# Chip-Scale Mass Spectrometry for Point-of-Care Breath Diagnostics

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## Background

COVID-19 pandemic has underscored the urgency of swiftly identifying infected individuals to intervene early and prevent the progression to severe illness, as well as to curb the transmission of infections within communities. Exhaled breath diagnostics can provide such rapid screening approach while being non-invasive, cost-efficient, and potentially adaptable to detect various infectious agents, sometimes even before symptoms appear. Traditional breath analysis methods often entail collecting breath samples using tubes or bags for transportation to labs where Gas Chromatography-Mass Spectrometry (GC-MS) is employed for detecting trace-level volatile organic compounds (VOCs). While considered the gold standard, this method is both costly and logistically cumbersome. To address this, Detect-ION has leveraged its cutting-edge "chip-scale mass spectrometry" technology, under the DTRA's EXHALE program, enabling a Point-of-Care Breath Diagnostics Platform called "CLARION", for screening exhaled breath VOCs for respiratory infections.

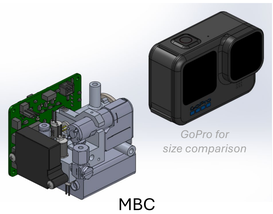
## Approach

We have established an institution review board (IRB) to enroll healthy and sick human subjects across two sequential breath collection campaigns of cohort sizes of 100 (Campaign-1) and 500 (Campaign-2) respectively. Subjects will provide breath specimens, as well as nasal swabs and sputum specimen. The sputum specimen will be applied to a multiplex molecular panel [*BioFire® Pneumonia Panel*] to screen against 33 pathogen targets most associated with common respiratory infections, such as influenza, adenovirus, coronavirus and streptococcus pneumoniae and these results will be considered ground truth. For breath analysis, we plan to collect breath specimen in CLARION for instantaneous analysis, as well as into sorbent tubes for lab analysis using High Resolution Mass Spectrometry (HRMS). CLARION data will be processed to generate VOC models consisting of calibrated retention times and chemical identities. These models along with the controls, which categorize each subject as uninfected or infected, will be provided as input to a Partial Least-Squares Discriminant Analysis (PLSDA) model building tool to develop infection detection algorithms.

## CLARION [Point-of-Care Breath Diagnostics]

A fieldable GC-MS system adapted to collect exhaled human breath can provide a versatile diagnostics capability for rapid screening of a large population. We have modified the trace gas analysis system called ACHILLES (originally developed under the IARPA MAEGLIN program), containing a pre-concentrator-thermal desorption GC-MS, by adding an embedded miniature breath collector (MBC) stage. System modifications and method optimizations have been completed for a breath sampling time of 2 minutes, while maintaining obtaining LODs in the low-PPB range required for identifying disease state biomarkers in exhaled breath.


Deployment pictures of the ACHILLES prototype




MBC

Envisioned CLARION Platform (7.5 L)

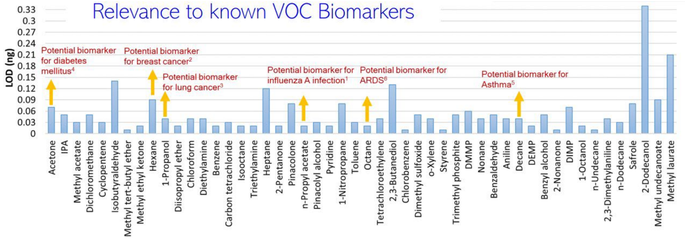



**Figure 1.** Top Left**:** ACHILLES (10-L ) modifications will integrate a miniature breath collector (middle) into a standalone CLARION platform for Point-of-Care breath collection and analysis system. Left: LODs for a subset of 50 VOCs from the MAEGLIN program's target chemical list. The relevant VOC's with as potential breath biomarkers are highlighted. Top Right: The envisioned CLARION system Detect-ION plans to demonstrate by applying a custom miniature turbo pump currently being developed under the EXHALE program.

## Miniature Breath Collector (MBC)

- User-triggered smart collection technology
- Volumetric breath sampling
- Embedded thermal desorption stage
- Visual and audio cues to user to facilitate breath collection
- Self-sealing & shelf-life monitoring to aid detection algorithm

### Key MBC features

**Figure 2.** The MBC has been successfully integrated into the CLARION platform. Initial studies of vapor phase analytical standards have shown sensitivity of the system in the low parts-per-billion to high parts-per-trillion range. Breath collection and subsequent GC-MS analysis for over 100 samples have been performed on the fully integrated prototype system, with battery powered operation.

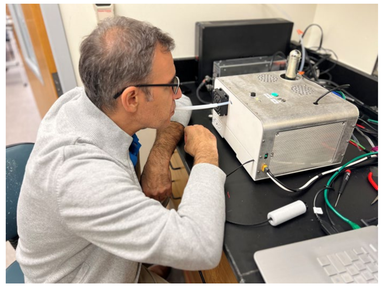


**Figure 3.** CLARION-α system being deployed at USF for breath collection campaign-1.

## Clinical Study & Preliminary Results

The IRB has been approved and breath specimen collection for campaign-1 is underway at University of South Florida, Tampa, through December 2024.

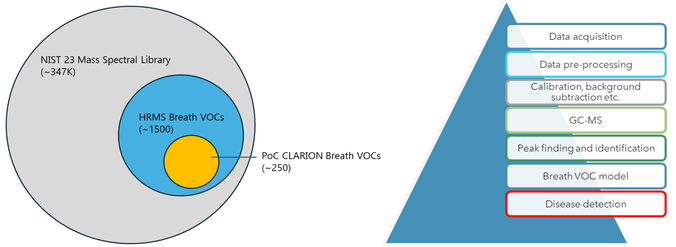



**Figure 4.** Left: We will leverage NIST 23 Mass Spectral Library and HRMS to facilitate the CLARION-specific breath VOC library development and biomarker discovery; Right: Batch processing of breath data developed in MATLAB will be used to build disease-specific VOC biomarker models.

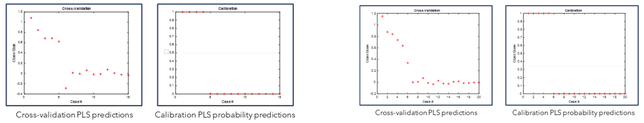



**Figure 5.** Left: Breath-based discrimination of sick (common flu) vs. healthy days of a subject using PLSDA model; Right: Addition of breath spiked with mint did not degrade the discrimination of sick vs. healthy days.

## Upcoming Work

- Complete breath campaign-1, process breath specimen and build VOC libraries for both HRMS and CLARION using the NIST 23 Mass Spectral Library.
- Leverage HRMS breath data and BioFire Pneumonia Panel results to perform biomarker discovery for most prevalent infection (s) detected in campaign-1.
- Down select biomarkers relevant to CLARION's LODs to develop VOC model for infection states and iteratively optimize the models to improve the ROC curve.

## Acknowledgments

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