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

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Background

The recent 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 organic compounds. 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, enabling a compact 10-L Preconcentrator-Thermal Desorption-Gas Chromatograph-Mass Spectrometer (TD-GC-MS) system, called “CLARION”, for analyzing exhaled breath.

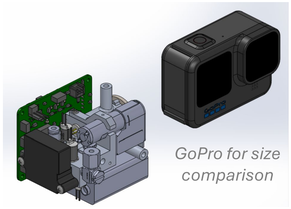
Approach

We have established an institution review board to enroll asymptomatic and symptomatic human subjects across two sequential breath collection campaigns of cohort sizes of 100 (Campaign-1) and 500 (Campaign-2) respectively. Human subjects enrolled for the study will provide breath specimens, as well as nasal and throat swabs. Rapid antigen tests will evaluate the specimens for influenza, SARS-CoV-2, RSV, and group A streptococcus. In addition, RT-PCR will also be performed as a secondary diagnostic to validate antigen testing, with plans to perform BioFire® Respiratory 2.1 panel to accurately detect and identify the pathogens most associated with respiratory infections. Breath samples will be collected into the portable CLARION device for analysis, and into Tedlar® bags and sorbent tubes for laboratory analysis on a commercial benchtop GC-MS. GC-MS data from the CLARION platform will be processed to generate a fingerprint pattern consisting of calibrated retention times and chemical identities for each VOC peak. These patterns 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 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 ACHILLES (IARPA MAEGLIN program), containing a pre-concentrator-thermal desorption GC-MS, adding an embedded miniature breath collector (MBC). System modifications and optimizations are ongoing to reduce sampling time (1-2 minutes), while obtaining sensitivity required for identifying disease state biomarkers in breath.

Deployment pictures of the ACHILLES prototype



MBC

Envisioned CLARION Platform (7.5 L)

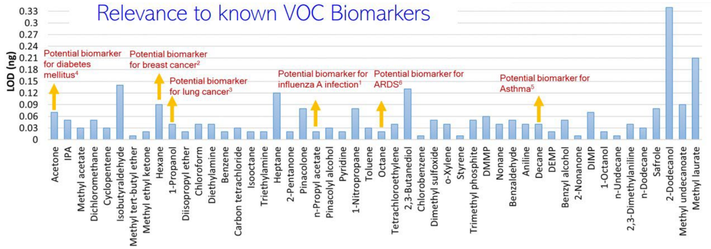


Figure 1. TOP: ACHILLES (10 L) modifications will integrate a miniature breath collector (middle) into a standalone CLARION platform for point-of-care breath collection and analysis platform. **BOTTOM**: LODs for a subset of 50 chemicals from the MAEGLIN program’s target chemical list. The Relevant VOC's with as potential breath biomarkers are highlighted.

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

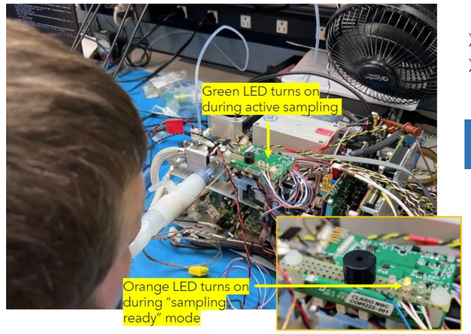


Figure 2. The first prototype of the MBC has been successfully integrated into the CLARION platform. Initial studies of vapor phase analytical standards have shown sensitivity of the system in the low parts-per-billion to high parts-per-trillion range. Breath collection and subsequent GC-MS analysis for over 50 samples have been performed on the prototype system.

Clinical Study & Preliminary Results

The IRB has been accepted and we plan to begin enrollment for Campaign-1 in Summer of 2024.

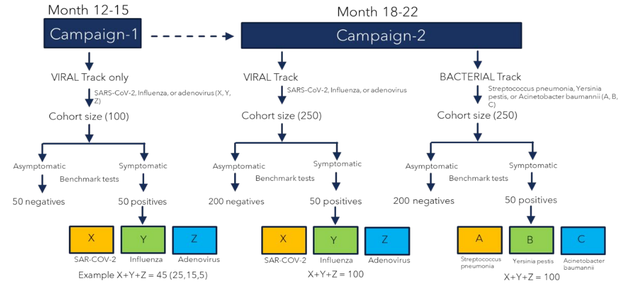


Figure 3. Clinical Study Design for two breath collection campaigns

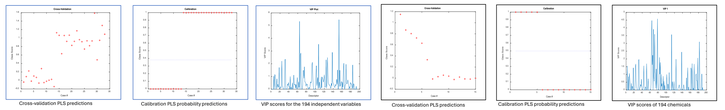


Figure 4. PLSDA model for mint study (L) and addition of Confounders for subjects with cold symptoms (R)

Upcoming Work

- Perform clinical studies and identify relevant VOC biomarkers in exhaled breath that distinguish between healthy population and infected individuals
- Leverage high resolution mass spectrometry to drive CLARION optimization
- Train CLARION system on established VOC algorithms and correlation patterns of VOC discriminators with specific disease states/pathogen infection.

Acknowledgments

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