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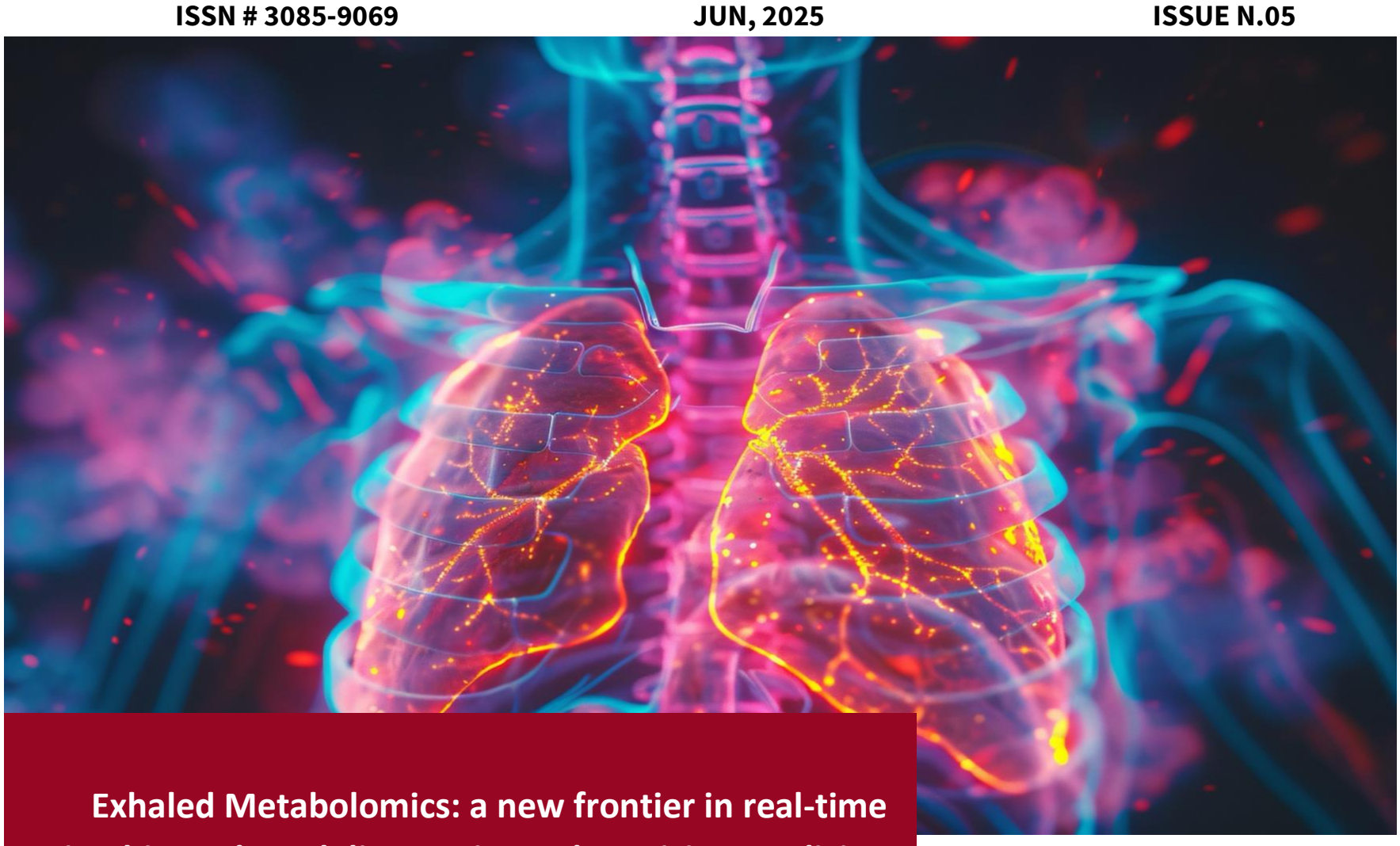


Exhaled Metabolomics: a new frontier in real-time microbiome-based diagnostics and precision medicine

Editor-in-Chief: Dr. Deivis O. Guimarães
Gon1 Biotech frontiersofbioscience@gon1.com.br
Av.N.S Navegantes, 955/719 Vitoria/ES CEP 29050335

Dr. Thulio Gandra
Dr. Deivis Guimarães

Exhaled metabolomics, also known as *breathomics*, is emerging as one of the most promising technological frontiers for assessing gut microbiota functionality in a non-invasive, real-time, and highly precise manner. This article explores the physiological pathway of volatile organic compounds (VOCs), from microbial production in the intestinal lumen to their detection in exhaled breath. We present recent advances in identifying VOCs reflective of fermentative, inflammatory, and metabolic processes, with a focus on short-chain fatty acids (SCFAs), sulfur compounds, and tryptophan derivatives. Cutting-edge technologies such as SIFT-MS and PTR-MS are examined in terms of clinical applicability, analytical sensitivity, and potential for integration with point-of-care devices. We conclude that exhaled metabolomics is poised to redefine the diagnosis and monitoring of gastrointestinal, neurobehavioral, and hepatic diseases, ushering in a new era of personalized medicine driven by dynamic metabolic data.

Introduction: a new frontier in non-invasive diagnostics

The gut microbiota is now considered a functional metabolic organ, influencing digestion, immune modulation, mental health, and pharmacological response. However, assessing its real-time activity remains one of the greatest diagnostic challenges. Conventional methods, such as fecal analysis or intestinal biopsies, are retrospective, invasive, and limited in terms of functional resolution.

In this context, exhaled breath emerges as an innovative diagnostic paradigm. Volatile compounds exhaled through the lungs directly reflect microbial metabolism, bypassing hepatic filtration and offering a chemical "window" into the gut's activity. Breathomics thus enables functional, dynamic, and immediate analysis, aligning with the principles of predictive, preventive, and personalized medicine.

From microbiota to lung: The physiological route of the exhaled metabolome

The trajectory of exhaled VOCs begins with microbial fermentation of substrates in the gut, generating gases such as hydrogen (H_2), methane (CH_4), sulfur compounds (H_2S), and short-chain fatty acids (SCFAs) like butyrate and propionate.

These compounds are absorbed through the intestinal epithelium, partially metabolized by the liver (first-pass effect), and then transported via the bloodstream to the pulmonary alveoli. Their excretion occurs during expiration, alongside CO_2. Thus, VOC concentrations in exhaled air offer an integrated snapshot of microbial production, intestinal permeability, hepatic metabolism and and pulmonary gas exchange.

Breathomics and precision biotechnology: innovative volatile analysis technologies

- Classic Gases (H_2, CH_4): Traditional SIBO and Intolerance Diagnostics

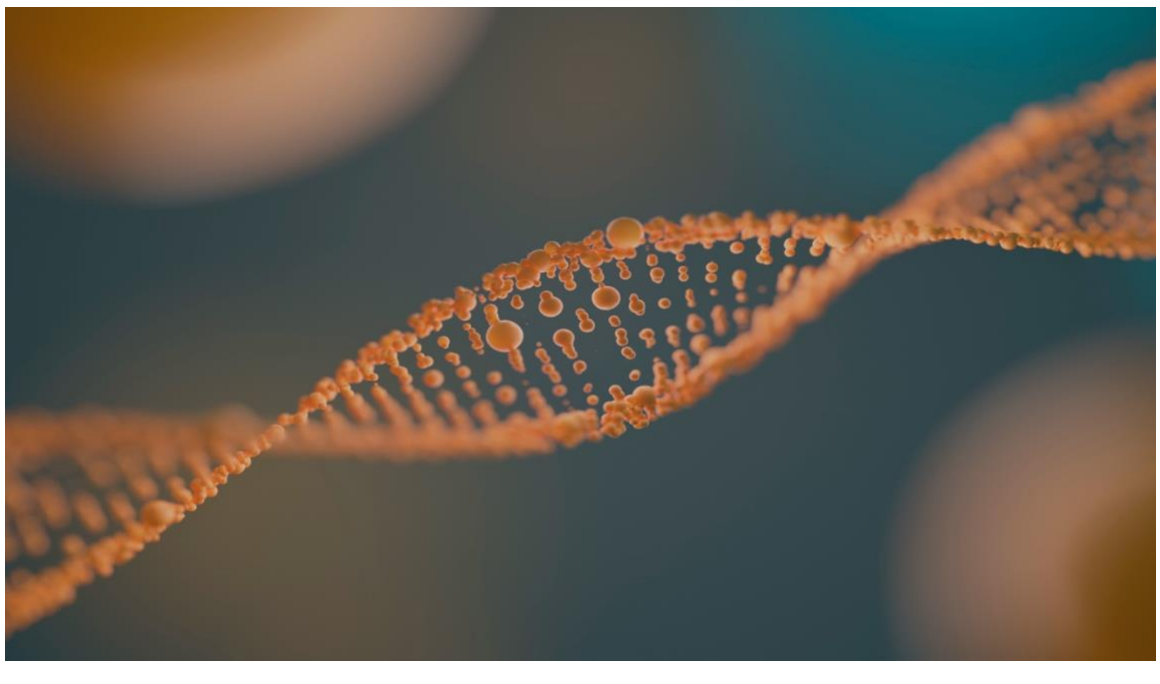
The historical foundation of breath testing lies in H_2 and CH_4 detection, associated with carbohydrate fermentation and small intestinal bacterial overgrowth (SIBO). However, these two gases fall short of representing the full metabolic complexity of the gut.

- Volatile Sulfur Compounds (VSCs): Markers of Inflammation and Dysbiosis

Hydrogen sulfide, methanethiol, and dimethyl sulfide—byproducts of sulfur-containing amino acid degradation—are biomarkers of inflammatory and proteolytic states, common in conditions such as ulcerative colitis, Crohn's disease, and colorectal cancer.

- SCFAs in Breath: The New Frontier

Detecting SCFAs or their derivatives (e.g., ketones, alcohols) in exhaled breath is one



Imagine diagnosing complex gut-related disorders not with invasive procedures or delayed lab tests, but with a single breath.

Exhaled metabolomics, or breathomics, is redefining how we access the hidden metabolic language of our microbiome in real time. At the intersection of biotechnology, microbiome science, and predictive diagnostics, this emerging field offers a revolutionary, non-invasive pathway to understand not only gastrointestinal function but also systemic and neurological health. With cutting-edge technologies now capable of detecting subtle molecular signatures in exhaled air, we are witnessing the rise of a new diagnostic paradigm—fast, personalized, and profoundly human-centered.

of the most valuable targets in breathomics. These acids serve as functional markers of beneficial fiber fermentation, enabling near-instantaneous assessment of nutritional interventions.Indole derivatives and intestinal barrier integrity

- Other Relevant Volatile Signatures

Indole, skatole, and amines: Linked to intestinal permeability and cardiovascular risk (via TMAO pathway).
Acetone and isoprene: Associated with systemic catabolic or metabolic states.

Emerging clinical applications: from gut to translational psychiatry

Breath-based metabolomics extends beyond gastrointestinal diagnostics, offering insights into:

SIBO and Functional Dysbiosis: Simultaneous measurement of H_2, CH_4, and H_2S using SIFT-MS allows precise identification of microbial overgrowth profiles.

Prebiotic and Fiber response: SCFA spikes in breath within minutes of ingestion provide real-time evidence of individual responsiveness to dietary fibers.

IBD and Celiac Disease: Profiles of sulfur compounds and putrefactive markers differentiate disease subtypes and phases.
Systemic and Hepatic Diseases: Dimethyl sulfide ("hepatic breath") is an early biomarker of liver failure and non-alcoholic fatty liver disease.

Pharmacomicrobiomics: Tracks microbial metabolism of drugs to guide dosing and prevent adverse effects.

Mental Health and Neuroscience: Emerging studies show correlations between breath VOCs and emotional states, opening doors to precision psychiatry.

Challenges and opportunities in scalability and regulation

Biological and Environmental Confounders

Diet, medications, smoking, and oral microbiota can influence breath composition. Standardized protocols and fasting procedures are essential for consistent data.

Standardization of equipment and interpretation

With varied analytical technologies, there is an urgent need for standardized reference scales, collection methods, and environmental controls.

Integration with artificial intelligence

Given the complexity of VOC profiles, large-scale databases and machine learning tools are critical to uncover clinically relevant patterns. The future of breathomics will be inseparable from bioinformatics and multi-omics platforms.

Conclusion: The future of health in a single breath

We are approaching a turning point in diagnostic medicine. Exhaled metabolomics combines accuracy, personalization, non-invasiveness, and real-time applicability. By integrating biotechnology, data analysis, and microbiome science, this approach emerges as a transformative platform for public health, preventive medicine, and personalized care. The diagnostics of tomorrow may begin with a single breath.

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Contacts:

frontiersofbioscience@gon1.com.br

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