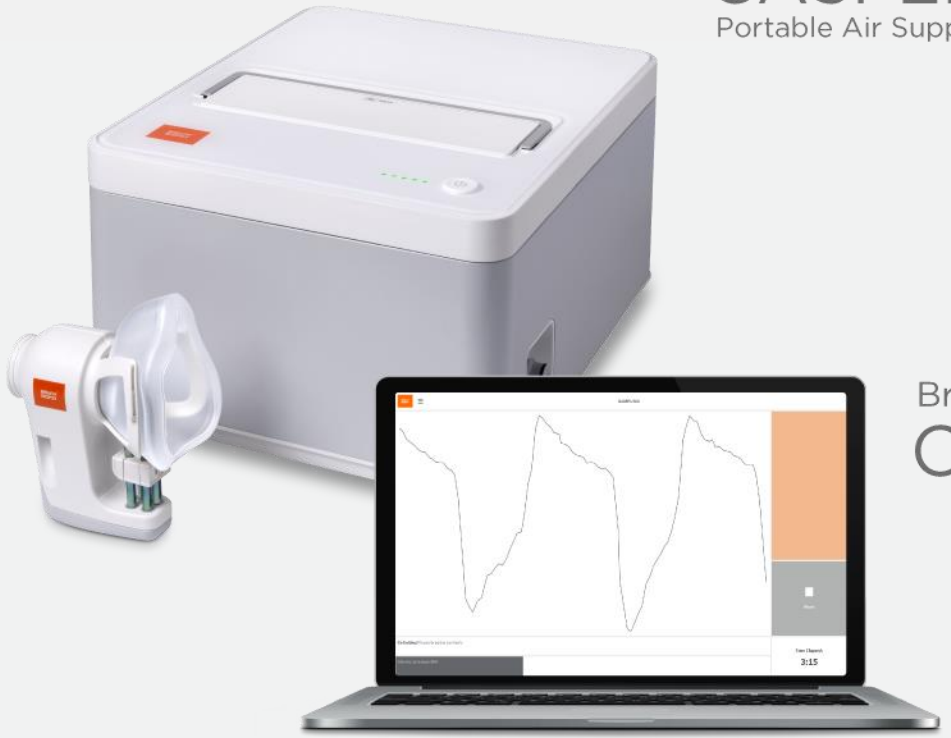
BREATH®
BIOPSY

CASPER™
Portable Air Supply



Breath Biopsy®
Collect

# ReCIVA®
## Breath Sampler

# Breath Biopsy® Services

## Breath Biopsy Conference 2019



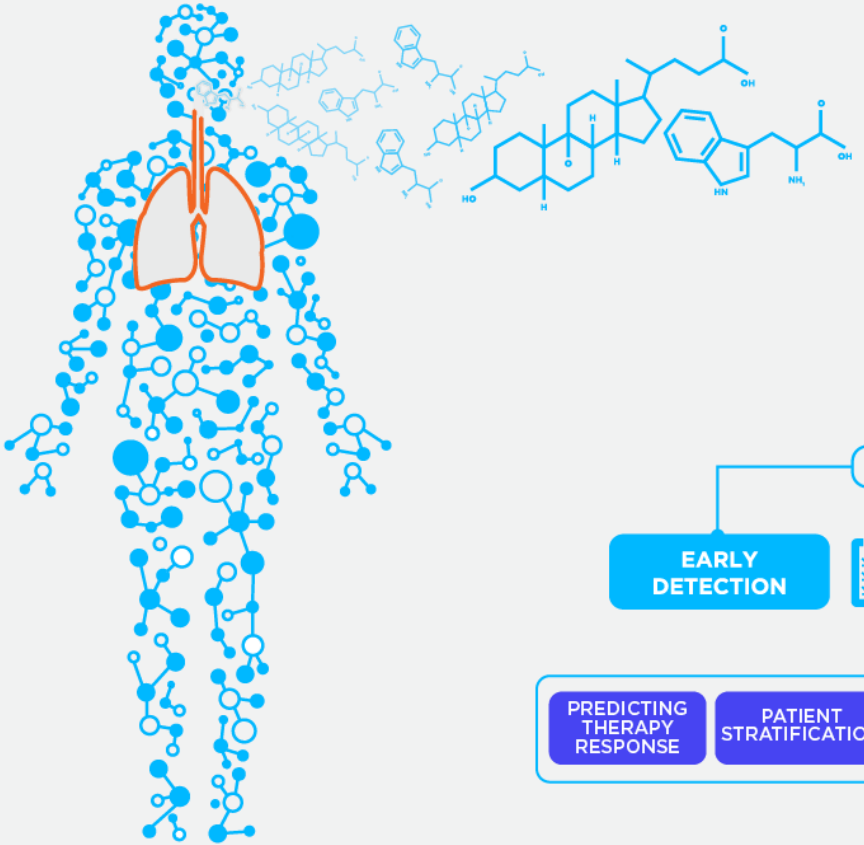
Huw Davies, PhD

huw.davies@owlstone.co.uk

**14th November 2019**

@owlstonemedical

# Breath Biopsy in Early Detection and Precision Medicine

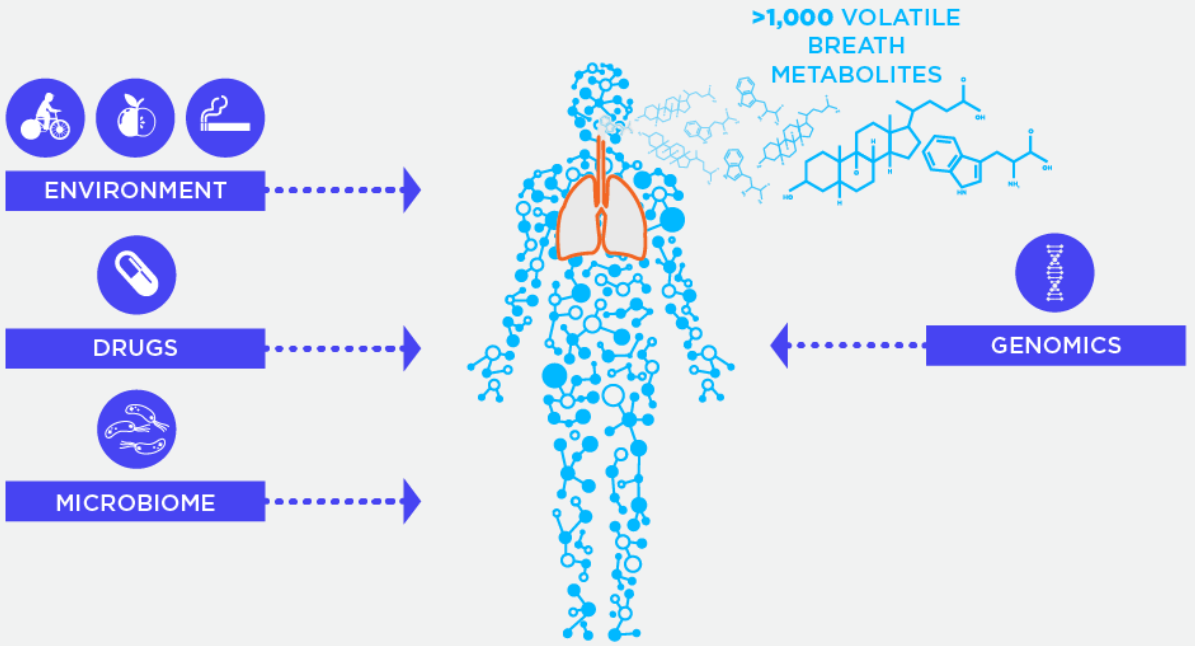


**>1,000 VOLATILE ORGANIC COMPOUNDS IN BREATH**

**BREATH BIOPSY® APPLICATIONS**

- **EARLY DETECTION**
- **PRECISION MEDICINE**
  - PREDICTING THERAPY RESPONSE
  - PATIENT STRATIFICATION
  - PREDICTING ADVERSE EVENTS
  - DISEASE PHENOTYPING
  - IDENTIFYING CONCURRENT INFECTIONS
  - DISEASE CONTROL/ MONITORING

# Sources of VOCs in Breath




**LIFESTYLE/EXPOSOME**

External factors like diet, exercise, medications, microbiota and even where we live influence our metabolic state.

**PHENOTYPE**

A snapshot of the current state of health that can be used to prevent, diagnose and treat disease or improve health.

**GENOTYPE**

Our genes can be markers of predisposition or presence of disease, but they do not necessarily give information about disease activity.

# Where Are We in Breathomics?

- Modern breath testing commenced in 1971, with the work of Nobel Prize-winner Linus Pauling
- Hundreds of scientific papers published suggesting the presence of VOC biomarkers across a range of diseases.

## SOME PUZZLING QUESTIONS

1 Why is there very little agreement in identified biomarkers within a disease?

2 Why is breath testing not used routinely in clinical settings?

## SOME HISTORICAL CHALLENGES

- Lack of maturity in breath sampling hardware and protocols for robust, repeatable sampling.

- Study design and size - small patient numbers in pilot studies and lack of blinded validation studies.

**WITHOUT ADDRESSING THESE CHALLENGES YOU CAN'T HAVE CONFIDENCE IN BIOMARKER DISCOVERY AND VALIDATION**

# ReCIVA® Breath Sampler for Collection of VOCs

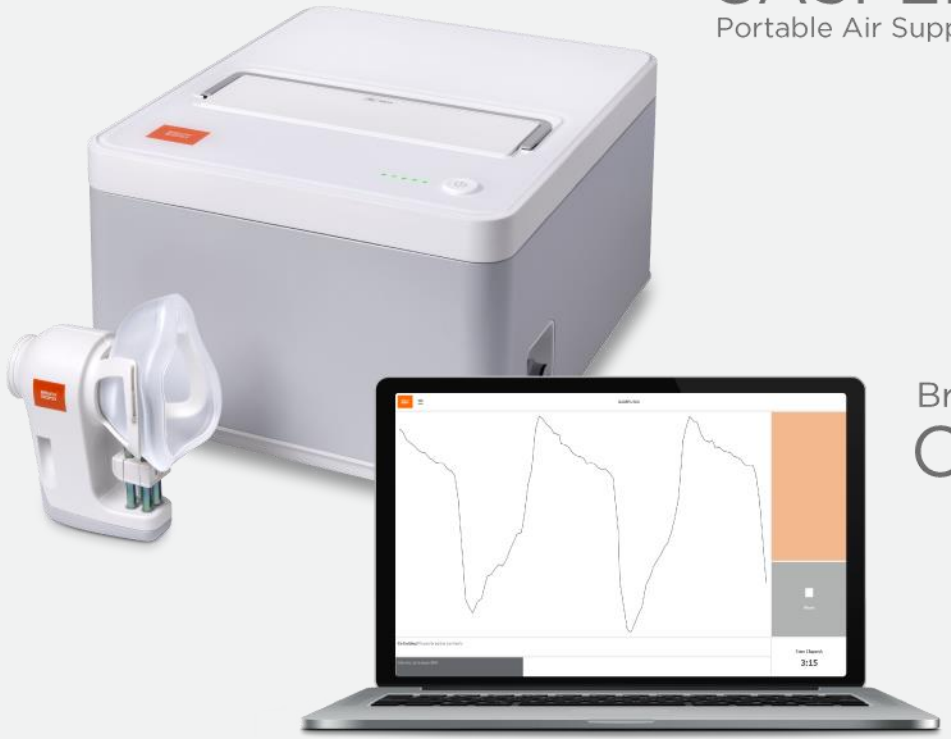

- Non-invasive, reliable and reproducible way to capture VOC biomarkers in breath samples
- Custom software learns individual breath profile to enable flexible breath collection. In-built $CO_2$ and pressure sensors facilitate selection of different volumes and fractions of breath through software (upper or lower airways or whole breath)
- Designed for ease of use with high patient safety and comfort
- No special handling or shipping requirements for breath samples
- CE marked and in use in over 100 clinics and academic settings

RECIVA SPEC SHEET

# Components of Collection Station

BREATH® BIOPSY

CASPER™
Portable Air Supply



ReCIVA®
Breath Sampler

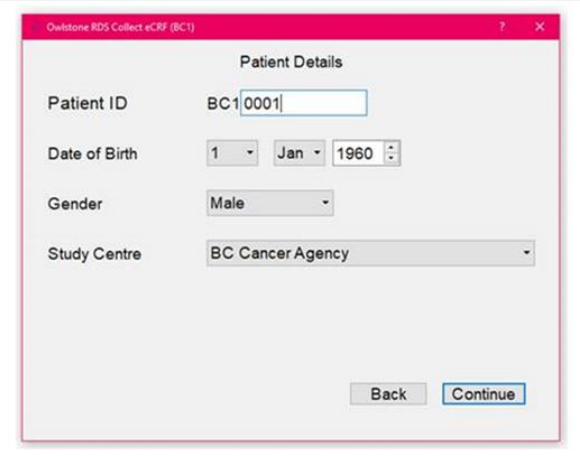
Breath Biopsy®
Collect

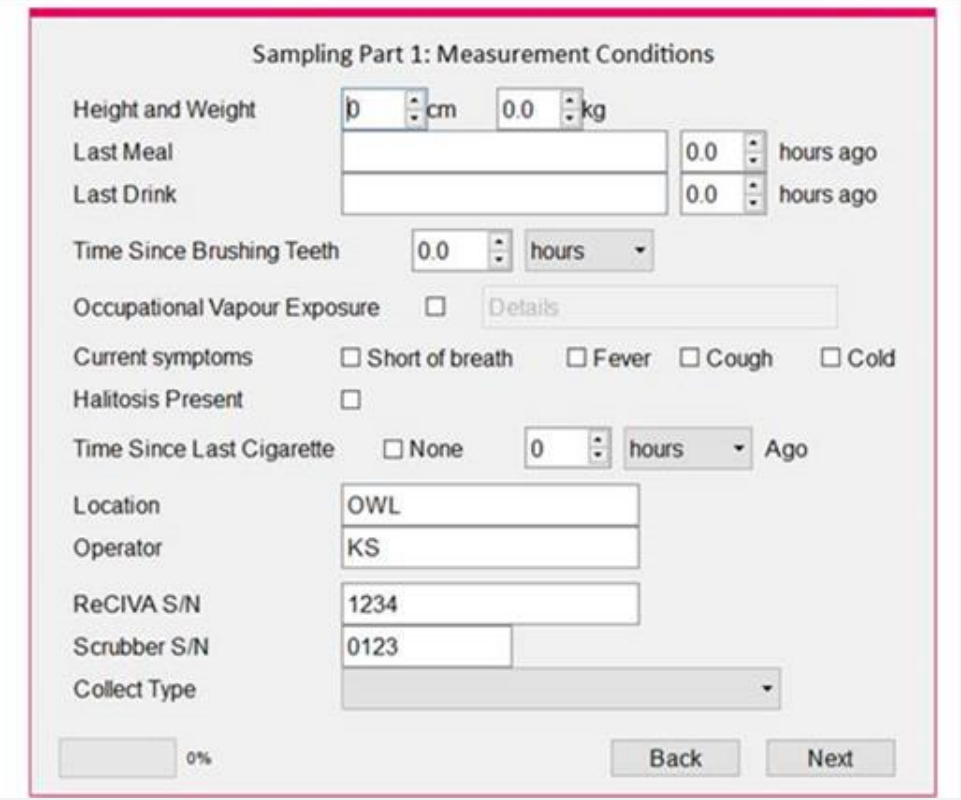
# Breath Biopsy Kits

Breath Biopsy Discovery VOC Kits

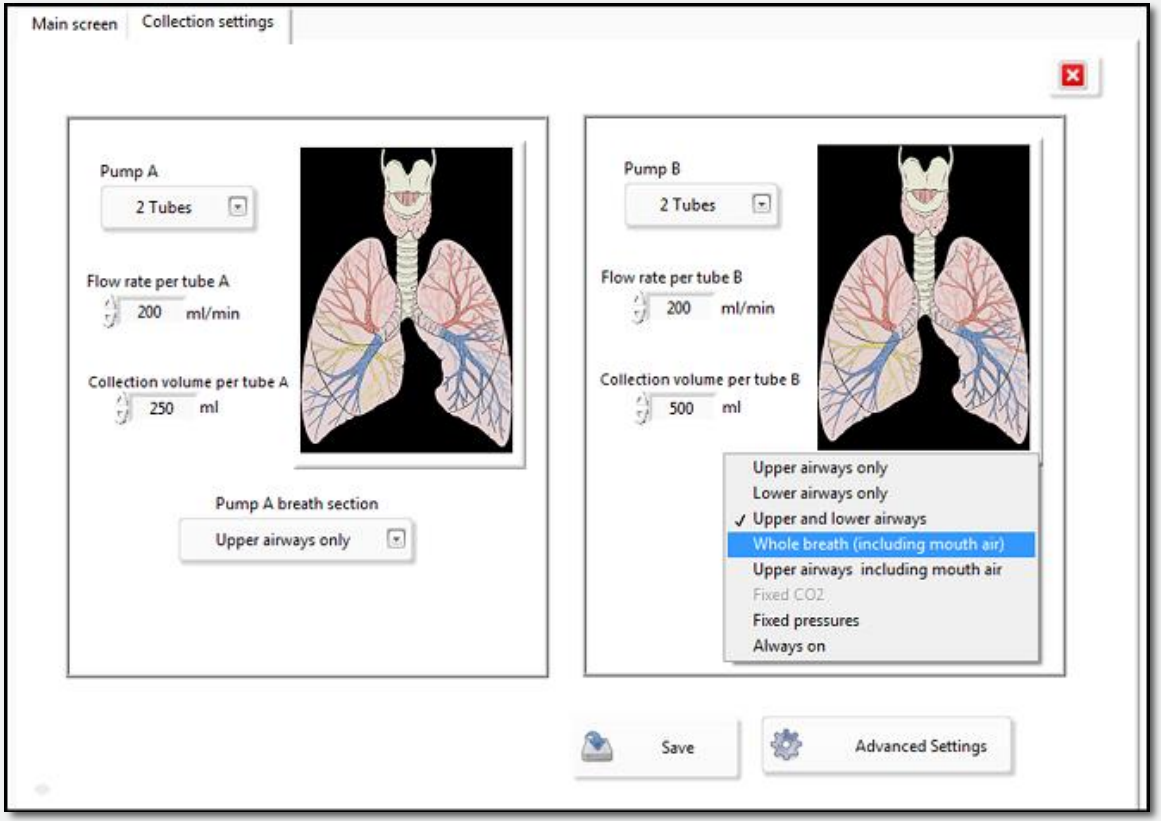
- Single use, conditioned mask
- Cartridge to store and ship VOC sample

# eCRF Questionnaire



# Breath Collection Parameters



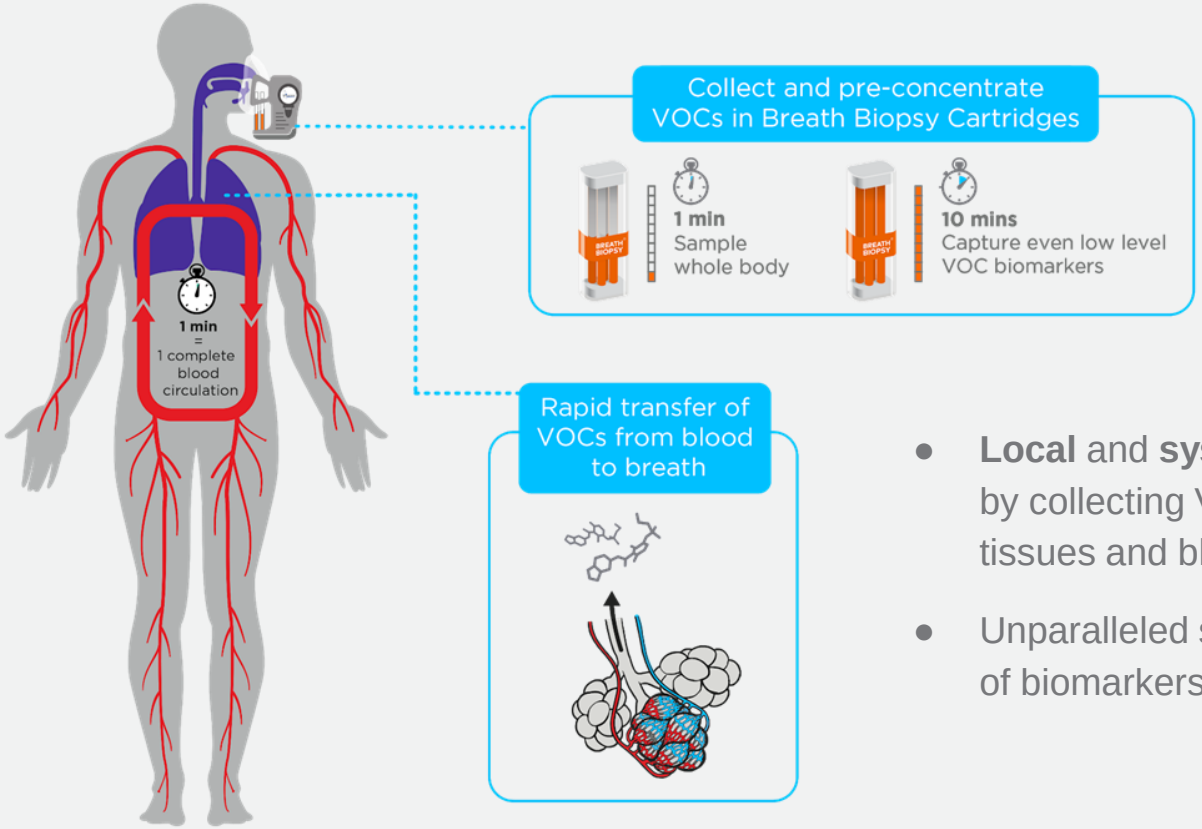

## Select your desired breath collection parameters

Using the straightforward software interface, breath collection parameters can be selected:

- Breath volume
- Breath fractions
- Flow rate

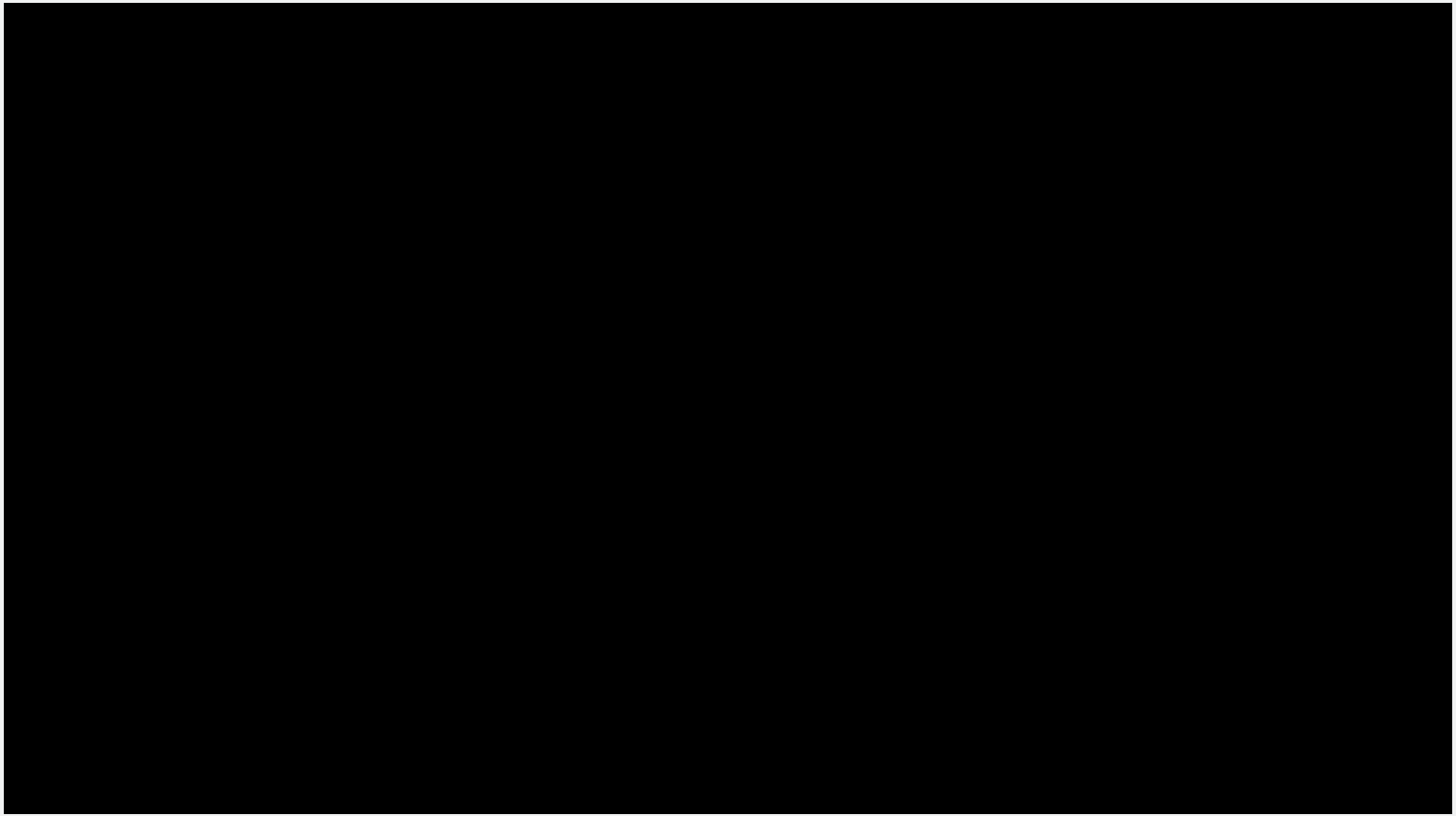
Replicate breath samples and/or different breath fractions can be obtained in a single collection event.

# Breath Biopsy: Whole Body VOC Sampling

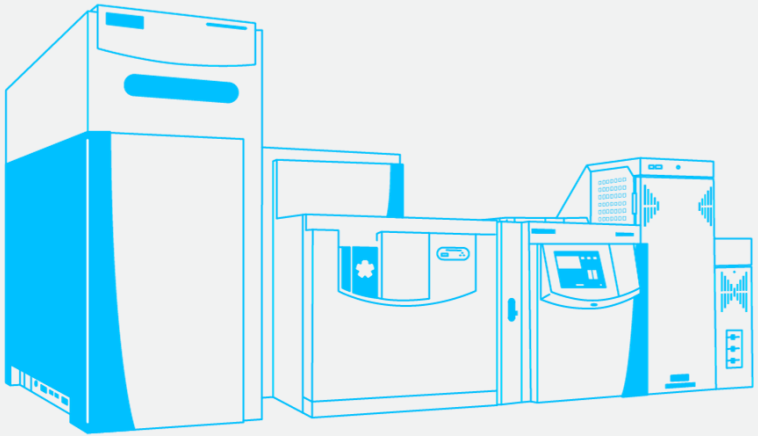


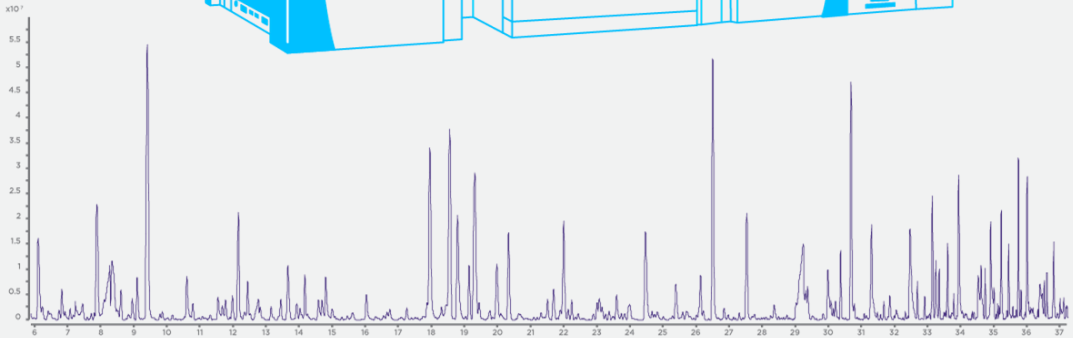

- **Local** and **systemic** disease information by collecting VOCs originating from tissues and blood **throughout the body**
- Unparalleled sensitivity for the detection of biomarkers in breath

# ReCIVA® Breath Sampler



# Breath Analysis Using TD-GC-MS





**TD-GC-MS (Orbitrap) -** the **Gold Standard** for biomarker discovery.

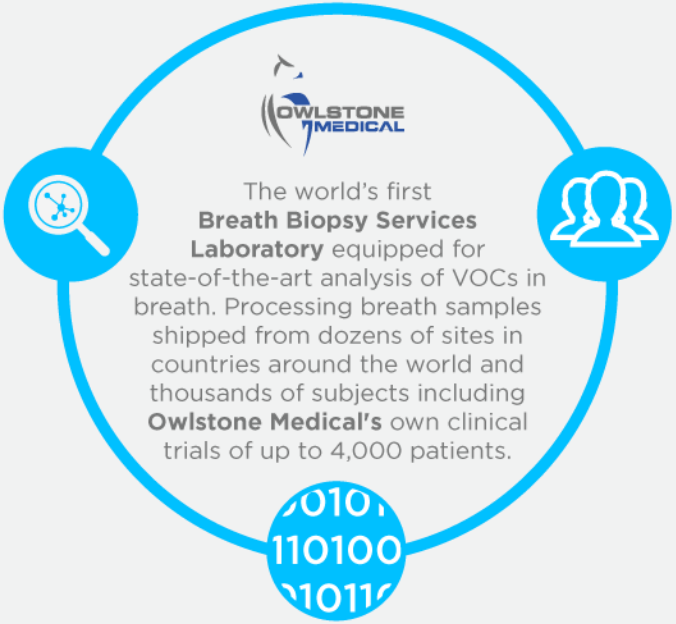
- Optimised to enable **identification of VOC biomarkers** from breath linking to biology
- Maximized potential for VOC detection with **high resolution** for separation of complex VOC mixtures
- **Detect low abundance biomarkers** in the parts per billion to parts per trillion range

**SERVICES INFO**

# Comprehensive Support to Integrate Breath Biopsy into your Clinical Trials

## Subject Matter Expertise

- Consultation, guidance and advice
- Customized study design
- Assistance with ethics submissions and patient information sheets




## Specialist Data Science Team

- Build statistical analysis plan in conjunction with you
- Statistical analysis including machine learning algorithms
- Comprehensive report including biological interpretation

## Clinical Trials Co-ordination

- Provision of training for clinical staff to ensure high quality sample collection
- Scheduled maintenance and on-line support
- Shipping logistics and sample return
- Site monitoring

# Breath Biopsy Services Workflow

**CLINICAL SITE**

Install **Breath Biopsy Collection Station** including **ReCIVA Breath Sampler** at clinical sites

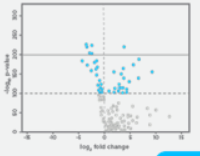
Regular supply of **Breath Biopsy Kits** including ready-to-use **Breath Biopsy Cartridge** and **Mask**


Collect **Breath Biopsy samples** and subject data in clinic

Store at 4 – 8 °C

Send **Breath Biopsy Cartridges** for analysis

Secure transfer of subject metadata to **Breath Biopsy digital biobank**

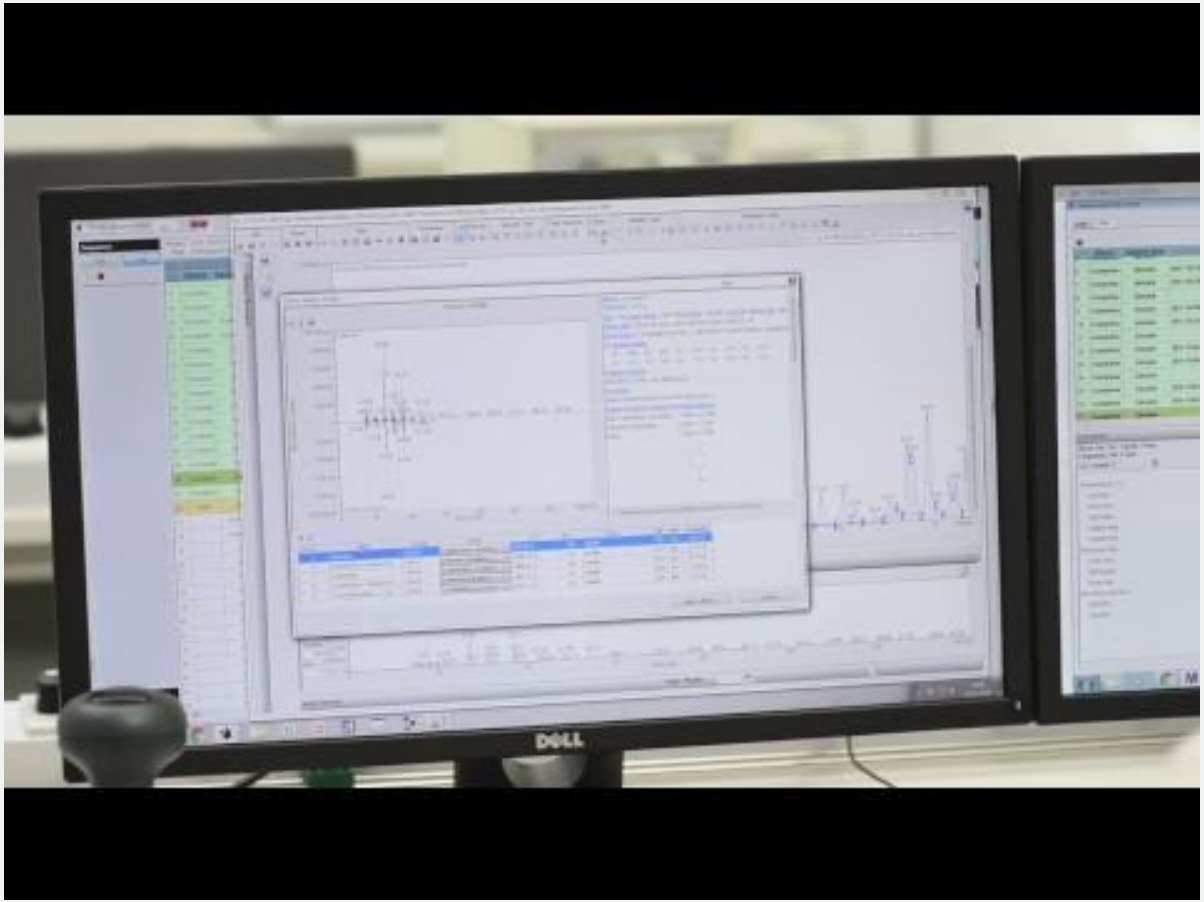


Comprehensive **discovery** analysis of candidate **VOC biomarkers**

Samples analyzed in **Owlstone Medical's Breath Biopsy Services Laboratory**

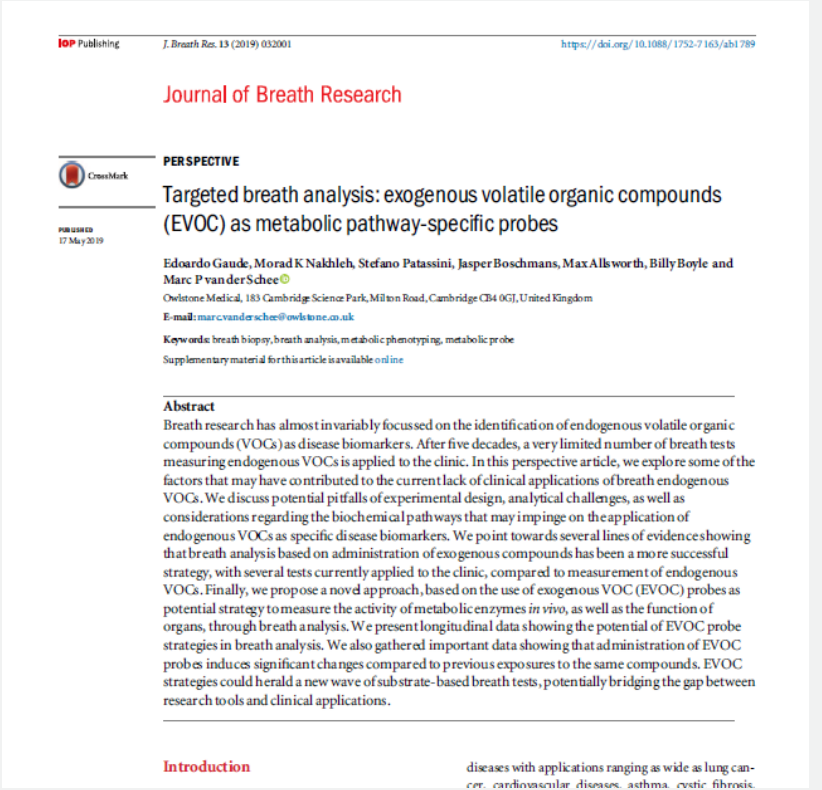
**OWLSTONE MEDICAL**

# Breath Biopsy Laboratory



# Targeted Analysis of VOCs on Breath

- Once promising biomarkers have been identified, a targeted analysis is possible
- The option to add a known compound or multiple compounds and analyse on breath with absolute quantitation
- Exogenous VOC (EVOC) probes can be used to amplify signal from specific enzyme systems and assess organ function



IOP Publishing J. Breath Res. 13 (2019) 032001 https://doi.org/10.1088/1752-7163/ab1789

Journal of Breath Research

PERSPECTIVE

## Targeted breath analysis: exogenous volatile organic compounds (EVOC) as metabolic pathway-specific probes

Edoardo Gaude, Morad K Nakhleh, Stefano Patassini, Jasper Boschmans, Max Allsworth, Billy Boyle and Marc P van der Schee

Owlstone Medical, 183 Cambridge Science Park, Milton Road, Cambridge CB4 0GJ, United Kingdom

E-mail: marc.vanderschee@owlstone.co.uk

Keywords: breath biopsy, breath analysis, metabolic phenotyping, metabolic probe

Supplementary material for this article is available online

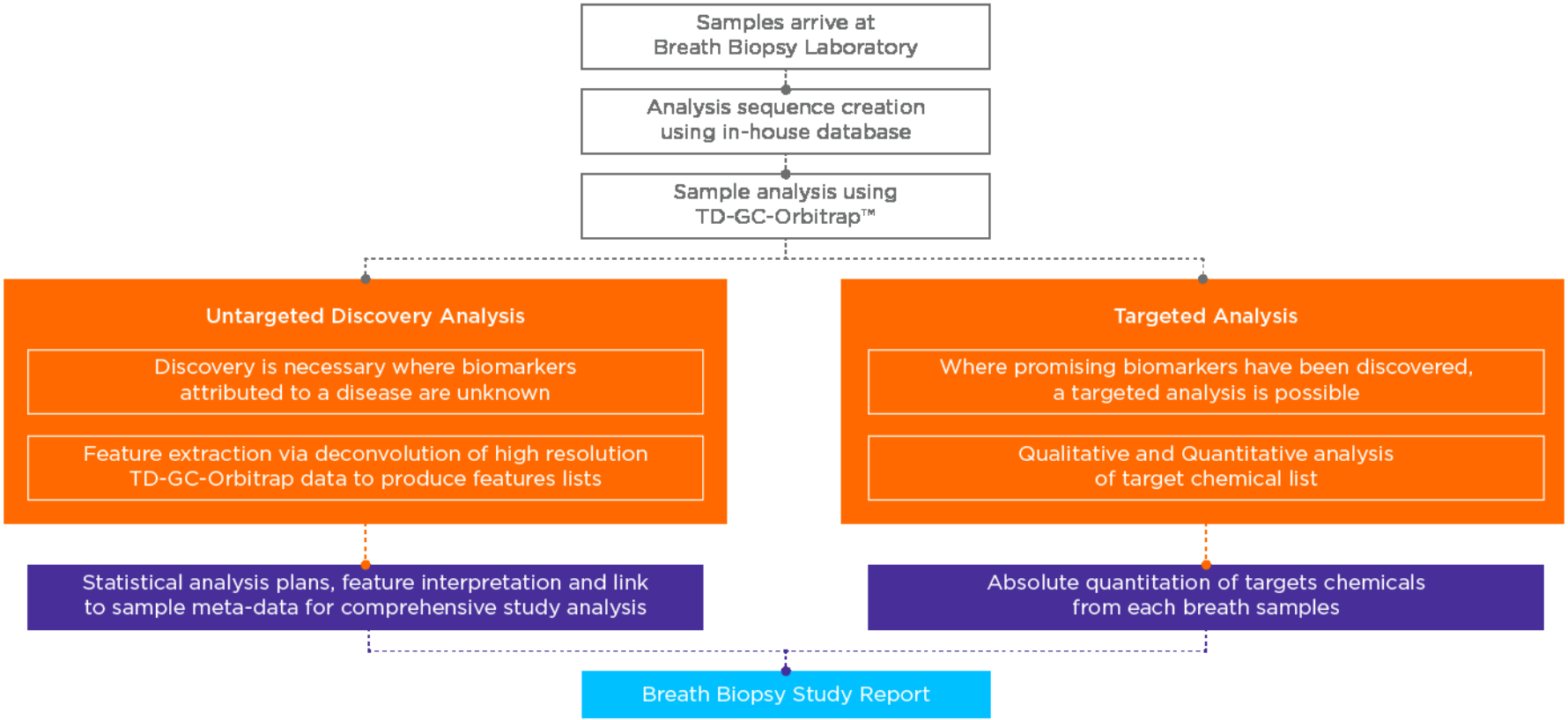
**Abstract**

Breath research has almost invariably focussed on the identification of endogenous volatile organic compounds (VOCs) as disease biomarkers. After five decades, a very limited number of breath tests measuring endogenous VOCs is applied to the clinic. In this perspective article, we explore some of the factors that may have contributed to the current lack of clinical applications of breath endogenous VOCs. We discuss potential pitfalls of experimental design, analytical challenges, as well as considerations regarding the biochemical pathways that may impinge on the application of endogenous VOCs as specific disease biomarkers. We point towards several lines of evidence showing that breath analysis based on administration of exogenous compounds has been a more successful strategy, with several tests currently applied to the clinic, compared to measurement of endogenous VOCs. Finally, we propose a novel approach, based on the use of exogenous VOC (EVOC) probes as potential strategy to measure the activity of metabolic enzymes *in vivo*, as well as the function of organs, through breath analysis. We present longitudinal data showing the potential of EVOC probe strategies in breath analysis. We also gathered important data showing that administration of EVOC probes induces significant changes compared to previous exposures to the same compounds. EVOC strategies could herald a new wave of substrate-based breath tests, potentially bridging the gap between research tools and clinical applications.

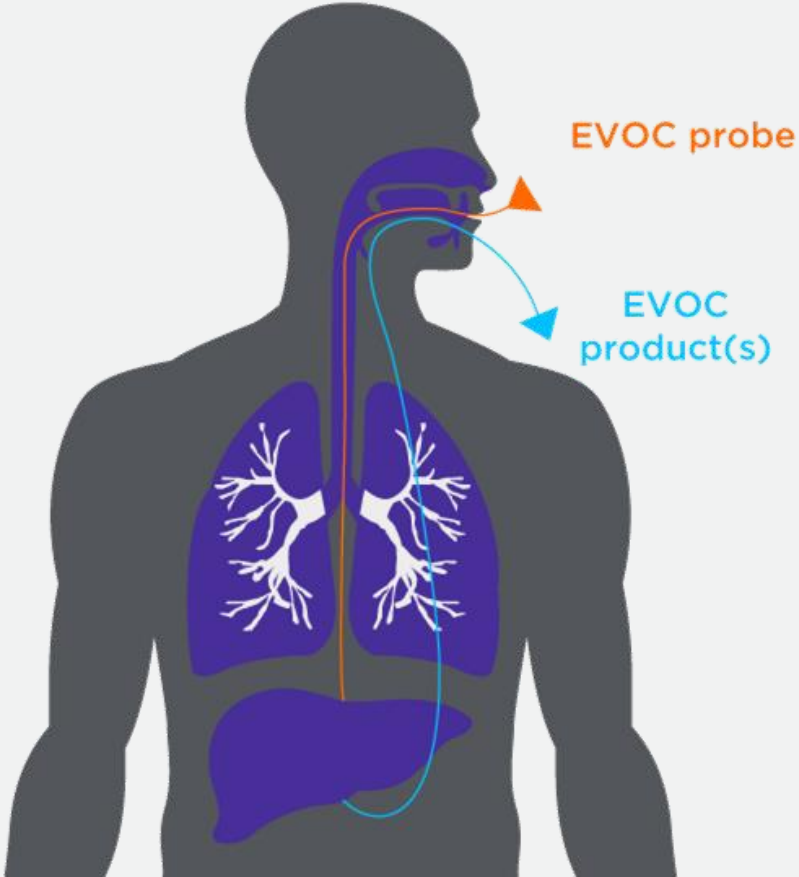
Introduction

diseases with applications ranging as wide as lung can-

# State-of-the-Art Breath Analysis Workflows



# Measurement of Enzymatic Activity and Organ Function using EVOC Probes




- It's possible to assess metabolic function *in vivo* using exogenous VOC (EVOC) probes
- The probe and any volatile metabolic products are rapidly secreted in breath
- Assess enzymatic activity by monitoring clearance of the EVOC probe from the system **and** the secretion of metabolic product(s) generated

\+ **Completely non-invasive**

\+ **Can administer cocktail of probes** - test multiple targets

\+ **No regulatory approval required**

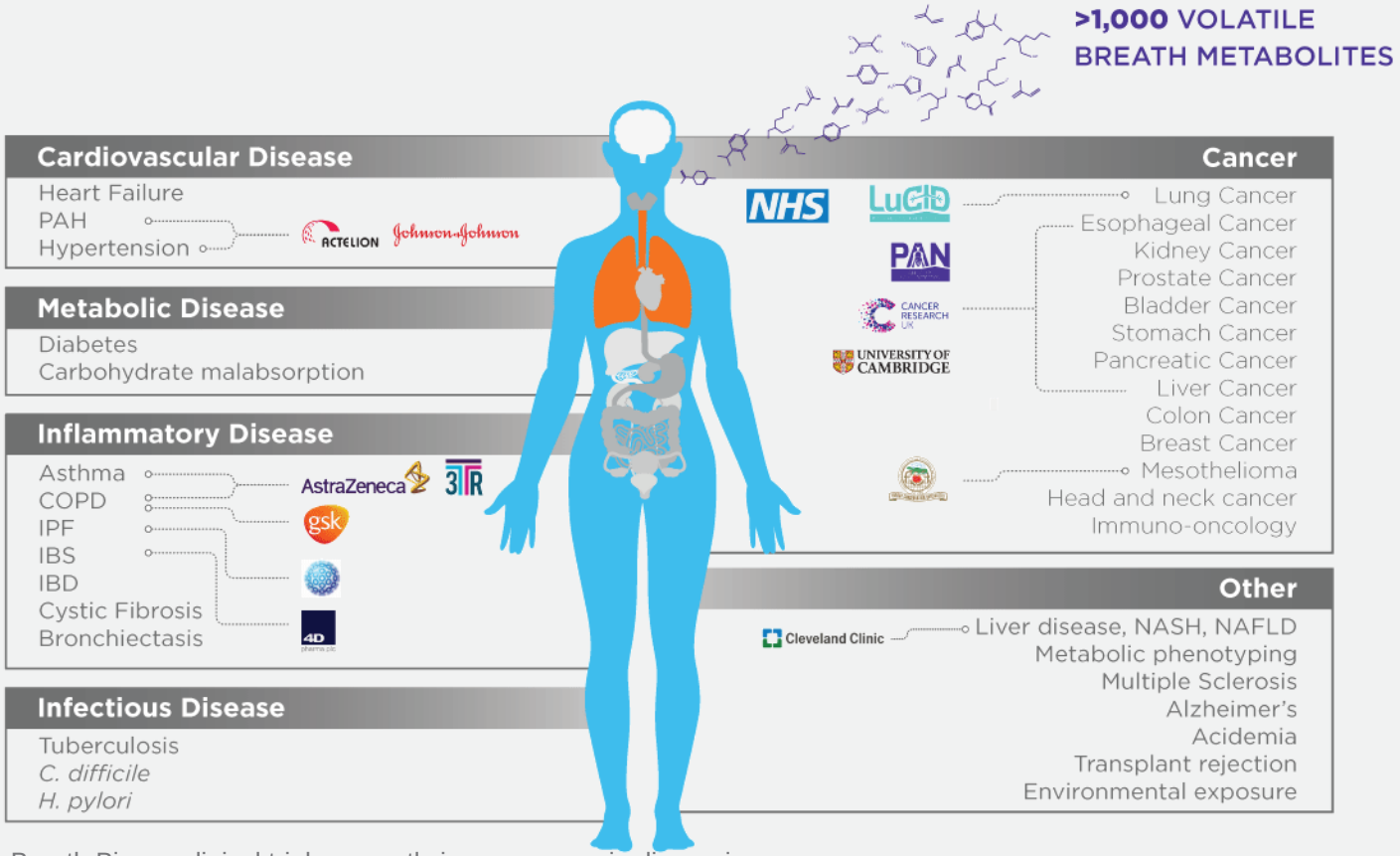
\+ **Low cost EVOC probe substrates**

# FAIMS Next Generation Detection Compatible with Near Patient Testing

- Platform technology - program target VOC biomarkers in software, hardware always remains the same
- High throughput - simultaneous detection of multiple VOC biomarkers in seconds
- Part per billion (ppb) sensitivity and high selectivity
- Small size - suitable for point of care (POC) or central lab

The company has developed a proprietary microchip chemical sensor called Field Asymmetric Ion Mobility Spectrometry (FAIMS). The FAIMS chip can be programmed in software to detect targeted disease VOCs with high sensitivity and selectivity. Firstly, the VOCs are ionized, meaning that the gaseous molecules become charged ions, allowing their path to be altered by electric fields. The second stage of the process takes advantage of this by applying an alternating voltage across the channels of the FAIMS chip that the ions are travelling through. This creates an alternating electric field that separates the ions depending on their mobility, which is different for each type of molecule. Finally, to detect the presence of a specific disease biomarker, a 'compensation voltage' is applied that steers the molecules of interest to the detector, where they are counted. Download Paper

# Breath Biopsy Clinical Trials




Breath Biopsy clinical trials currently in progress or in discussion.

# Breath VOC Biomarkers in Respiratory Diseases

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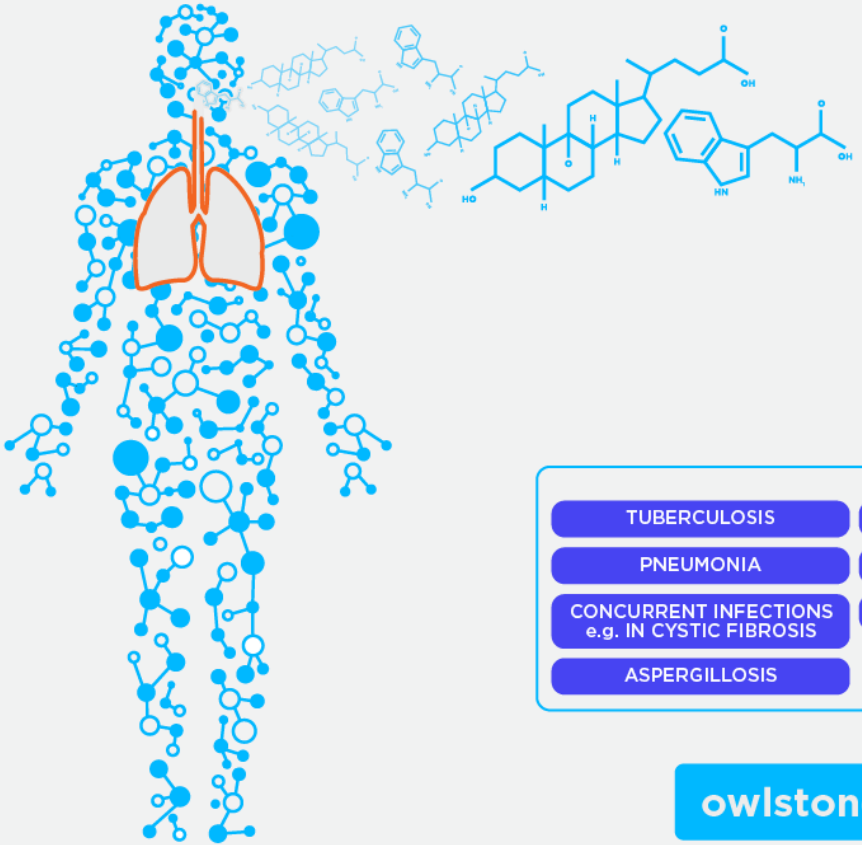
# Breath Biopsy and VOC Biomarkers for Respiratory Disease



**>1,000 VOLATILE ORGANIC COMPOUNDS IN BREATH**

**RESPIRATORY DISEASES**

- TUBERCULOSIS
- PNEUMONIA
- CONCURRENT INFECTIONS e.g. IN CYSTIC FIBROSIS
- ASPERGILLOSIS
- ASTHMA
- COPD
- EMPHYSEMA
- IDIOPATHIC PULMONARY FIBROSIS
- ACUTE RESPIRATORY DISTRESS SYNDROME
- PULMONARY EMBOLISM
- LUNG CANCER
- MESOTHELIOMA

FIND OUT MORE AT

**owlstonemedical.com/respiratory**

# Breath VOC Biomarkers in Asthma and COPD

DUE TO **LACK OF STRATIFYING DIAGNOSTICS** CURRENT **INTERNATIONAL ASTHMA GUIDELINES** ADVOCATE A '**TRIAL** AND **ERROR**' APPROACH WITH PROGRESSIVE ESCALATION OF TREATMENT

THERE IS AN **URGENT NEED** FOR

**PRECISION MEDICINE TOOLS**

TO MATCH THE **RIGHT PATIENT** WITH THE **RIGHT TREATMENT** AT THE **RIGHT TIME**

# Limitations of Existing Diagnostic Tests

## Systemic blood markers

**IgE, periostin, blood eosinophils**

- Well-established technique
- x Poor correlation to activity
- x Limited positive predictive potential for stratification

## Airway cell counts

**Induced sputum, bronchial lavage**

- Shows inflammatory subtypes (e.g. eosinophil, neutrophil)
- x Too invasive
- x Time consuming, not scalable


## $F_ENO$

**Fractional exhaled nitric oxide**

- Local inflammation response
- Correlates to corticosteroid responsiveness and adherence
- x Single marker, limited phenotypic stratification

# VOCs Biomarkers Highlighted for Asthma

REVIEW

## Metabolomics in asthma: where do we stand?

*Helena Pité[a,b], Mário Morais-Almeida[a], and Sílvia M. Rocha[c]*

**Purpose of review**
Metabolomics has been used to uncover the metabolic signatures of asthma, both for biomarker identification and pathophysiologic mechanisms research. We aimed to review recent advances in this field, published since 2016, and discuss these findings implications to future research and application into clinical practice.

**Recent findings**
Experimental asthma models and clinical studies in both children and adults supported independent metabolic signatures of asthma. Common reported pathways included purine, glycerophospholipid, glutathione, fatty acids, and arginine and proline metabolism. Metabolomics-based studies identified candidate biomarkers related to asthma severity and corticosteroid resistance, and supported the definitio of the obesity-related phenotype at the molecular level. A systematic review with meta-analysis and recent prospective studies favored exhaled volatile organic compounds as one of the most promising biomarkers in asthma diagnosis and monitoring.

**Summary**
Metabolomics has provided unique and novel insights into asthma profiling at the molecular level. Curren challenges include procedures standardization and control of potentially confounding variables for extern validation. Point-of-care technology developments bring metabolomics closer to clinical practice. In additi to biomarkers identification, relating metabolites to their biologic role will serve as critical foundations for understanding the biology underpinning asthma heterogeneity and for specific-targeted therapies.
**Video Abstract**: http://links.lww.com/COPM/A22

**Keywords**
asthma, biomarker, composite signature, metabolomics, phenotype

### INTRODUCTION

In the last two decades, the 'omics' disciplines have emerged as important tools in medical research. Metabolomics is a postgenomic discipline that combines high-throughput analytic techniques with bioinformatics to provide a comprehensive analysis of metabolites in biological specimens (Table 1) [1▪▪,2▪▪,3,4]. This profiling of metabolites in biofluids, cells and tissues provides an instantaneous snapshot of a biological system status and can enable the detection of composite metabolic signatures or fin-

traits, namely regarding clinical presentation, related comorbidities, environmental triggers, lung function impairment, inflammation patterns, airway remodeling features, prognosis, and therapeutic responses [5]. Presently, no strong relationship has been found between pathophysiologic characteristics and particular clinical features or treatment response [5,6]. Metabolomics is the 'omics' field that is closest to phenotype expression and is well suited to reflect the genome–environmental interactions occurring in asthma. While targeted metabolomics approaches

Pité et al.,
Metabolomics in asthma: where do we stand?,
Curr Opin Pulm Med,
2017

> A systematic review with meta-analysis and recent prospective studies favored ***exhaled volatile organic compounds*** as one of ***the most promising biomarkers*** in asthma diagnosis and monitoring.

# Precision Medicine for Asthma and COPD

PHENOTYPES

INFLAMMATORY SUBTYPES

ENDOTYPES
(Molecular mechanism or treatment response)

ALTERED METABOLIC SIGNATURES*


PREDOMINANTLY EOSINOPHILIC

RESPONDS TO GLUCOCORTICOIDS


PREDOMINANTLY NEUTROPHILIC

LACK OF RESPONSE TO GLUCOCORTICOIDS

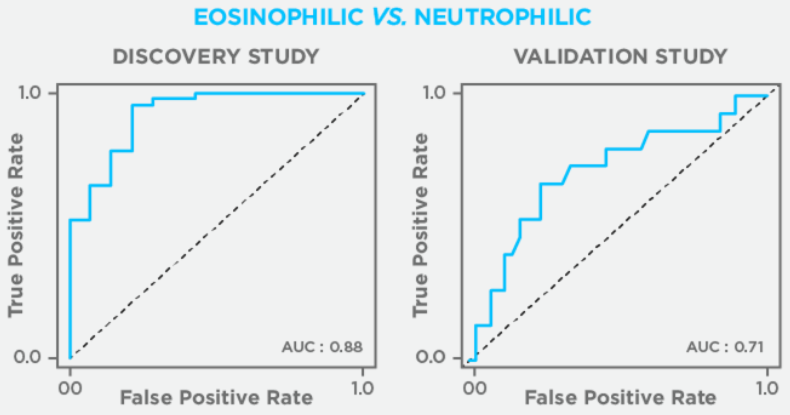
BIOMARKERS TO IDENTIFY DISEASE ENDOTYPES / TREATABLE TRAITS

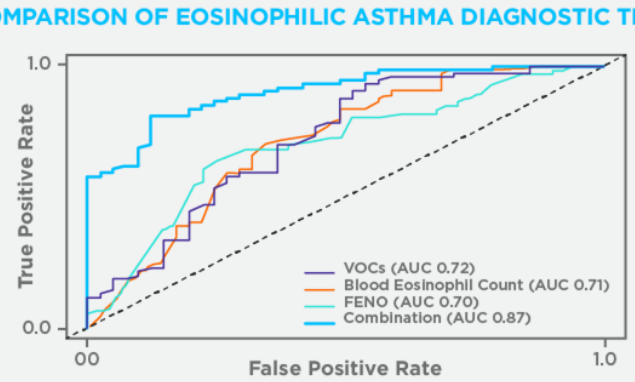
*Reinke *et al*., Eur Resp J, 2017

# Using Breath VOCs to Stratify Asthma Patients

Four VOCs can distinguish between eosinophilic and neutrophilic asthma with reliability comparable to existing tests.

- VOCs: nonanal, 1-propanol, hexane and 2-hexanone
- Samples collected from over 500 patients in Liege, Belgium (276 discovery, 245 validation)
- VOC testing for eosinophilic asthma prediction has equivalent accuracy to results from existing FeNO testing and combining techniques gives even stronger results
- Detection of neutrophilic asthma with 76% accuracy. No current reliable non-invasive tests for this form of asthma
- Signal not confounded by age, smoking status, or treatments



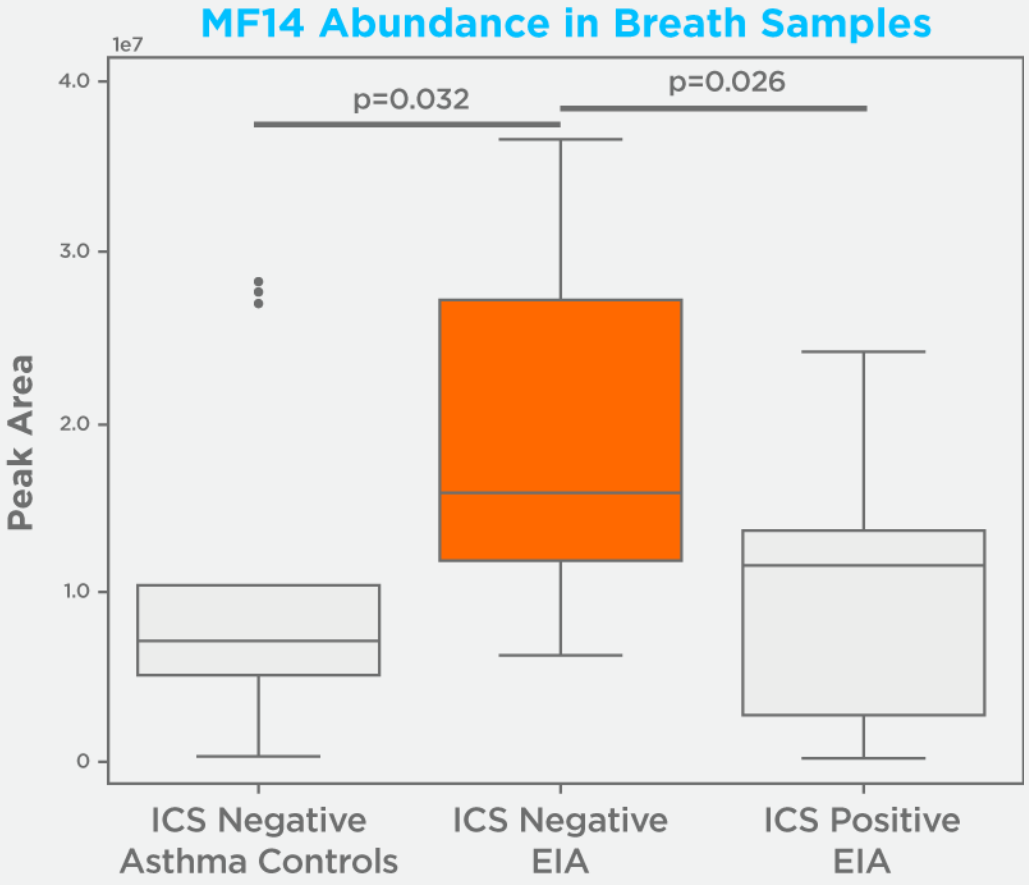




Schleich et al., *Am J Respir Crit Care Med* (2019)

# Suppression of EIA VOCs by steroid use

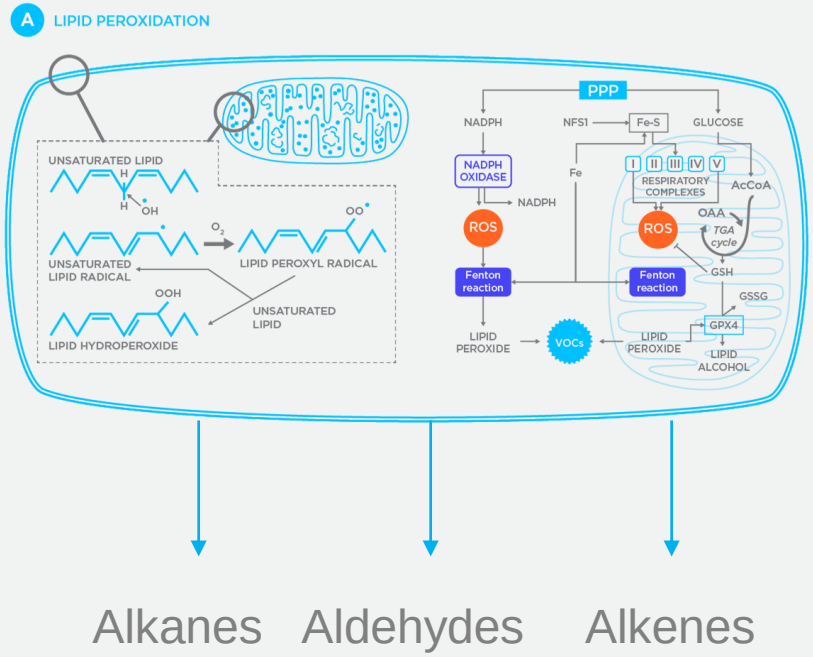
- Octanal and Dodecane/Tetradecane VOC levels appear to be indicative of Exercise Induced Asthma (EIA) in steroid naïve subjects
- Changes are suppressed by steroid treatment suggesting VOCs could be used to monitor response to treatment in EIA subjects
- The ability to measure steroid response provides a proxy for eosinophil detection

*Owlstone project conducted with Jean Driessen et al at MST, Enschede, NL*



# VOCs Related to Oxidative Stress

- Oxidative stress is the imbalance of reactive oxygen species and antioxidants in cells
- An excess of reactive oxygen species can damage nucleic acids, amino acids and proteins
- The most damaging effect is believed to be the induction of lipid peroxidation
- Cell membranes, lipid mediators such as arachidonic acid and prostaglandins are composed of poly-unsaturated fatty acids and are a primary target for reactive oxygen attack
- The VOC by-products of this attack include aldehydes, alcohols, ketones and alkanes



# Breath VOC Biomarkers in Liver Diseases

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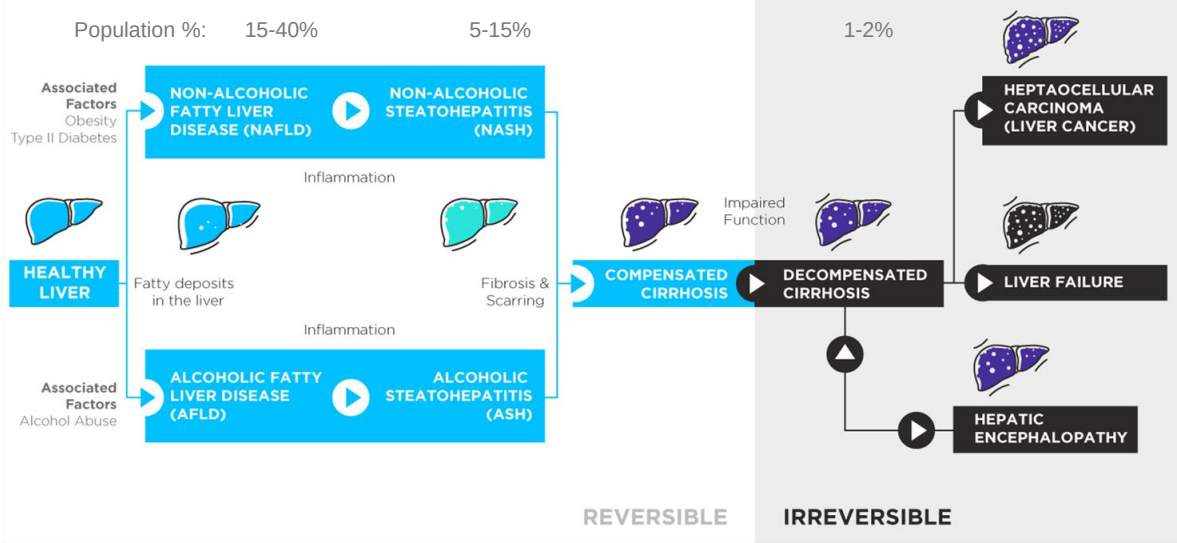
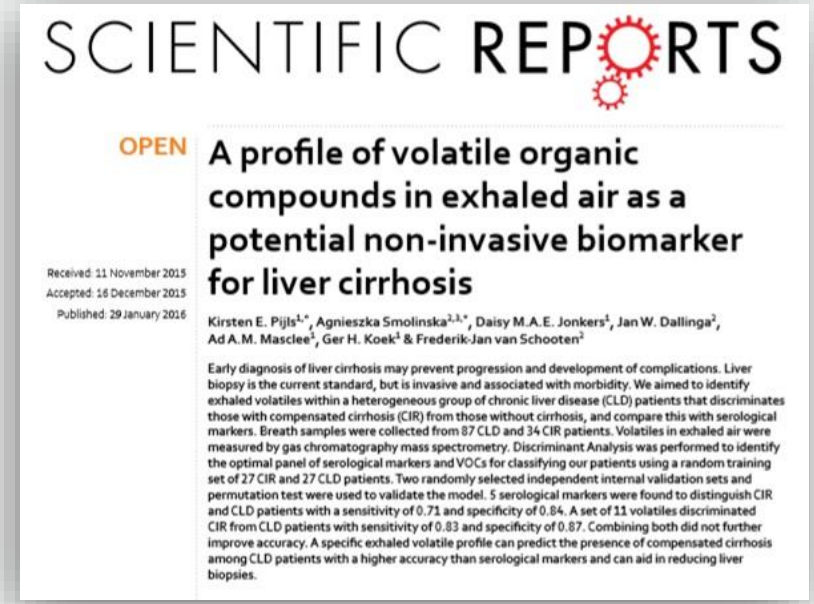
# Unmet Need for Non-Invasive Biomarkers of Liver Disease

- NASH affects 9-15 million people in US alone
- Asymptomatic until later stages that lead to permanent liver damage
- Only means of diagnosing NASH is by liver biopsy (invasive, expensive, painful, inaccurate)
- Drug development hampered by lack of reliable non-invasive biomarkers
- To properly treat patients and develop effective new therapies new non-invasive measures of liver health must be developed




*Steatosis is the initial NAFLD stage characterised by fat accumulation. Subsequent inflammation accelerates progression to NASH following by liver cirrhosis which may leads to HCC. Both steatosis and NASH are reversible.*

# VOCs in Exhaled Air as Potential Biomarkers for Cirrhosis - Study Design



SCIENTIFIC REPORTS

OPEN

## A profile of volatile organic compounds in exhaled air as a potential non-invasive biomarker for liver cirrhosis

Received: 11 November 2015
Accepted: 16 December 2015
Published: 29 January 2016

Kirsten E. Pijls[1,*], Agnieszka Smolinska[2,3,*], Daisy M.A.E. Jonkers[1], Jan W. Dallinga[2], Ad A.M. Masclee[1], Ger H. Koek[1] & Frederik-Jan van Schooten[2]

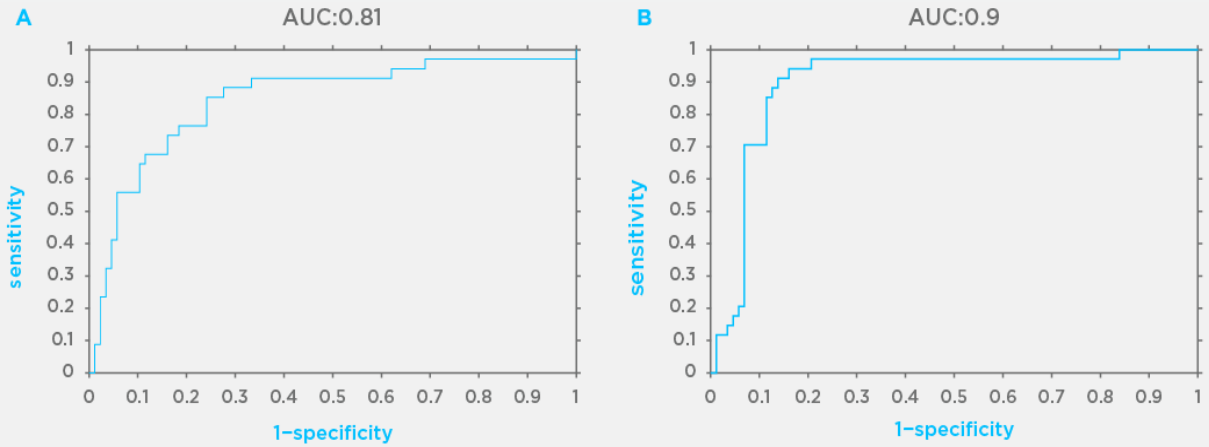
Early diagnosis of liver cirrhosis may prevent progression and development of complications. Liver biopsy is the current standard, but is invasive and associated with morbidity. We aimed to identify exhaled volatiles within a heterogeneous group of chronic liver disease (CLD) patients that discriminates those with compensated cirrhosis (CIR) from those without cirrhosis, and compare this with serological markers. Breath samples were collected from 87 CLD and 34 CIR patients. Volatiles in exhaled air were measured by gas chromatography mass spectrometry. Discriminant Analysis was performed to identify the optimal panel of serological markers and VOCs for classifying our patients using a random training set of 27 CIR and 27 CLD patients. Two randomly selected independent internal validation sets and permutation test were used to validate the model. 5 serological markers were found to distinguish CIR and CLD patients with a sensitivity of 0.71 and specificity of 0.84. A set of 11 volatiles discriminated CIR from CLD patients with sensitivity of 0.83 and specificity of 0.87. Combining both did not further improve accuracy. A specific exhaled volatile profile can predict the presence of compensated cirrhosis among CLD patients with a higher accuracy than serological markers and can aid in reducing liver biopsies.

- Breath samples collected from
  - 87 patients with chronic liver disease (CLD)
  - 34 with compensated cirrhosis (CIR)
  - 31 healthy volunteers
- Patients recruited from a hepatology outpatient clinic
- GI diseases, chronic lung diseases and/or RA excluded
- Diagnosis based on liver histology and/or clinical, laboratory and/or endoscopic findings
- Cirrhosis severity assessed according to Child-Pugh classification and Model for End Stage Liver Disease (MELD) score
- Air exhaled into 5 litre Tedlar® gas sampling bags, with VOCs measured by TD-GC-MS

Pijls et al. *Nature* (2016)

# VOCs in Exhaled Air as Potential Biomarkers for Cirrhosis - Results

Validation of PLS-DA classification model for CLD vs CIR




5 selected serological markers* AUC: 0.81 (95% confidence interval 0.77-0.91)

11 discriminatory VOCs, AUC: 0.90 (95% confidence interval 0.86-0.96)

Subsets of VOC compounds were able to differentiate CLD and CIR patients from the control group with AUC of 100% and 93.75% respectively (Data not shown)

*GGT, ALT, bilirubin, albumin, and thrombocytes

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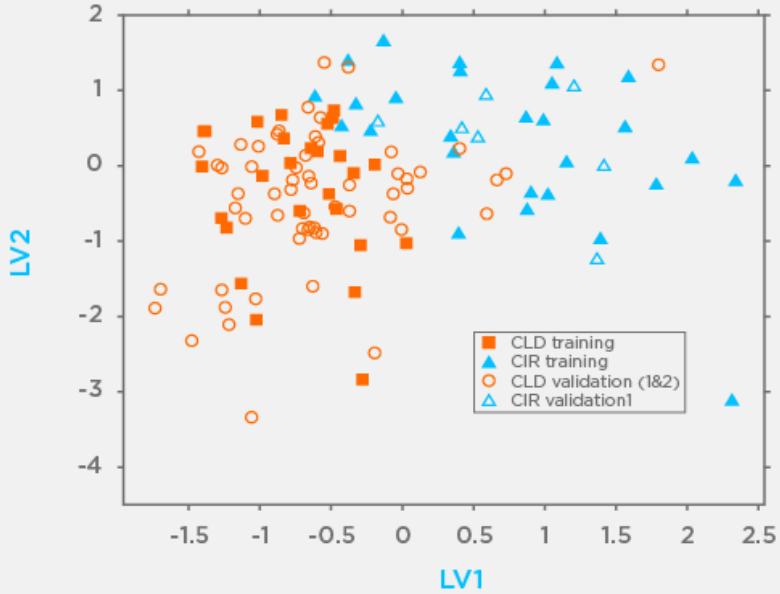
- Profile of 11 VOCs predict presence of cirrhosis with sensitivity of 0.83 a specificity of 0.87
- Hydrocarbons related to oxidative stress and/or impaired metabolism by cytochrome P450 enzymes in the liver

PLS-DA score plot of the final classification model




| Nr. | Chemical Identity | Change |
|---|---|---|
| 1 | 3-methylbutanal | ( - ) |
| 2 | Propanoic Acid | ( + ) |
| 3 | Octane | ( + ) |
| 4 | Terpene ($C_{10}H_{16}$) | ( + ) |
| 5 | Terpenoid: ∝-pinene | ( + ) |
| 6 | 3-carene | ( + ) |
| 7 | Unknown | ( + ) |
| 8 | Branched $C_{16}H_{34}$ | ( + ) |
| 9 | 1-hexadecanol | ( - ) |
| 10 | Branched $C_{16}H_{34}$ | ( - ) |
| 11 | Dimethyl disulfide | ( + ) |

# Limonene Normalisation after Transplantation

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Research Paper

## Volatile Biomarkers in Breath Associated With Liver Cirrhosis — Comparisons of Pre- and Post-liver Transplant Breath Samples

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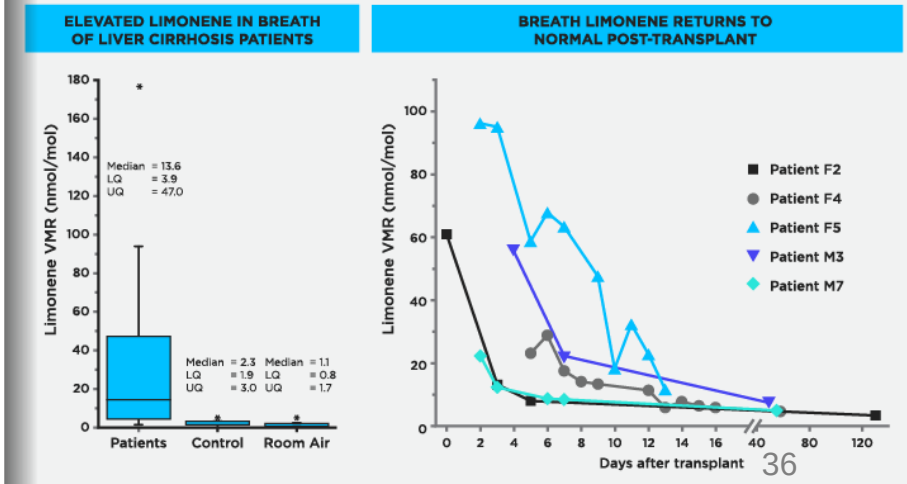
ABSTRACT

*Background:* The burden of liver disease in the UK has risen dramatically and there is a need for improved diagnostics.
*Aims:* To determine which breath volatiles are associated with the cirrhotic liver and hence diagnostically useful.
*Methods:* A two-stage biomarker discovery procedure was used. Alveolar breath samples of 31 patients with cirrhosis and 30 healthy controls were mass spectrometrically analysed and compared (stage 1). 12 of these patients had their breath analysed after liver transplant (stage 2). Five patients were followed longitudinally as in-patients in the post-transplant period.
*Results:* Seven volatiles were elevated in the breath of patients versus controls. Of these, five showed statistically significant decrease post-transplant: limonene, methanol, 2-pentanone, 2-butanone and carbon disulfide. On an individual basis limonene has the best diagnostic capability (the area under a receiver operating characteristic curve (AUROC) is 0.91), but this is improved by combining methanol, 2-pentanone and limonene (AUROC curve 0.95). Following transplant, limonene shows wash-out characteristics.
*Conclusions:* Limonene, methanol and 2-pentanone are breath markers for a cirrhotic liver. This study raises the potential to investigate these volatiles as markers for early-stage liver disease. By monitoring the wash-out of limonene following transplant, graft liver function can be non-invasively assessed.


### 1. Introduction

The publication of the 2014 Lancet Commission on liver disease has highlighted how the burden of liver disease in the UK has risen sharply over the past few decades and that it poses a major public health issue for 83% of deaths (Davies, 2012). It is the third biggest cause of premature mortality, with three quarters of liver deaths due to alcohol (Williams et al., 2014). Liver disease has a widespread effect not only to the patient, encompassing physical and psychological morbidity and mortality, but also incurring significant societal costs. One of the

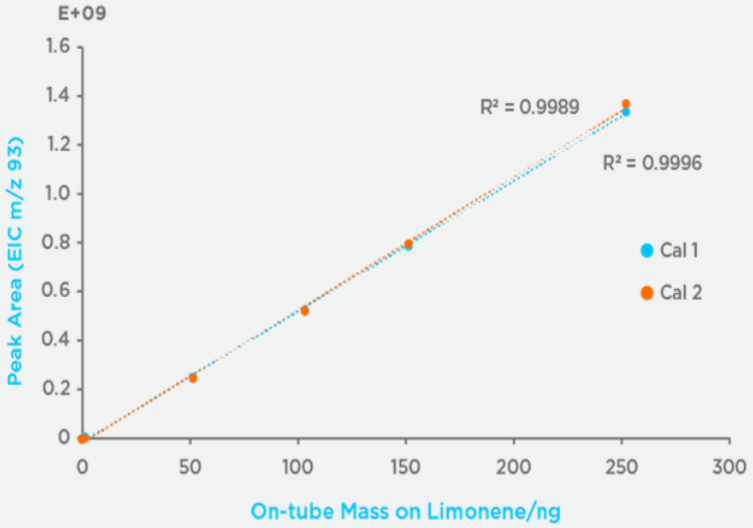
- Patients suffering from liver cirrhosis have raised levels of limonene in their breath due to the liver failing to produce enzymes for metabolism.
- After liver transplant, limonene levels in exhaled breath returned to normal as the metabolism resumed
- Shows VOCs in breath can be used to monitor a patient's response to therapeutic intervention.

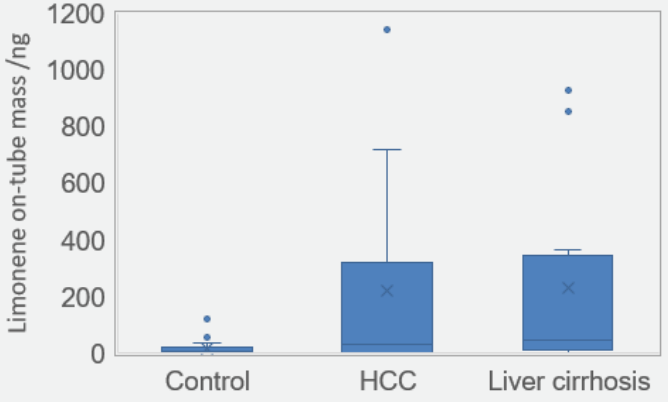


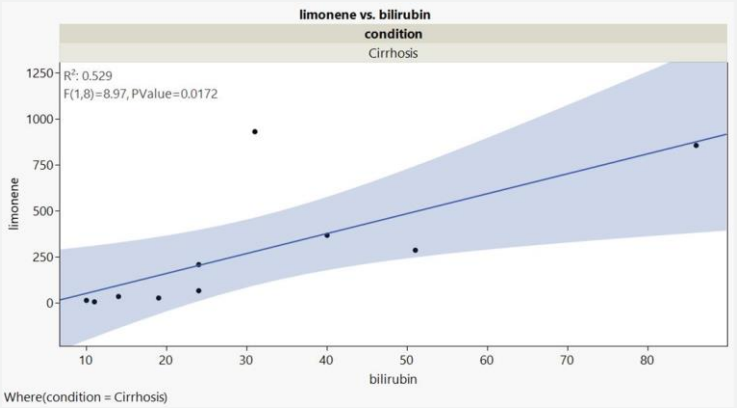



Fernández del Río R et al., EBioMedicine (2015); 2(9); 1243–1250

# Breath Limonene Targeted Assay Preliminary Results



# Combining targeted and non-targeted approaches


- Owlstone will be refining and validating VOC biomarker panels and associated EVOC probes for respiratory, liver and other major diseases building on the work done by other groups and our own studies
- Possibility to access these fully quantitative targeted panels for RUO in combination with our non-targeted Breath Biopsy discovery offering on our new platform
- Open to discussions with academic and biopharma partners who would like to participate in these and other disease areas or incorporate Breath Biopsy in upcoming clinical trials
- End goal is to develop breath tests that can be deployed in clinical routine

# Thank you

**Breath Biopsy**
Creating a new industry category and dominating the entire value chain

**Early Detection**
We will save lives by improving rates of early detection

**Precision medicine**
Matching the right patient to the right treatment at the right time

**World leader**
with proven technology, team and supportive shareholders

Targeting billion dollar markets in lung and colon cancer screening

Near term commercialisation of lung cancer nodule management in USA

Saving money by increasing the effectiveness of current pharmaceuticals

Revenue generating today - deep pipeline with pharma partners and significant licensing upside

Poised to transform healthcare, both patient outcomes and economics

## OUR **MISSION** - SAVE **100,000** LIVES