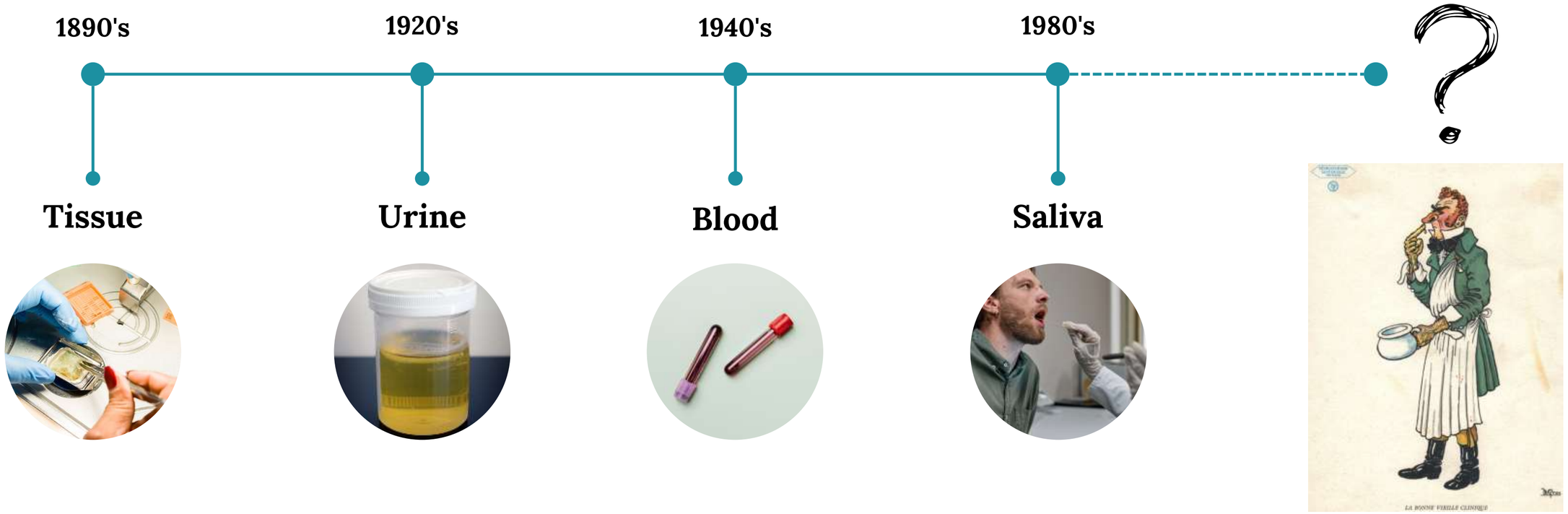
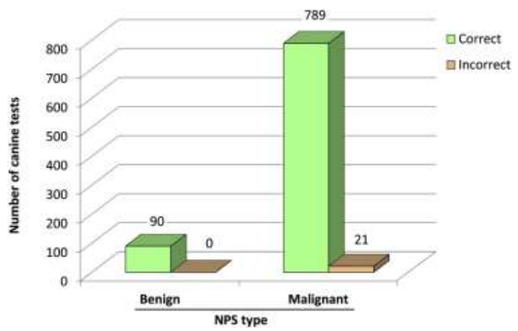


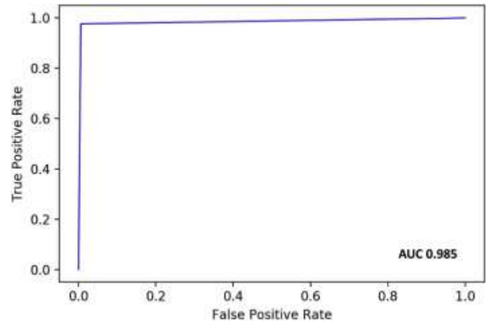
Each new method has unlocked unprecedented insights, revolutionizing medical diagnostics and treatment strategies. **Is there something left to explore?**

The olfactive signature of diseases

Dogs have demonstrated that **humans produce and emit specific chemicals through their breath that can lead to highly accurate diagnostics**.



Nodule pulmonaire solitaire



Guaro *et al., Lung Cancer*, 2019

Olfactive analysis advantages

Even though **dogs may be superior to some aspects of reference methods, their lack of standardization means they can't reach clinical adoption.**

Gold Standards

- Imaging
- Molecular biology
- Blood tests
- Histopathology

VS

✗	**Non-invasiveness**	✓
✗	**Speed**	✓
✗	**Cost-effectiveness**	✓
✓	**Standardization**	✗

Breath analysis medical device

A real-time breath analysis medical device would allow for standardized, mesurable, and highly reproducible breath diagnostics, making its mainstream adoption possible.

Non-invasiveness

Speed

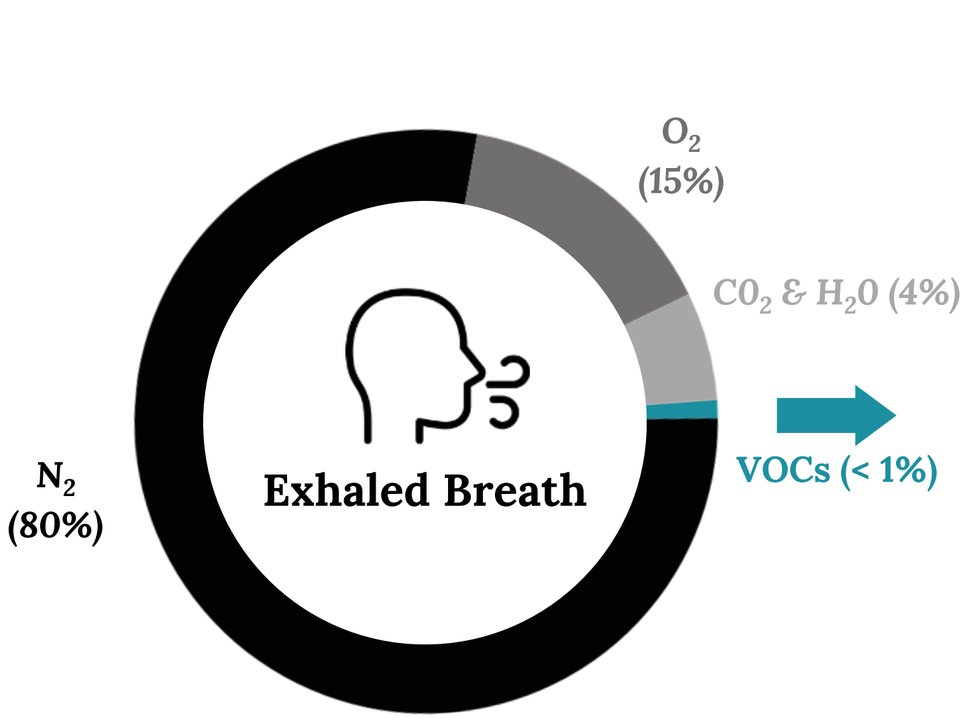
Cost-effectiveness

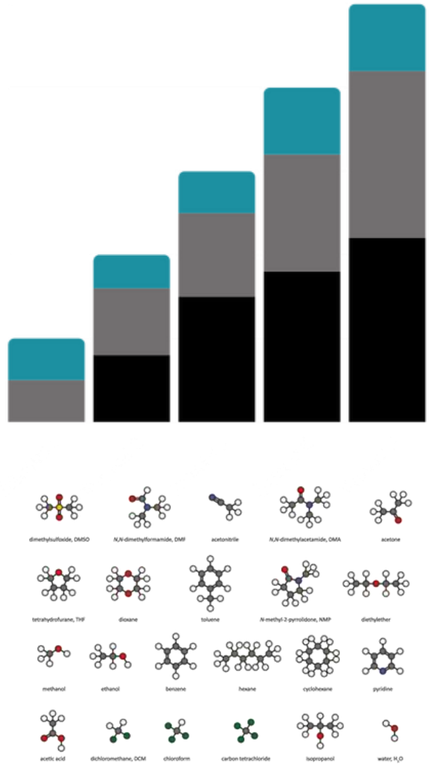
Standardization

The science behind

By analysing **Volatile Organic Compounds** in breath we gain access to patient-specific information:

Breath-Based Biomarkers





Breath signatures

- Diagnostics
- Endotyping
- Treatable traits

The science behind

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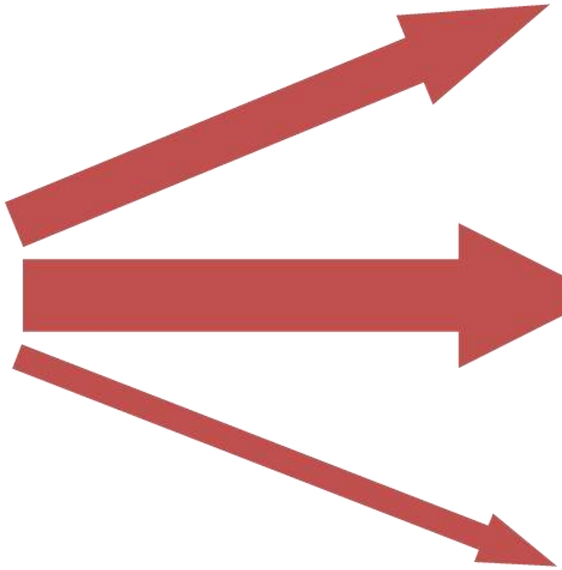
Breath-Based Biomarkers

Metabolite

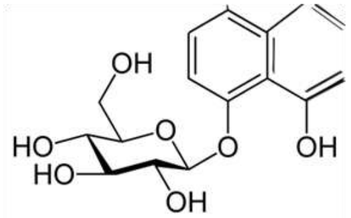


VOC VOC VOC

VOC VOC VOC VOC VOC VOC VOC VOC VOC

- **Lung diseases ++**
- **Oncology (bladder, prostate, breast...)**
- **Alzheimer's disease**
- **Diabetes**
- **Liver cirrhosis**
- **Heart or kidney failure...**

VOC



Current attempts

	Non-invasiveness	Speed	Cost-effectiveness	Accuracy	
E-Noses	✓	✓	✓	✗	
GC-MS	✓	✗	✗	✓	

- **GC-MS (*Gas Chromatography-Mass Spectrometry*)**: *A technique that separates and identifies compounds in a sample based on their mass.*
- **E-Noses (Electronic Noses):** *Devices that mimic the human sense of smell to detect and identify complex odors and volatile organic compounds through sensor arrays and pattern recognition algorithms.*

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A novel approach

E-Nose *GC-MS* *Real-time MS?*

World's most advanced real-time gas analyzer

Perfect for our Robotic Dog?

Current utilization

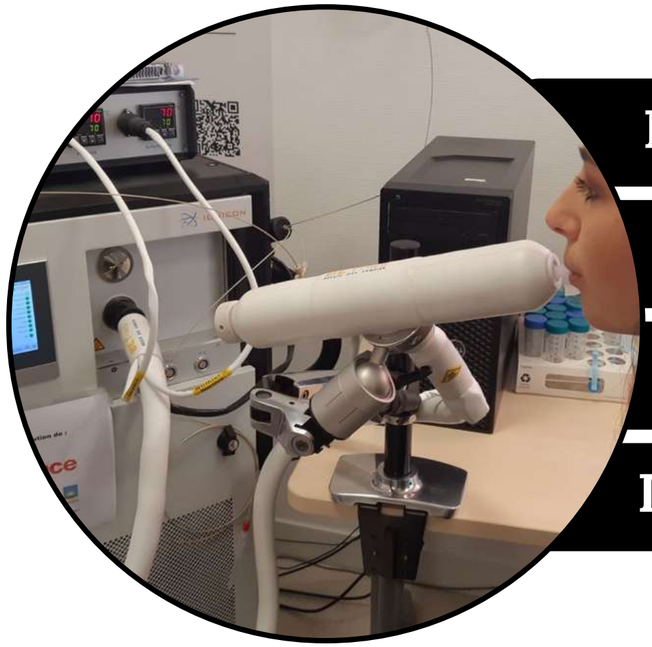
- Air quality monitoring
- Biological research
- Semiconductors

- **Non-invasive**
- **Rapid**
- **Cost-effective**
- **Accuracy**

In 2018, a team from Hospital Foch and Université Paris - Saclay / UVSQ medicine faculty partnered together to **explore a different technological approach**

Real-time breath analysis

Diagnosis in < 1 minute



Early diagnosis

Phenotyping

Monitoring

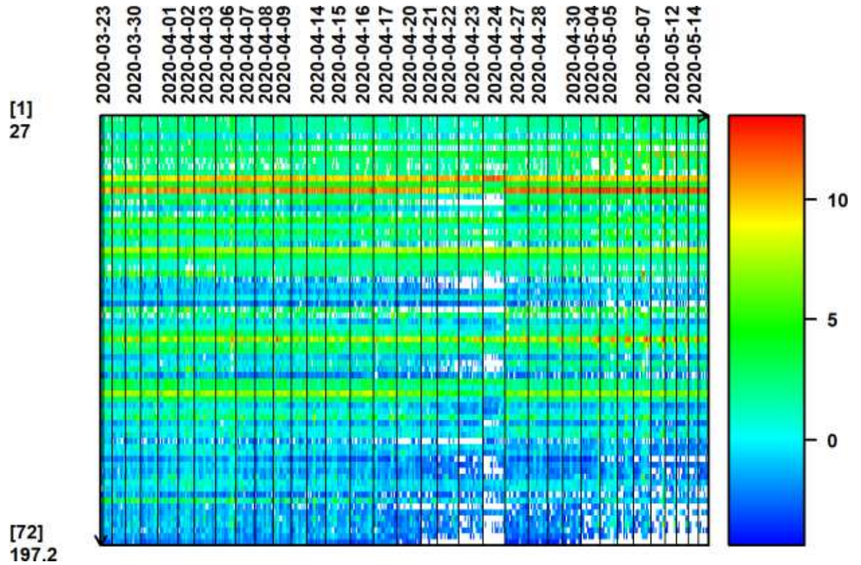
Drug response

COVID-19

RECORDS study: intubated, mechanically ventilated patients

Longitudinal analysis of exhaled breath from 40 ARDS patients: 299 measurements

	COVID-19 ARDS	Non-COVID-19 ARDS
Number of patients (*n*)	28	12
Males/females (*n*)	20/8	6/6
Age (years)	61 [55-72]	72 [54-79]
Body weight (kg)	80·0 [66·6-87·6]	86·5 [65·3-94·1]
Height (cm)	170 [164-175]	173 [169-175]
Body mass index (kg/m^2)	26·3 [23·7-32·4]	28·9 [23·0-30·9]
SAPS II score in the first 24 hours	62 [49-68]	46 [40-57]
SOFA score in the first 24 hours	11 [7-12]	8 [5-12]



ptairMS

Bioinformatics, 38(7), 2022, 1930–1937
https://doi.org/10.1093/bioinformatics/btac031
Advance Access Publication Date: 19 January 2022
Original Paper

OXFORD

Gene expression

ptairMS: real-time processing and analysis of PTR-TOF-MS data for biomarker discovery in exhaled breath

Camille Roquencourt [1,*], Stanislas Grassin-Delyle[2,3,4] and Etienne A. Thévenot [5]

Roquencourt *et al.*, *Bioinformatics*, 2022; Grassin Delyle *et al.*, *EBioMedicine*, 2021

COVID-19

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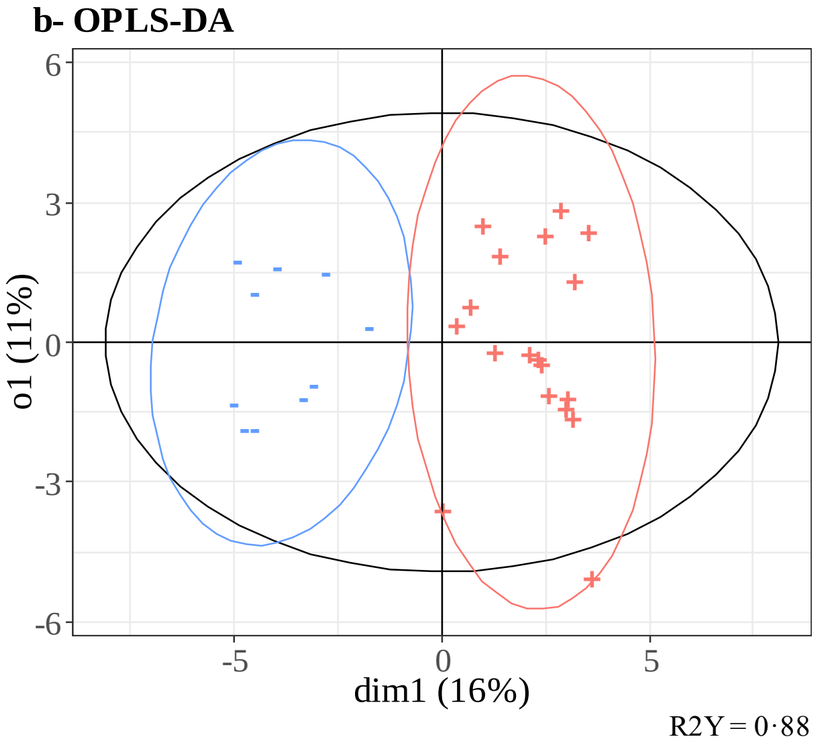

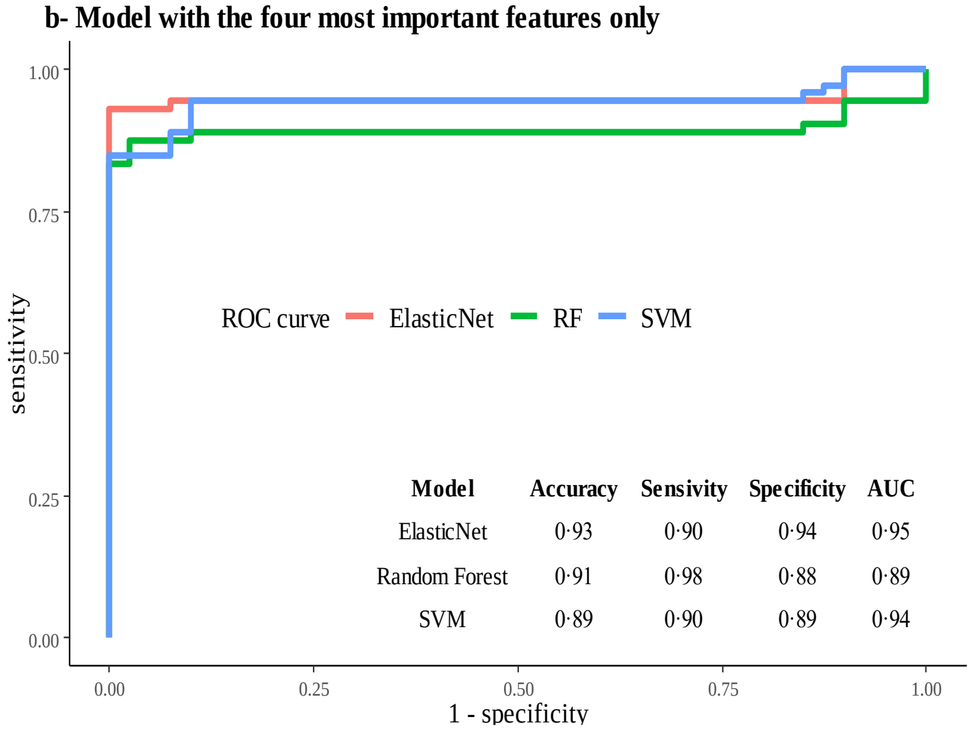

Grassin Delyle *et al.*, *EBioMedicine*, 2021

COVID-19

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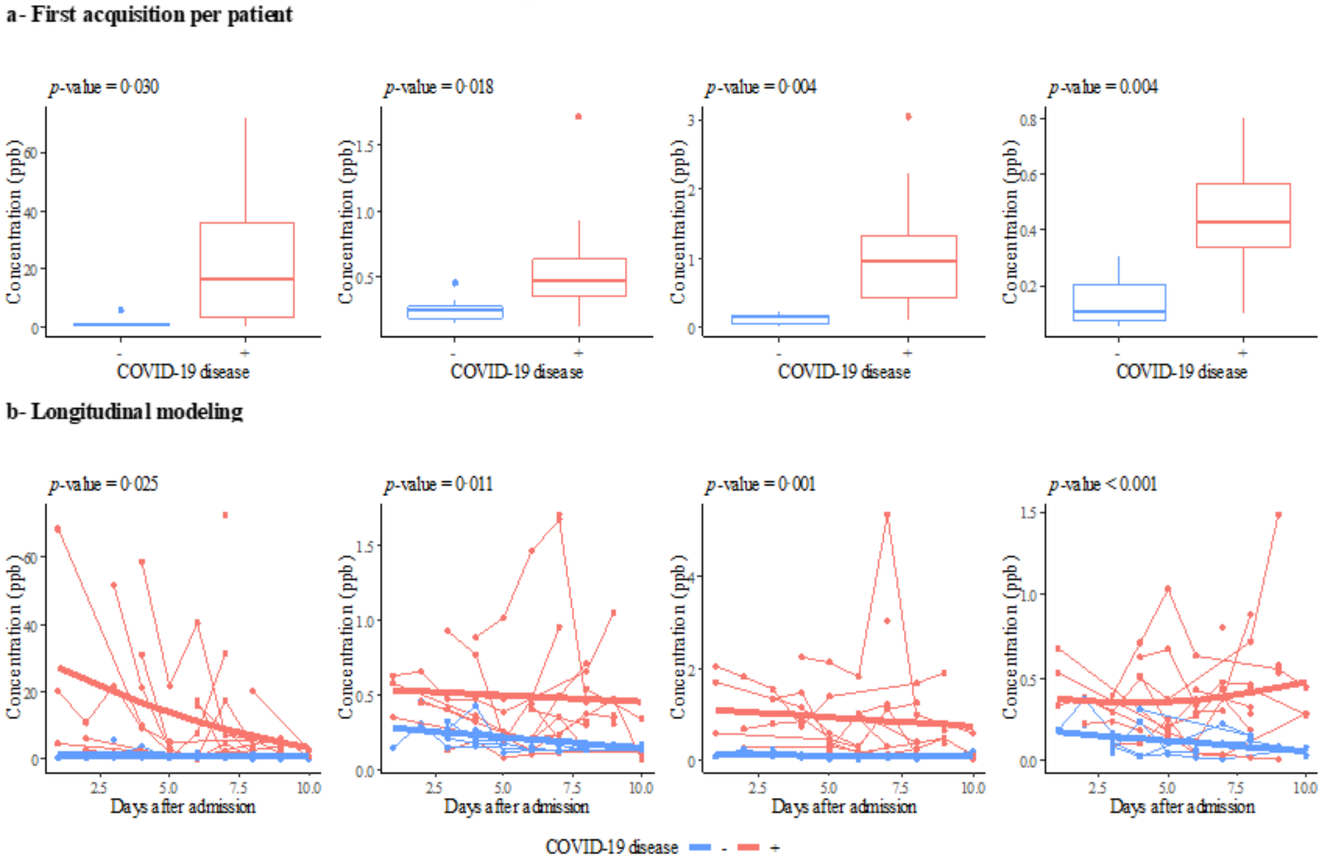
Longitudinal analysis



Patent WO 2022/058796

Grassin Delyle *et al.*, *EBioMedicine*, 2021

COVID-19

Is artificial-intelligence-enhanced real-time MS breath analysis a reliable, safe, rapid means of screening **ambulatory patients** for COVID-19?

COVID-19

	COVID - (*n* = 106)	COVID + (*n* = 67)	*p* value
Sex (M/F)	50/56	31/36	1
Age	46 ± 18	56 ± 14	<0.001
Patients / volunteers (*n*)	97 / 9	67 / 0	-
Presence of: (*n* (%))			
- Fever	15 (14.2%)	32 (47.8%)	<0.001
- Cough	12 (11.3%)	39 (58.2%)	<0.001
- Dyspnoea	12 (11.3%)	34 (50.7%)	<0.001
- Anosmia	3 (2.8%)	10 (14.9%)	0.003
- Ageusia	1 (0.9%)	7 (10.4%)	0.004
- Fatigue	8 (7.5%)	30 (44.8%)	<0.001
- Aches	6 (5.7%)	17 (25.4%)	<0.001
Symptom score:	0.32 ± 0.66	2.2 ± 1.1	<0.001
Medical history: (*n* (%))			
- High blood pressure	12 (11.3%)	19 (28.4%)	0.008
- Asthma	3 (2.8%)	9 (13.4%)	0.018
- Overweight	5 (4.7%)	8 (11.9%)	0.144
- Diabetes	5 (4.7%)	7 (10.4%)	0.255
- Organ transplant	1 (0.9%)	4 (6.0%)	0.055
Previous COVID-19 infection	12 (11.3%)	0 (0%)	-
COVID-19 vaccination:	79 (74.6%)	13 (19.4%)	<0.001
Previous treatment with corticosteroids	5 (4.7%)	33 (49.3%)	<0.001

- Two **prospective, open, interventional studies**
- University hospital: Foch Hospital, Suresnes, France
- **Metabolomic analysis of exhaled breath** *vs* RT-PCR
- Proton transfer reaction time-of-flight mass spec.
- **Artificial intelligence** and machine learning techniques

173 participants

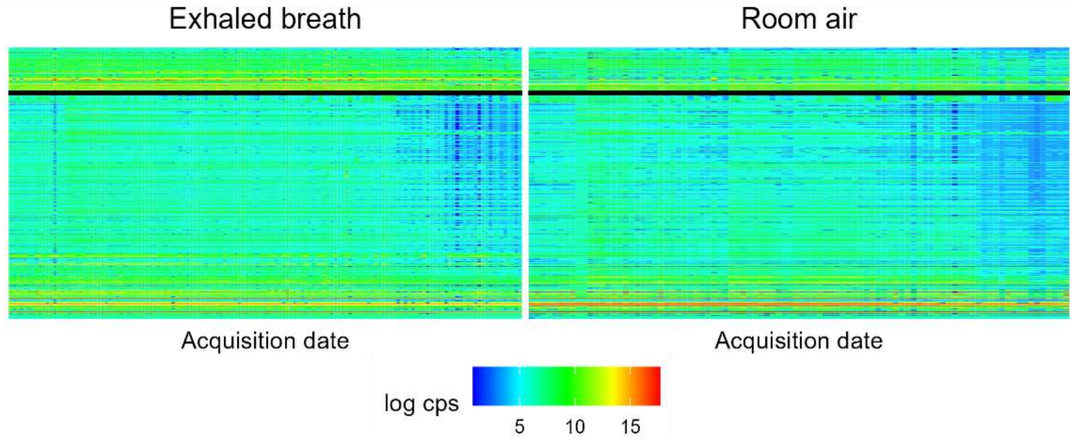
Roquencourt *et al.*, *ERJ. Open Res.*, 2023

COVID-19

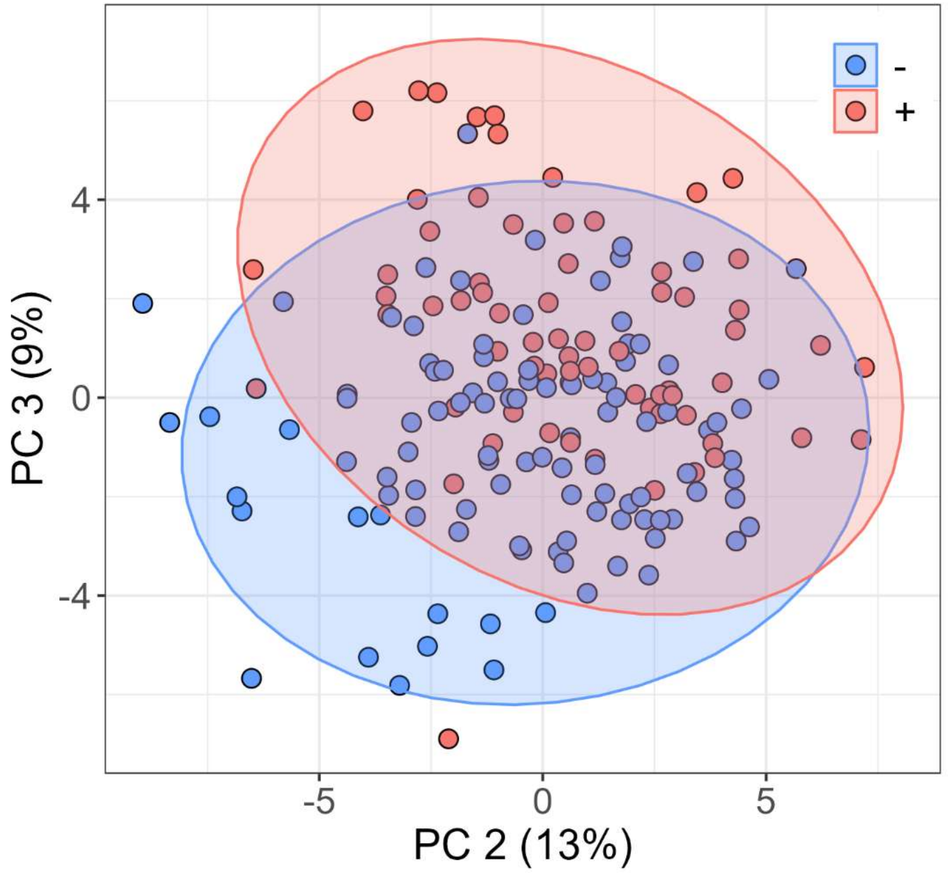
Volatile organic compounds

347 features detected

71 VOCs



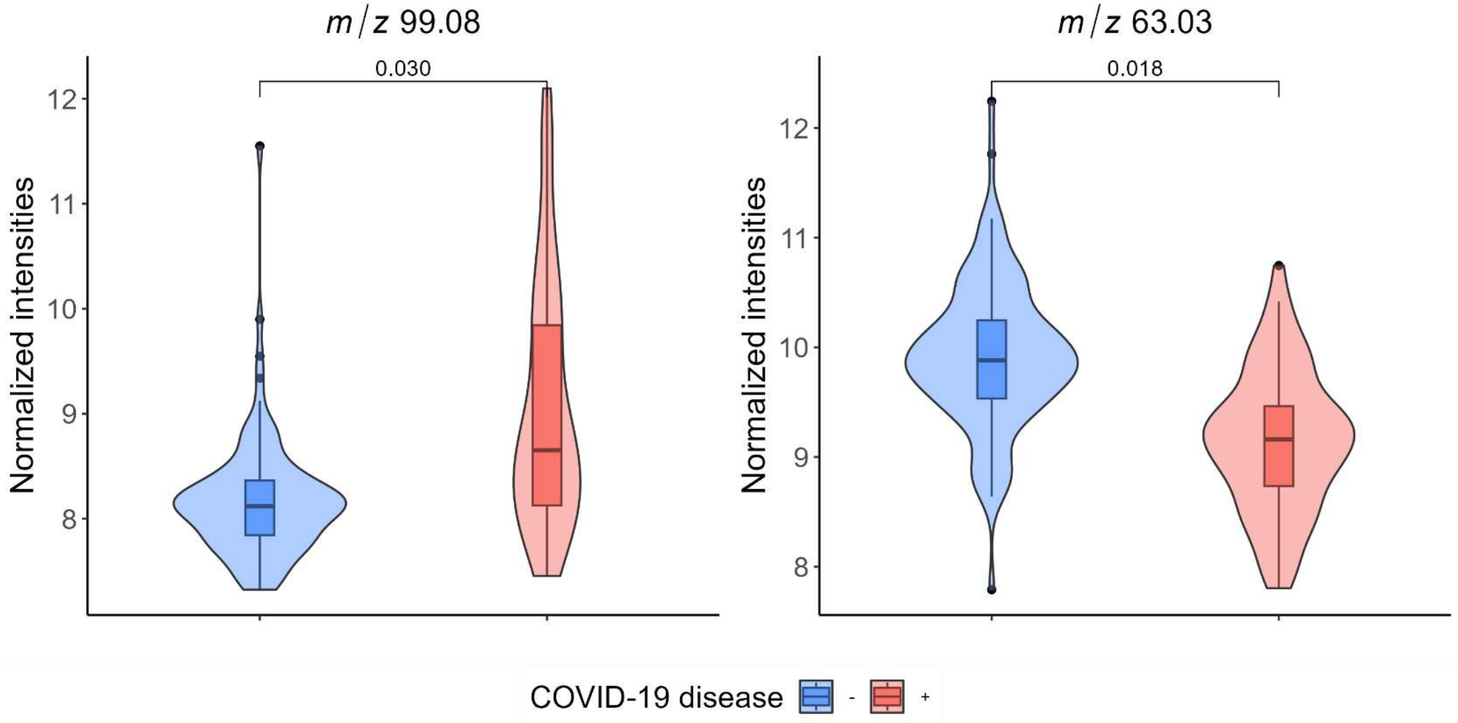
Unsupervised analysis



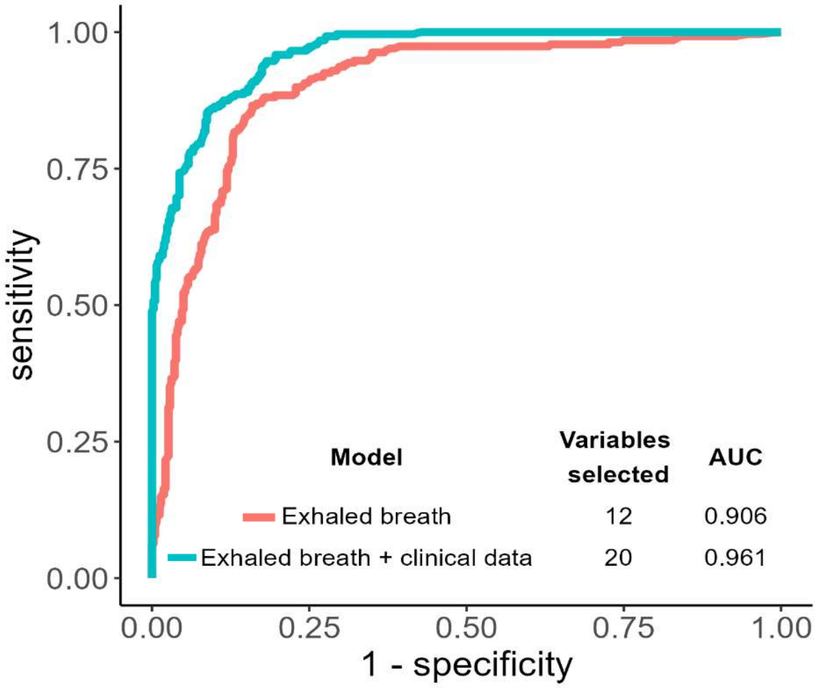
Roquencourt *et al.*, *ERJ. Open Res.*, 2023

COVID-19

Set of VOC biomarkers



Diagnostic performance



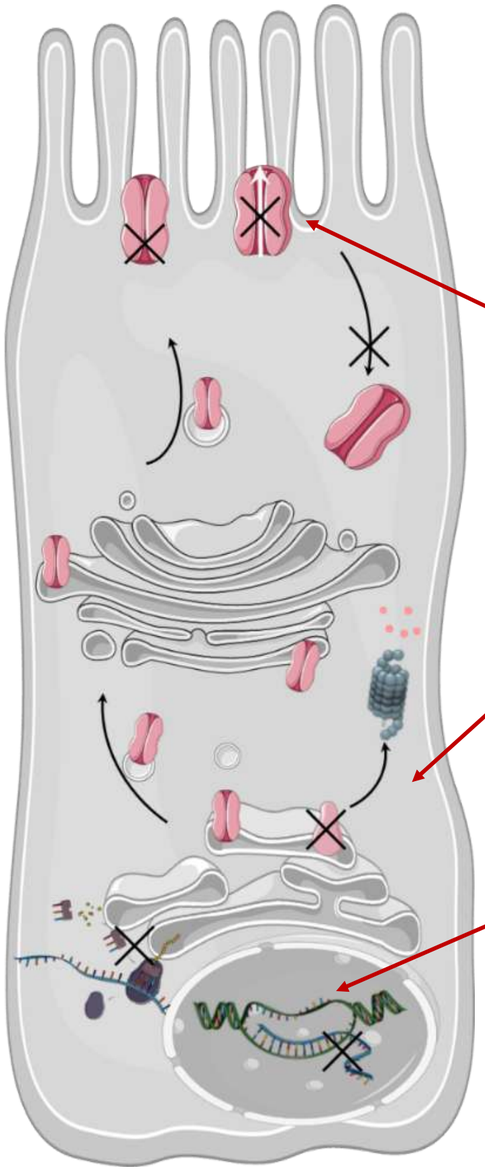
Predictive performance similar for asymptomatic, weakly symptomatic and symptomatic participants and not biased by the COVID-19 vaccination status

Sensitivity: 98% Specificity: 74%
Negative predictive value: 98%
Positive predictive value: 72%

IA for combining breath analysis and patient metadata → predictive performances improved

Roquencourt *et al.*, *ERJ. Open Res.*, 2023

Cystic fibrosis: drug therapy with CFTR modulators



Impaired functionning or stability

Impaired trafficking

F508del

Impaired production

G542X

- Potentiators: Ivacaftor
- Correctors: Tezacaftor + Elexacaftor

Kaftrio®

➢ CFTR modulators restore the CFTR protein at the membrane

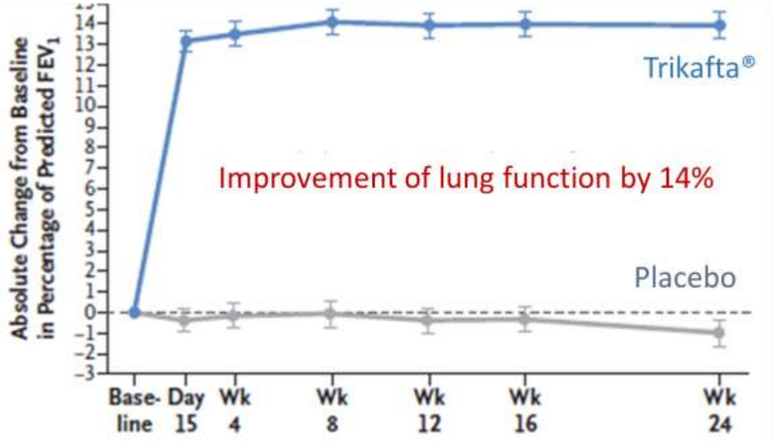
Pranke et al, Front Pharmacol. 2019

Projet Emmanuelle Bardin

Collaboration I. Sermet (Necker) + S. Fowler (U. Manchester)

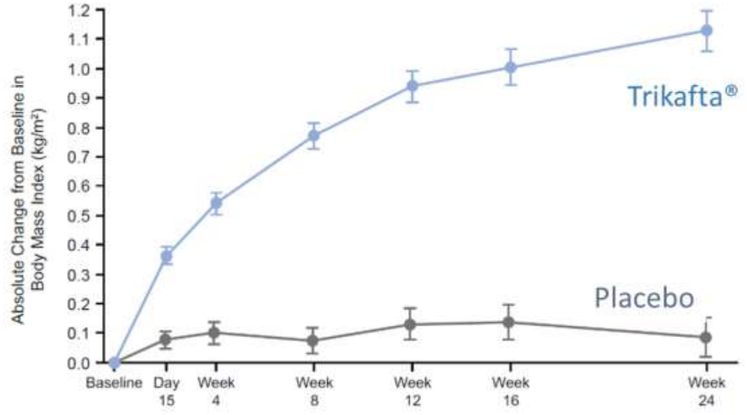
Cystic fibrosis: drug therapy with CFTR modulators

- Lung function

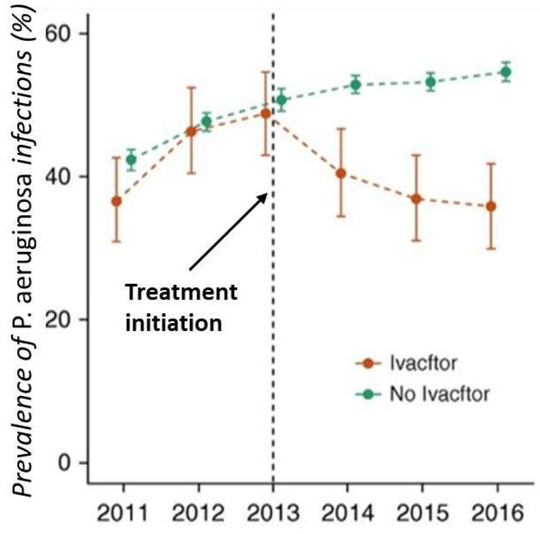


Middleton et al, NEJM 2019

- BMI



- Infection rate

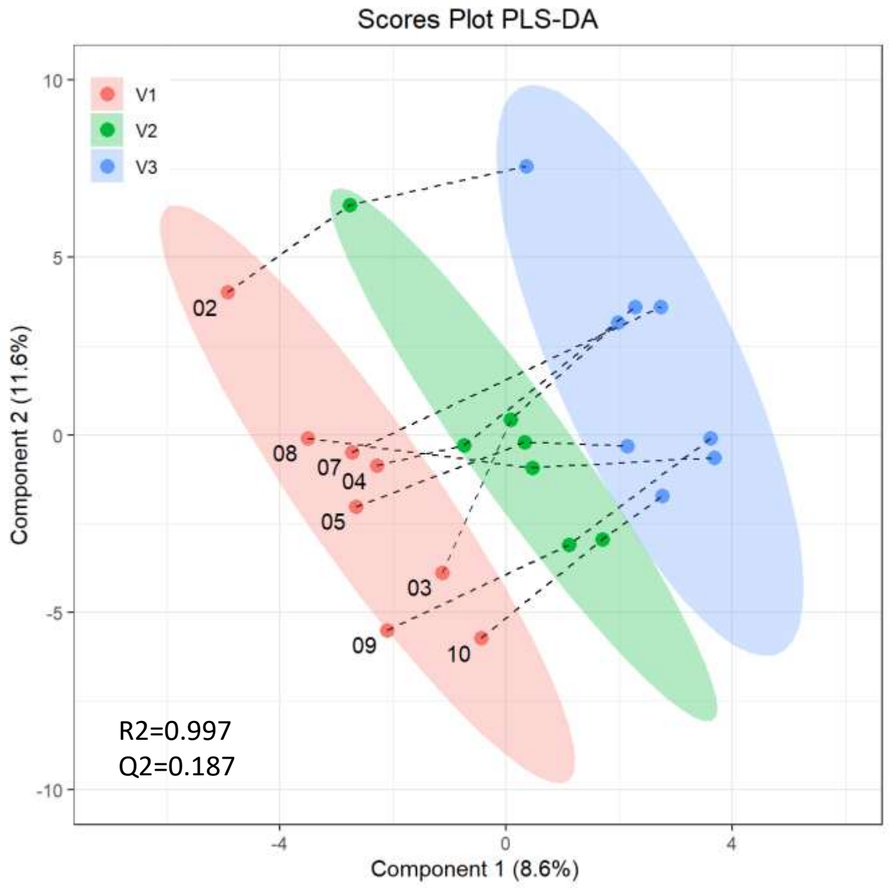


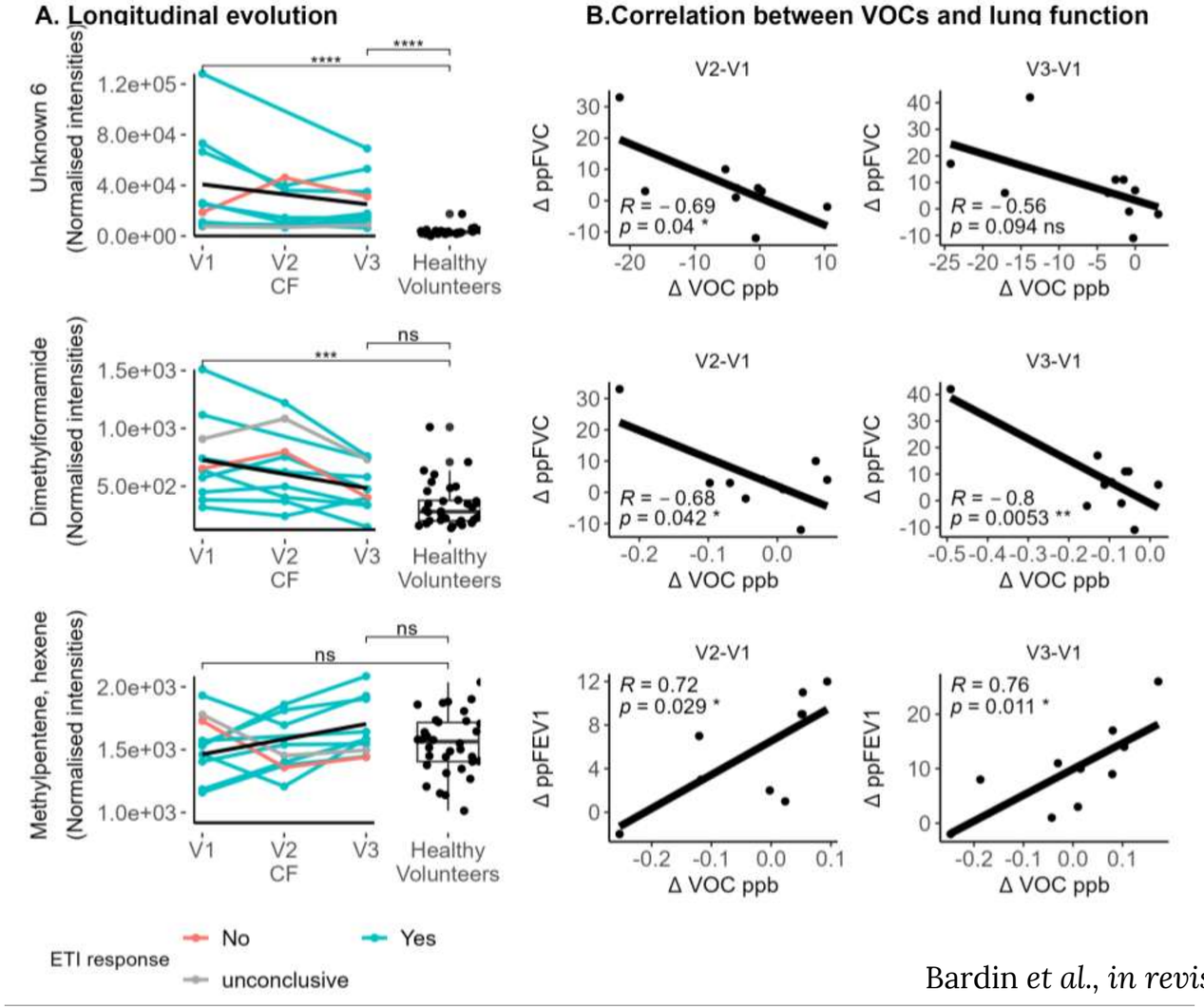
Frost et al. Annals American Thorac Soc 2019

⇒ Identification / monitoring of responders / non-responders?

Cystic fibrosis: drug therapy with CFTR modulators

VOC-Kaftrio study: adult cohort (10) initiating ETI

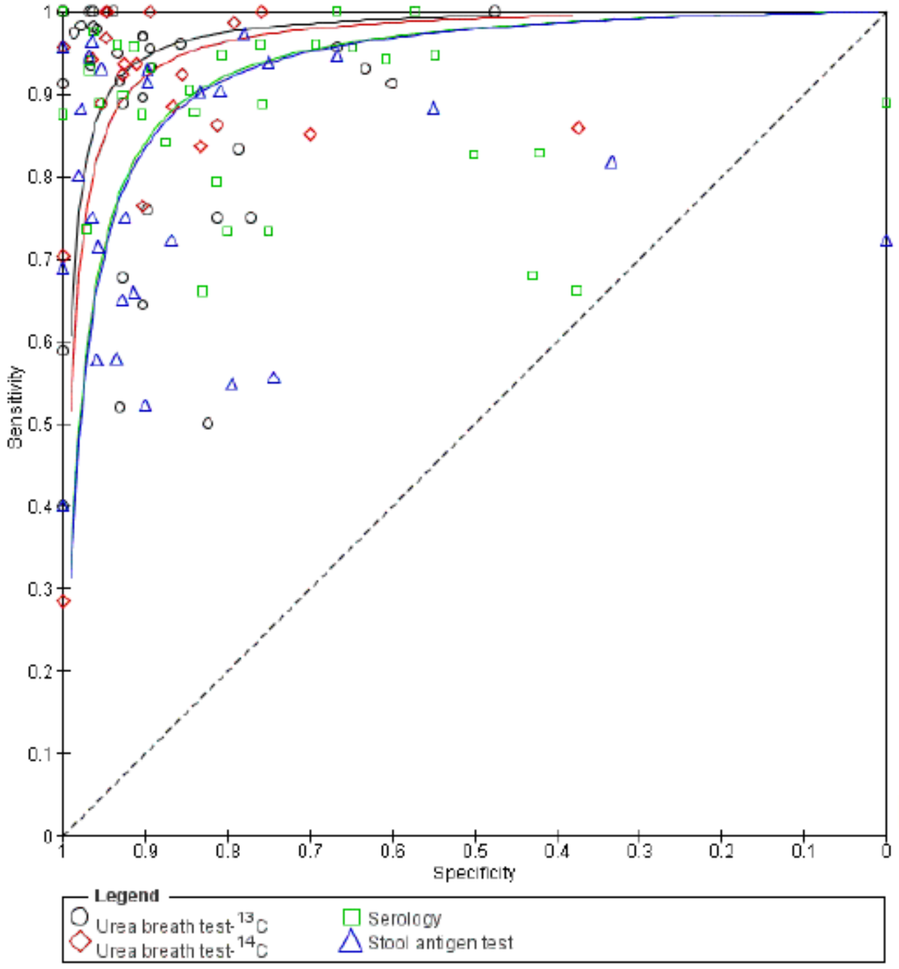




Bardin *et al.*, *in revision*

Current tests: offline breath analysis

Urea test for the diagnosis of *Helicobacter pylori* infection



HAS
HAUTE AUTORITÉ DE SANTÉ

CNPHGE
Conseil National Professionnel d'Hépato-Gastroentérologie

PERTINENCE DES SOINS

Diagnostic de l'infection par *Helicobacter pylori* chez l'adulte

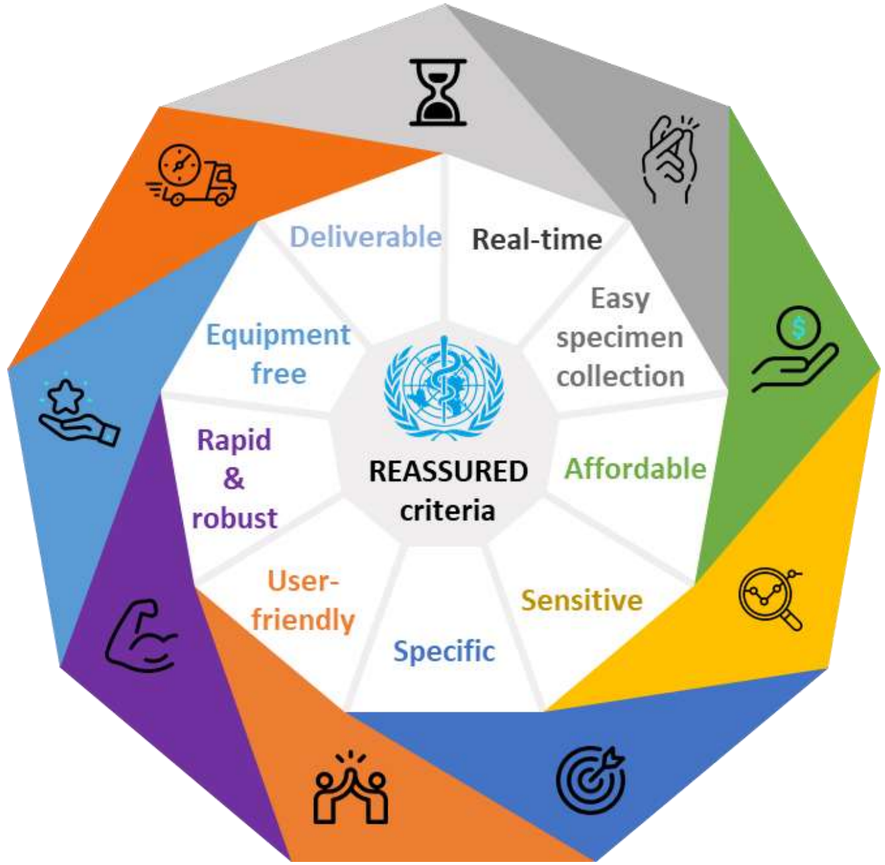
Mai 2017

→ **Le test respiratoire est performant pour le diagnostic avant traitement et pour le contrôle d'éradication mais il n'est remboursé que pour le contrôle d'éradication.**

Best *et al.*, *Cochrane Database Syst. Rev.*, 2018

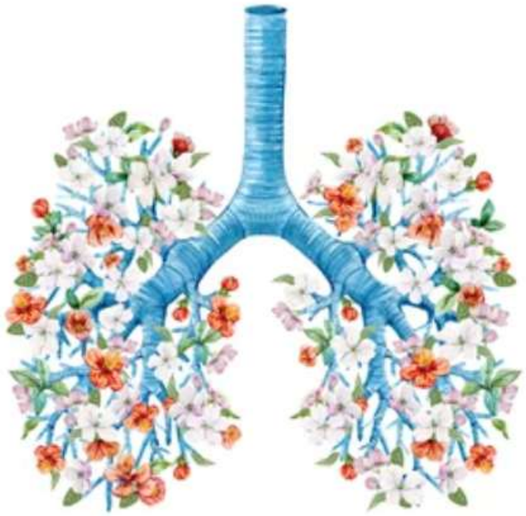
Real-time breath diagnostic tests

Meets most of **REASSURED criteria from WHO for an ideal test** that can be used at the point-of-care



World Health Organization

Thank You



EXHALOMICS

UVSQ université PARIS-SACLAY — UFR Simone Veil - Santé — CAMPUS DE SAINT-QUENTIN-EN-YVELINES

HOPITAL FOCH — Pour votre santé, Foch s'engage

université PARIS-SACLAY

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

SAINT QUENTIN EN YVELINES — Terre d'innovations

COMPREHENSIVE SEPSIS CENTER

FHU SEPSIS — Personalized Interventions

INVESTIR L'AVENIR

PROJET FINANCÉ PAR L'ANR — ANR — PROJECT FUNDED BY THE ANR

DE LA RECHERCHE À L'INDUSTRIE — cea

Inserm — La science pour la santé — From science to health

DIM 1 health — Un monde, une seule santé

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