Exhaled Breath Analysis: From Laboratory Test to Wearable Sensing

Wenzheng Heng, Shukun Yin, Yonglin Chen, and Wei Gao, *Senior Member, IEEE*

***Abstract*—Breath analysis and monitoring have emerged as pivotal components in both clinical research and daily health management, particularly in addressing the global health challenges posed by respiratory and metabolic disorders. The advancement of breath analysis strategies necessitates a multidisciplinary approach, seamlessly integrating expertise from medicine, biology, engineering, and materials science. Recent innovations in laboratory methodologies and wearable sensing technologies have ushered in an era of precise, real-time, and *in situ* breath analysis and monitoring. This comprehensive review elucidates the physical and chemical aspects of breath analysis, encompassing respiratory parameters and both volatile and non-volatile constituents. It emphasizes their physiological and clinical significance, while also exploring cutting-edge laboratory testing techniques and state-of-the-art wearable devices. Furthermore, the review delves into the application of sophisticated data processing technologies in the burgeoning field of breathomics and examines the potential of breath control in human-machine interaction paradigms. Additionally, it provides insights into the challenges of translating innovative laboratory and wearable concepts into mainstream clinical and daily practice. Continued innovation and interdisciplinary collaboration will drive progress in breath analysis, potentially revolutionizing personalized medicine through entirely non-invasive breath methodology.**

***Index Terms*—Breath analysis, respiratory monitoring, VOCs, nonvolatile substance, exhaled breath condensate, personalized medicine, wearable biosensor.**

I. Introduction

BREATH is an intricate physiological process that orchestrates gas exchange between the body's internal milieu and the external environment through the human airway. This process is precisely regulated by the central nervous system through the synchronized activity of respiratory muscles, including the diaphragm and intercostal muscles, which induce periodic volume changes in the thoracic cavity and lungs [1]. The ceaseless, autonomous activity of respiratory and cardiac muscles is essential for sustaining fundamental life processes. Under normal physiological conditions, adults engage in approximately 12-20 respiratory cycles per minute, facilitating the uptake of about 250 mL of oxygen for metabolic processes while expelling approximately 200 mL of carbon dioxide. This cyclical gas exchange not only satisfies cellular metabolic requirements but also plays a pivotal role in maintaining blood pH homeostasis [2]. The physiological significance of breathing extends far beyond gas exchange. Emerging research indicates that the respiratory process exerts substantial influences on olfactory signal processing [3], circadian rhythm regulation [4], emotional modulation [5], and cognitive function [6]. Given the fundamental role of breathing in maintaining life and its far-reaching impacts on various physiological and psychological processes, the imperative to comprehend and address respiratory health cannot be overstated.

Respiratory-related diseases present a formidable challenge to global health. Over the past five years, coronavirus disease (COVID-19) has emerged as a representative global infectious disease, directly claiming ~7 million lives, and indirectly contributing to a death toll surpassing 15 million [7]. This emergence, coupled with other respiratory epidemics such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and pandemics like H1N1 underscores the urgent and critical necessity for extensive research into the respiratory system [8]. As a key research field in modern medicine, respiratory diseases, such as pneumonia, chronic obstructive pulmonary disease (COPD), and lung cancer, among other diseases, pose serious threats to human health and constitute major burdens on global public health expenditures. COPD, an irreversible and progressive pulmonary disease, annually causes more than 3 million deaths, ranking as the third leading single cause of death globally and posing a significant threat to the health of billions worldwide [9]. According to data from the World Health Organization (WHO), approximately 262 million people globally suffer from asthma [10]. Lung cancer, with an annual diagnosis rate exceeding 2.2 million and a death toll of 1.8 million, is equally serious [11]. Even relatively minor respiratory issues, such as obstructive sleep apnea syndrome (commonly known as snoring), can significantly impact the quality of life for patients and their partners, increasing the risk of cardiovascular diseases and cognitive impairments [12]. The prevalence of respiratory infectious diseases and the prominence of respiratory disorders further highlight the imperative to propel research

Manuscript received 4 August 2024; revised 4 October 2024 and 13 October 2024; accepted 13 October 2024. Date of publication 16 October 2024; date of current version 30 January 2025. This work was supported in part by the National Science Foundation under Grant 2145802, in part by the National Institutes of Health under Grant R01HL155815 and Grant R21DK13266, in part by the American Cancer Society Research Scholar under Grant RSG-21-181-01-CTPS, in part by the Army Research Office under Grant W911NF-23-1-0041, in part by the US Army Medical Research Acquisition Activity under Grant HT9425-24-1-0249, and in part by the Heritage Medical Research Institute. *(Corresponding author: Wei Gao.)*

The authors are with the California Institute of Technology (Caltech), Pasadena, CA 91125 USA (e-mail: weigao@caltech.edu).

Digital Object Identifier 10.1109/RBME.2024.3481360

efforts aimed at addressing the multifaceted challenges in breath analysis.

The significant value of breath analysis in the diagnosis and monitoring of various non-respiratory diseases has also been increasingly demonstrated. Studies have shown that breath analysis can be utilized to assess diabetes. Patients with diabetic ketoacidosis are often characterized by an olfactory signature reminiscent of "rotten apples," attributable to alterations in the levels of acetone and other ketone bodies in their exhaled breath, reflecting perturbed lipid metabolism. In cases of renal dysfunction, blood urea nitrogen levels can be non-invasively evaluated by quantifying ammonia concentrations in exhaled breath. Consequently, a "urinous" odor in the breath often implies compromised kidney function. Furthermore, breath analysis is gaining prominence in liver disease diagnosis, as evidenced by elevated sulfide concentrations in the exhaled breath of cirrhosis patients. These applications underscore the potential of breath analysis as a non-invasive diagnostic tool in the management of systemic disorders [13].

In the realm of respiratory medicine, routine examinations encompass a spectrum of diagnostic modalities, including radiological assessments, bronchoscopic evaluations, pulmonary function tests, and symptom assessments, each offering distinct clinical insights. Despite significant strides in respiratory system research over recent decades, these examinations are not without inherent limitations. Imaging techniques such as X-rays and computed tomography (CT) are limited by their inability to discern subtle structural changes and concomitant radiation exposure. Bronchoscopy, while informative, faces restrictions in routine application due to its invasive nature. Pulmonary physiological measurements, including respiratory rate and tidal volume measurements, are hampered by manual measurement instability and a lack of disease specificity. Symptom assessment is subjective, varies between individuals, and symptoms are often not apparent in early stages. Notably, in contrast to routinely monitored physiological parameters such as heart rate, blood pressure, and body temperature, physical respiratory monitoring and assessment have not received commensurate attention in clinical and daily health management paradigms [14]. This discrepancy primarily stems from the paucity of economical, portable, and accurate respiratory monitoring devices. High-precision respiratory function testing equipment, while available, is typically cost-prohibitive, operationally complex, and challenging to implement widely in quotidian health monitoring scenarios. Consequently, at present, one of the few breath parameters that people often pay attention to is respiratory rate, but its measurement in clinical settings still often relies mainly on manual operation. Concurrently, the significance of biochemical molecular changes as crucial triggers, manifestations, and primary diagnostic criteria for numerous diseases underscores the importance of comprehensive biochemical information. However, routine clinical and everyday breath analysis and monitoring frequently lack detailed biochemical detection capabilities. These limitations in existing physical respiratory monitoring technologies, coupled with the dearth of detailed biochemical information in breath analysis, illuminate the transformative potential of non-invasive, quantitative, and daily monitoring of both physical and biochemical respiratory parameters. Such advancements hold the promise of revolutionizing our understanding of the breath process and its intricate dynamics [15].

This comprehensive review aims to systematically explore the multifaceted aspects of breath analysis and monitoring, encompassing physical and chemical information, relevant biological and clinical contexts, advanced laboratory-based methodologies, and cutting-edge wearable breath monitoring devices (Fig. 1). We begin with an in-depth analysis of the physical parameters of respiration, including respiratory rate, volume, and flow rate. These parameters are examined in the context of various physiological and pathological conditions, elucidating their clinical significance. Subsequently, we delve into the gaseous chemical composition of exhaled breath, focusing on dynamic changes in oxygen and carbon dioxide concentrations, as well as the burgeoning field of volatile organic compounds (VOCs) and their potential in disease diagnosis and health monitoring. The review then extends to the biochemical characteristics of non-volatile substances in breath, exploring their value in non-invasive disease diagnosis and metabolic state tracking. Finally, we explore the emerging field of breathomics and associated data processing methods, discuss the innovative use of breath in human-machine interaction (HMI), and present our vision for the integration of these diverse analysis and monitoring technologies into a non-invasive breath-based healthcare landscape.

II. Physical Monitoring

In current respiratory monitoring, the measurement and analysis of physical parameters are key to assessing respiratory health and overall health (see Fig. 2). These parameters include respiratory rate, volume, flow rate, breath sounds, breath temperature and humidity. Backed by extensive research, substantial data, and clinical validation, these metrics are widely recognized for their utility in clinical and daily health monitoring.

A. Respiratory Rate, Volume & Flow Rate

1) Rate: Respiratory rate stands as one of the most clinically significant and easily measurable physiological parameters. As a vital sign, alongside heart rate, blood pressure, and body temperature, it serves as a fundamental indicator of human health status [16]. The normal respiratory rate for adults is usually between 12 and 20 breaths per minute, but this range may vary depending on age, physical condition, and environmental factors. Deviations from this range, such as tachypnea (>25 breaths/minute) or bradypnea (<8 breaths/minute), often signal pathological states and may serve as early warning signs for various serious conditions, including lung infections, heart failure, metabolic disorders, or neurological issues [17]. Therefore, in clinical practice, monitoring of respiratory rate is of key importance for the timely detection and evaluation of critically ill patients [17]. The respiratory rate exhibits complex interactions with the cardiopulmonary and cardiovascular systems [5], [18], primarily through cardiopulmonary coupling mechanisms. These interactions directly influence heart rate variability and blood pressure fluctuations [19], [20], [21]. Further studies have shown that conscious regulation of breathing rhythm,

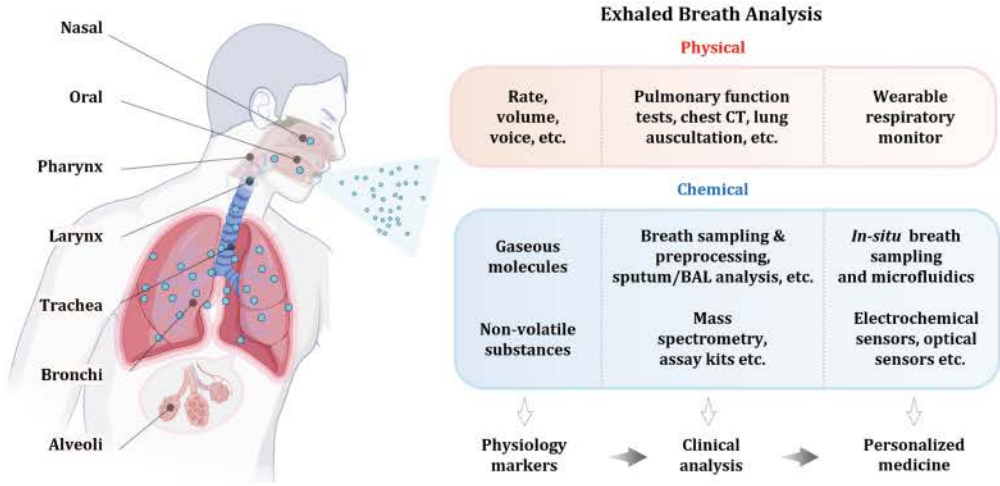

Fig. 1. Overview of exhaled breath analysis - from physiological markers to clinical and personalized medicine. BAL, bronchoalveolar lavage; CT, computer tomography.

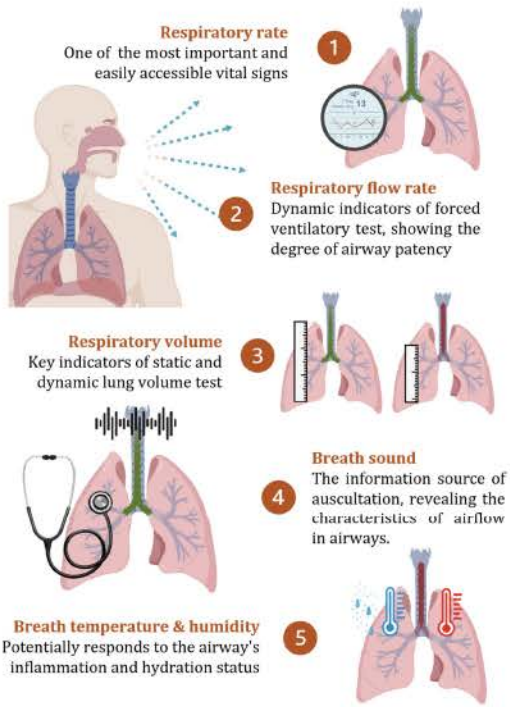

Fig. 2. Physical breath monitoring in the precision medicine via emerging wearable devices.

particularly slow, deep breaths, can significantly modulate autonomic nervous system activity [22]. In addition, respiratory rate also closely correlates with an individual's mental state and emotional experience. Stress or anxiety typically induces rapid, shallow breathing, while relaxation promotes slow, deep breaths [23]. This phenomenon not only reflects current mental states but also offers potential for active emotional regulation. Consequently, many psychological relaxation techniques and meditation practices incorporate breathing regulation as a central element. For instance, various yoga breathing exercises aim to influence the autonomic nervous system, promoting physical and mental relaxation and stress relief [24]. These techniques are not only useful in the field of mental health but have also shown positive results in the adjunctive treatment of certain diseases. For example, in asthma patients, specific breathing exercises can help improve lung function, reduce the frequency of exacerbations and improve quality of life [25].

2) Volume: Respiratory volumetric indices can be categorized into static and dynamic categories, also known as lung volume and pulmonary ventilation function [26]. These indicators can provide crucial insights into lung health and performance.

Static lung function is primarily assessed through total lung capacity (TLC) and vital capacity (VC). TLC is particularly important in evaluating restrictive lung diseases such as pulmonary fibrosis. Decreased TLC are often indicative of parenchymal lung lesions, thoracic deformities, or neuromuscular diseases [26]. For VC measurement and application, spirometry plays a vital role in assessing growth and development in children [27] and physical fitness in athletes [28], [29]. In the critical care setting, tidal volume (TV) is a key parameter for assessing and guiding ventilation strategies, with low tidal volume approaches showing improved prognosis in acute respiratory distress syndrome (ARDS) patients [30].

Dynamic lung function mainly consists of metrics such as forceful lung volume (FVC) and forceful expiratory volume in the first second (FEV1). These indices are very sensitive to most of the diseases involving the lungs. The FEV1/FVC ratio is the most used index for determining how good or bad airway patency is, and it is also one of the most important reference parameters for the diagnosis of obstructive lung disease. The FEV1/FVC ratio is greater than 80% in normal subjects [26]. Bronchodilator testing to observe changes in FEV1/FVC can be used to differentiate reactive reversible changes in the airways and is often used in the diagnosis and differentiation of COPD and asthma [31], [32].

3) Flow Rate: Respiratory flow rate primarily reflects airway patency and respiratory muscle strength. Key indicators

include Peak Expiratory Flow (PEF) [33] and forced expiratory flow (FEF) at different percentages of vital capacity ($FEF_{XX}\%$) [34], [35]. These parameters are crucial for assessing airway obstruction and pulmonary function impairment. Peak flow meters, due to their simplicity, are widely used in the basic measurement of PEF and management of asthma [36]. Furthermore, exhaled breath velocity has significant implications for gas exchange and viral transmission, rendering it of considerable importance to public health [37], [38].

4) Interrelationship: The intricate interplay among respiratory rate, volume, and flow rate forms the foundation for numerous areas of respiratory science research and clinical practice. In a single breath, the velocity-volume relationship creates a flow-volume loop, offering intuitive respiratory diagnostic information [39]. Over multiple breaths, the rate-volume relationship is reflected in minute ventilation. Resting and maximal ventilation (MV and MVV, respectively) indicate the volume of air breathed over a period in resting and forced states, respectively, serving as important indicators of metabolic and cardiopulmonary capacity [40].

This complex interrelationship guides clinical respiratory strategies and exercise regimens, which are tailored to different types of lung diseases. Patients with restrictive lung diseases (e.g., pulmonary fibrosis, asbestosis, and morbid obesity) typically exhibit rapid, shallow breathing patterns due to the higher pressures required for lung expansion. Conversely, patients with obstructive lung diseases (e.g., asthma and COPD) benefit from deep, slow breathing patterns, as airway obstruction necessitates higher pressures to overcome flow resistance, resulting in reduced tidal volumes [41].

5) Measurement Methods: The monitoring methodologies for the three respiratory parameters mentioned above can be classified into direct and indirect techniques. Direct measurement analyzes airflow parameters, while indirect methods focus on measuring changes in body or thoracic volume during respiration [42], [43]. Direct measurement encompasses mechanical, pressure differential, and thermosensitive approaches [44]. While mechanical methods, historically prevalent in spirometry, have largely been superseded due to sensitivity limitations and apparatus complexity, pressure differential and thermosensitive methods have gained prominence. These latter methods offer enhanced sensitivity and facilitate seamless integration into modern electronic systems [45]. However, they are susceptible to ambient temperature and humidity fluctuations, necessitating real-time compensation [46]. Recent advancements in ultrasonic flow meters have led to more sensitive measurements by mitigating interference from temperature and humidity fluctuations in the airflow [47], [48]. While direct measurement techniques excel in providing high-fidelity, detailed flow measurements, they typically require breath inlets or masks, potentially compromising wearer comfort.

Indirect respiratory measurements primarily focus on volumetric changes in the body or thorax during respiration. Body plethysmography, a well-established clinical method, employs air pressure measurements at various positions within a sealed space to estimate a range of respiratory parameters. This technique has proven particularly efficacious in quantifying airway resistance and has become instrumental in the diagnosis and management of obstructive pulmonary disorders [49]. Other indirect technologies include electromagnetic [50], optical [51], and acoustic [52] measurement systems, which leverage radar technology, sophisticated image processing algorithms, and sound analysis, respectively, to assess thoracic movement. These non-invasive methodologies offer superior patient comfort, rendering them especially suitable for pediatric and critically ill populations. However, the optimal implementation of these techniques typically requires fixed equipment configurations and specialized professional oversight [53].

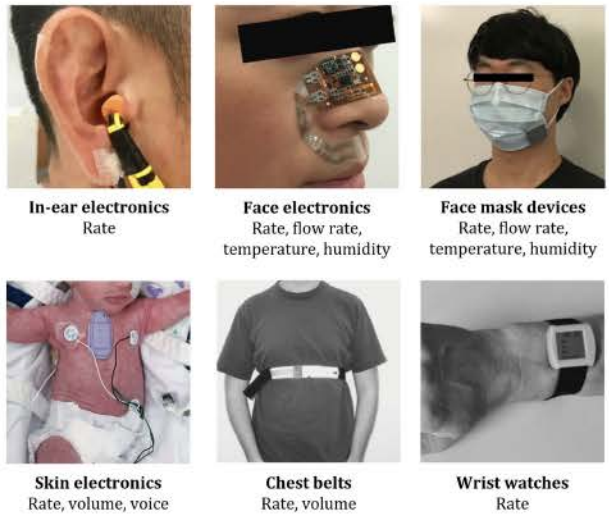

Fig. 3. Physical breath monitoring in the precision medicine via emerging wearable devices. [76], [55], [58], [85], [70], [74].

6) Wearable Devices: In recent years, wearable smart devices for respiratory monitoring have gained considerable attention [54], as shown in Fig. 3. While these devices may have certain limitations in temporal resolution and precision, they offer a distinct advantage as they enable continuous, real-time monitoring in everyday settings. This functionality offers a practical alternative to high-precision respiratory monitoring systems, which are often expensive, bulky, and impractical for routine use.

The most intuitive approach to respiratory parameter monitoring involves attaching devices to the facial region, providing direct access to breath airflow [55], [56], [57]. Face masks, now ubiquitous wearable items, serve as an ideal platform for such breath monitoring [58], [59]. with some capable of self-recharging to achieve filtration of pathogens and particulate matter [60], [61]. Current research in this domain focuses on measuring airflow vibrations [62], pressure [63], humidity [64], and temperature [65] to derive insights into respiratory health. However, several factors complicate quantitative analysis, including the spontaneous nasal cycle during human respiration, variations in device placement, and non-enclosed respiratory mask spaces. Consequently, research has predominantly yielded qualitative results, primarily regarding respiratory rate, with fewer accurate quantitative studies on respiratory velocity and volume. While some devices utilize enclosed masks for qualitative respiratory analysis, the complexity of these systems

precludes their suitability for daily use [66], [67]. Alternative approaches like chest strips utilizing electrical analysis techniques, such as electrical impedance tomography (EIT) [68] and strain [69], [70], [71] measurements, allow for respiratory analysis (rate and volume) during sleep or exercise. Concurrently, motion detection [72] and photoplethysmography (PPG) devices [73], like smart wristbands [74] and earphones [75], [76], show promise in estimating respiratory rates through algorithm-based approaches. However, these wearable devices often focus on qualitative measurements of respiratory rate or relative intensity, with limited quantitative information [77].

B. Breath Voice

Breath sounds, encompassing both audible respiratory sounds and those detected through auscultation, are vital indicators in clinical assessments. These acoustic phenomena originate from mechanical vibrations generated as air traverses the complex architecture of the respiratory system. Meticulous auscultation and analysis of these sounds enable clinicians to identify manifestations of numerous pathological conditions, including pneumonia, asthma, pulmonary infections, and obstructive sleep apnea [78]. The diverse typology of respiratory sounds provides a wealth of diagnostic information. Wheezes are characteristically associated with asthma, while crackles are indicative of conditions such as pneumonia, pulmonary fibrosis, and pulmonary edema. Stridor, conversely, signifies upper airway obstruction external to the thoracic cavity [79], [80]. Moreover, cough sounds, characterized by sudden expulsion of air accompanied by distinctive sounds, serve as important clinical markers in over 100 diseases and medically significant conditions [81]. As an example, breath and cough sounds can be used to distinguish and diagnose COVID-19 [82].

Clinically, the assessment of respiratory sounds primarily relies on the use of stethoscopes to auscultate various thoracic regions, facilitating the acquisition of acoustic information from diverse pulmonary structures. However, the accurate interpretation of these acoustic signals often necessitates substantial clinical experience and can be highly subjective [80]. The advent of digital stethoscopes and artificial intelligence has precipitated revolutionary changes in auscultation techniques [83], [84]. For instance, a flexible wireless auscultation device, incorporating miniature wireless chips and filtering functions, has demonstrated the feasibility of remote breath voice monitoring. This technology has proven to be a viable solution for remote monitoring of breath voice, particularly in critical cases such as premature infants, where it can help detect airway obstructions, and in patients with pulmonary surgical conditions [85].

C. Breath Temperature & Humidity

Exhaled breath temperature (EBT) has shown potential correlations with airway inflammation, particularly in conditions like asthma and COPD [86]. Two primary parameters are considered: temperature rise time and plateau temperature [86], which may reflect microvascular function, inflammation status, or airway remodeling in the small airways. [87]. In asthma, elevated EBT may be associated with bronchial congestion due to inflammation or increased microvasculature resulting from airway remodeling [88]. Conversely, lower EBT in COPD might indicate reduced bronchial vascular function [89], [90]. However, it's important to note that monitoring methods and devices can significantly influence EBT, necessitating standardized protocols [91].

The relative humidity of exhaled breath typically ranges between 60-80% [92]. Some studies suggest a potential link between breath humidity and body hydration status, with factors such as alcohol consumption and physical exercise potentially influencing these measurements [93]. Furthermore, other research implies that breath humidity may serve as an indicator of certain pulmonary inflammations or diseases [94], [95]. Despite these intriguing findings, medical research on exhaled breath humidity remains limited in its clinical promise and applicability.

Wearable temperature and humidity sensors have undergone significant advancements, primarily attributed to their streamlined system architecture and exceptionally rapid response times. These characteristics render them particularly suitable for quantifying respiratory rate and intensity [96], [97], [98]. Notably, nanomaterial-based sensors have emerged as a promising avenue for respiratory temperature and humidity monitoring, due to the unique properties conferred by their microstructures [99], [100].

III. Exhaled Gaseous Detection

Breath, as a gaseous medium, facilitates the continuous exchange of molecules between the body's internal milieu and the external environment. With the advent of non-invasive research, the analysis of respiratory gaseous molecules has become a burgeoning area of interest. From the fundamental basis of breathing - the inhalation of oxygen and expulsion of carbon dioxide - to everyday oral odors and alcohol breath, to the apple-like scent or urine odor of patients' breath, the human body continuously manifests its health status through the composition of gaseous molecules it exhaled (Fig. 4).

A. Sampling Methods

Breath gas monitoring methodologies can be categorized into offline analysis and online real-time monitoring. The former typically involves the collection of exhaled breath in polymer receptacles, followed by preprocessing techniques such as adsorption or enrichment. Afterward, thermal desorption is performed prior to analysis [101]. While offline analysis offers more reliable and precise results, it lacks the dynamic nature and convenience of real-time detection for tracking temporal changes and long-term trends. Online real-time breath monitoring imposes stringent requirements on response time, demanding a duration significantly shorter than a single respiratory cycle (approximately 4 seconds) [102]. Additionally, some online real-time monitoring devices incorporate air pumping systems to refresh gas within the detection chamber, enhancing accuracy but increasing their size [103]. When it comes to the physiological sources of breath sampling, it is imperative to understand the unique nature of the airway as a semi-open gas environment. This environment consists of two key components: alveolar end-tidal air and dead

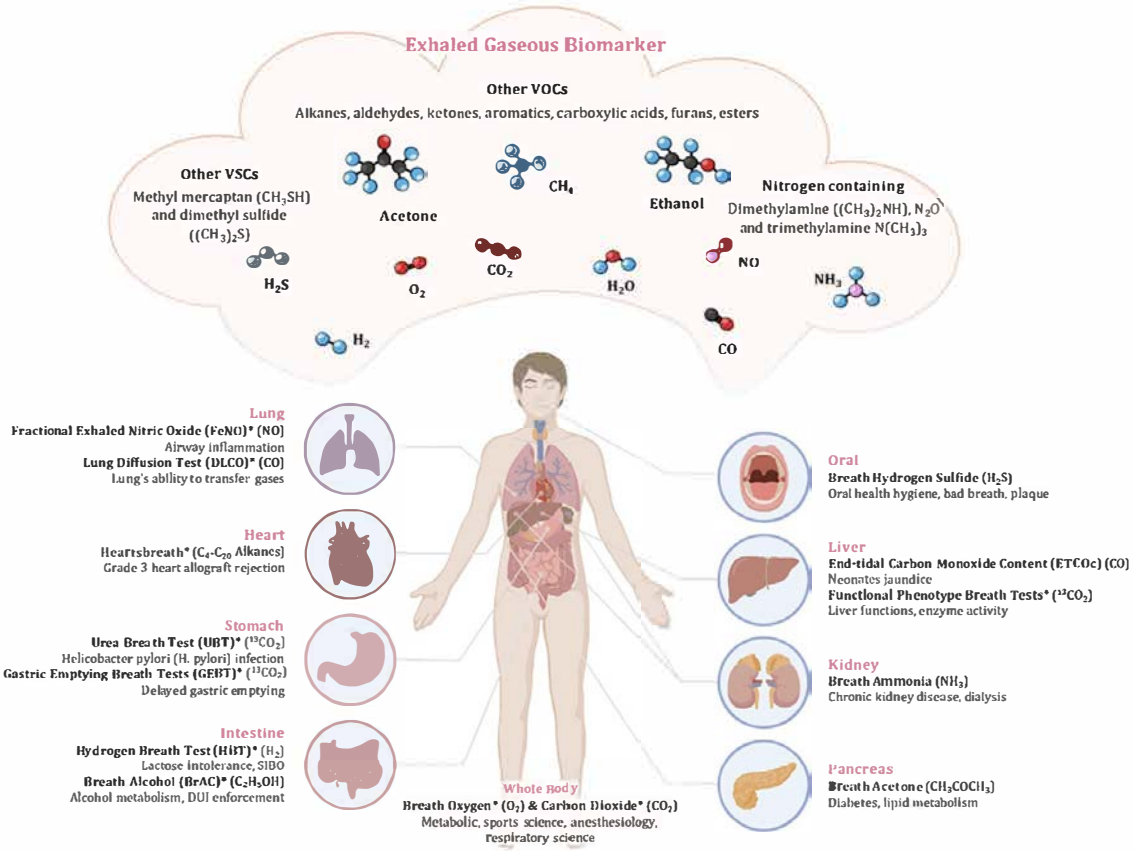

Fig. 4. Representative gaseous chemical biomarkers in human exhaled breath and corresponding organ disorders. * means approved by U.S. food and drug administration (FDA); SIBO, small intestinal bacterial overgrowth; DUI, driving under the influence.

TABLE I
CHARACTERISTICS OF EXHALED GAS MOLECULAR DETECTION METHODS

Detection technology	Sensitivity/ LOD	Selectivity	Response time	Cost	Miniaturization/ Wearability	Advantages	Shortcomings	Biomarker examples
Mass spectrometry	Excellent; ppb-ppt	Excellent	(GC-based) minutes; (Direct MS) seconds	High	Limited	Detect multiple gases simultaneously; Analyze unknown samples	Requires professional operation and complex sample preparation	$^{13}CO_2$, VOCs,
Semiconductor	Moderate; ppb-ppm	Low	Seconds-minutes	Low	Easy	User-friendly; Suitable for gas pattern analysis	Poor selectivity and stability; Temperature and humidity interfering	Specific VOCs
Electrochemical	Moderate; ppb-ppm	High	Seconds-minutes	Low	Easy	Low power consumption	Limited lifespan; Need for periodic recalibration	Alcohol, NO,CO, H_2, O_2
Optical	Moderate; ppb	Moderate	Sub-seconds	Moderate	Feasible	Non-consumption analysis; Real-time monitoring capability	Depends on gas optical propetery and light path	CO_2
Chemiluminescent	High; ppb	Excellent	Seconds	High	Limited	Detect low concentration specific gases	Only applicable to specific gases; May require reagents	NO

space air. The varying compositions of these components play a crucial role in influencing the concentration of analytes originating from diverse physiological sources. By adopting specific breath collection modes, it becomes possible to exert control over these gas sources [104].

B. Detection Methods

A myriad of methodologies is available for the detection of breath gases (Table 1), each offering distinct advantages and specific applications. As illustrated in Fig. 5, sensors based on electromagnetic, chemical, and optical principles provide a comprehensive toolkit for exhaled gas analysis.

1) Gas Chromatography: A widely utilized technique for separation and detection, GC leverages the difference in partition coefficients between the stationary and mobile phases to achieve separation. Samples are injected into a column coated with a liquid or solid stationary phase using a carrier gas. The varying interactions of each component with the stationary phase result in different migration rates, facilitating separation. GC is often coupled with detection techniques like mass spectrometry (MS), flame ionization, and ion migration spectrometry (IMS) [105]. It is regarded as the gold standard for detecting exhaled volatile gases due to its exceptional sensitivity, specificity, and accuracy. However, GC necessitates complex sample preparation, has lower detection throughput, and is not conducive to real-time measurements [106], [107].

2) Direct Mass Spectroscopy: Direct MS technologies like proton transfer reaction mass spectrometry (PTR-MS) and

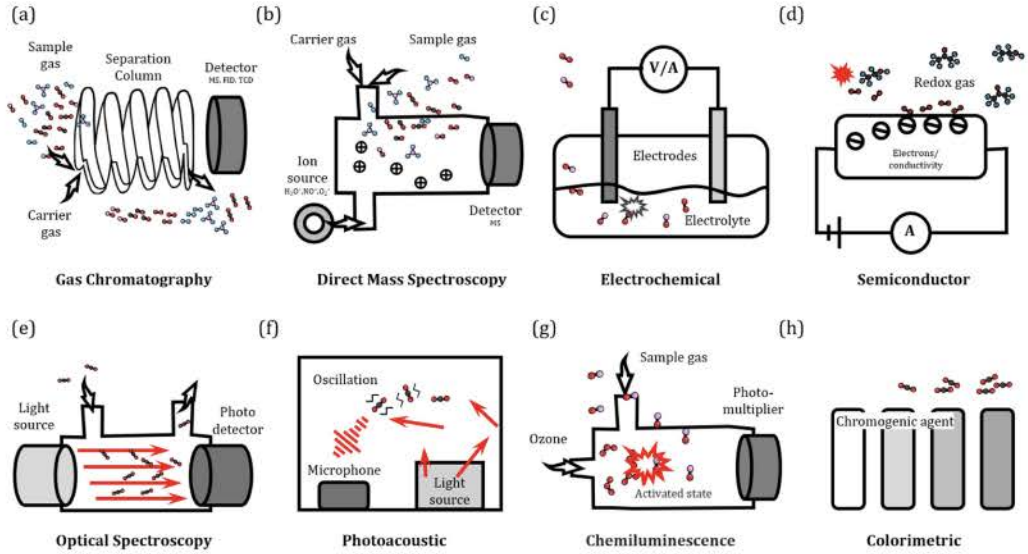

Fig. 5. Emerging gas sensing strategies in breath analysis. Thermionic Ionization Detector (TID), and Thermal conductivity detector (TCD).

selected ion flow tube mass spectrometry (SIFT-MS) techniques have gained prominence for their online real-time detection capabilities in breath gas analysis [108]. These methods directly ionize compounds in exhaled gases and measure their mass-to-charge ratios. While they offer advantages such as low fragmentation ionization and the absence of pre-enrichment or pre-separation, they have limitations in molecular identification and complex sample analysis. Despite these challenges, they are evolving as ideal alternatives or complementary technologies to traditional mass spectrometry. Specifically, PTR-MS has some limitations in detecting molecules with low proton affinity due to its inherent H_3O^+ ionization mechanism; whereas SIFT-MS provides a broad selection of ion sources such as H_3O^+, NO^+, and O_2^+, expanding the detection range. However, the high cost of the equipment and the relatively complex operation limit their applications in daily life to some extent [109].

3) Electrochemical: As one of the earliest methodologies for breath analysis [110], electrochemical sensors detect redox reactions of electroactive gaseous substances on electrode surfaces or pH changes in electrolytes due to gas dissolution [111]. Electrochemical sensors are cost-effective and portable, rendering them suitable for real-time and wearable monitoring in both daily life and clinical settings [112], see Fig. 6(a). Recent advancements in solid electrolyte research have enabled electrochemical sensors to operate at ambient solution-free environments for prolonged periods [113]. However, these sensors are constrained by specific gas species, require regular calibration, have lower sensitivity, and are less suitable for very trace gas detection.

4) Semiconductor: Semiconductor sensors exploit the interaction between gas molecules and semiconductor surfaces (e.g., metal oxides, carbon-based materials) for target gas detection. The reaction between the gas molecule and the semiconductor surface induces changes in carrier concentration or produces adsorption effects, altering conductivity [114]. Semiconductor sensors are cost-effective, exhibit rapid response times, and are easily integrated, making them the most extensively researched wearable gas sensors. However, their detection principle, based on the redox properties of gas molecules, can lead to poor selectivity and challenges in accurately distinguishing specific gas molecules [115]. To address this, arrayed semiconductor sensors coupled with machine learning algorithms for array data analysis offer enhanced discrimination and molecular specificity in complex gaseous environments [116]. Furthermore, certain semiconductor materials also necessitate high-temperature environments and are prone to humidity interference [117], [118]. Consequently, as depicted in Fig. 6(b), pre-removal of interfering components from exhaled gas prior to detection appears to be a viable option.

5) Optical Spectroscopy: Spectroscopy is based on the absorption of specific light wavelengths by target gas molecules. Specifically, as light passes through a target gas-containing matrix, molecules absorb light at frequencies matching their characteristic vibrations, producing absorption peaks in the incident light's energy spectrum [119]. This technique offers real-time analysis and simplicity [120]. Recent advancements in semiconductor laser diodes and photodetectors have led to the miniaturization of spectrometric equipment, including portable devices [121]. However, achieving high sensitivity requires a sufficiently long effective gas path length, posing challenges for further miniaturization and limiting its application in wearable devices.

6) Chemiluminescent: Chemiluminescence is a detection technique relies on the emission of light from energy transitions and releases during specific chemical processes. The quantification of analyte concentration is achieved indirectly through the measurement of chemiluminescent signal intensity. The selection of chemical reaction systems or sensor materials that catalyze the luminescent reaction is crucial [122]. Chemiluminescence is characterized by its simplicity, high sensitivity, and excellent specificity, and it does not require external excitation sources. It finds particular utility in detecting nitric oxide in

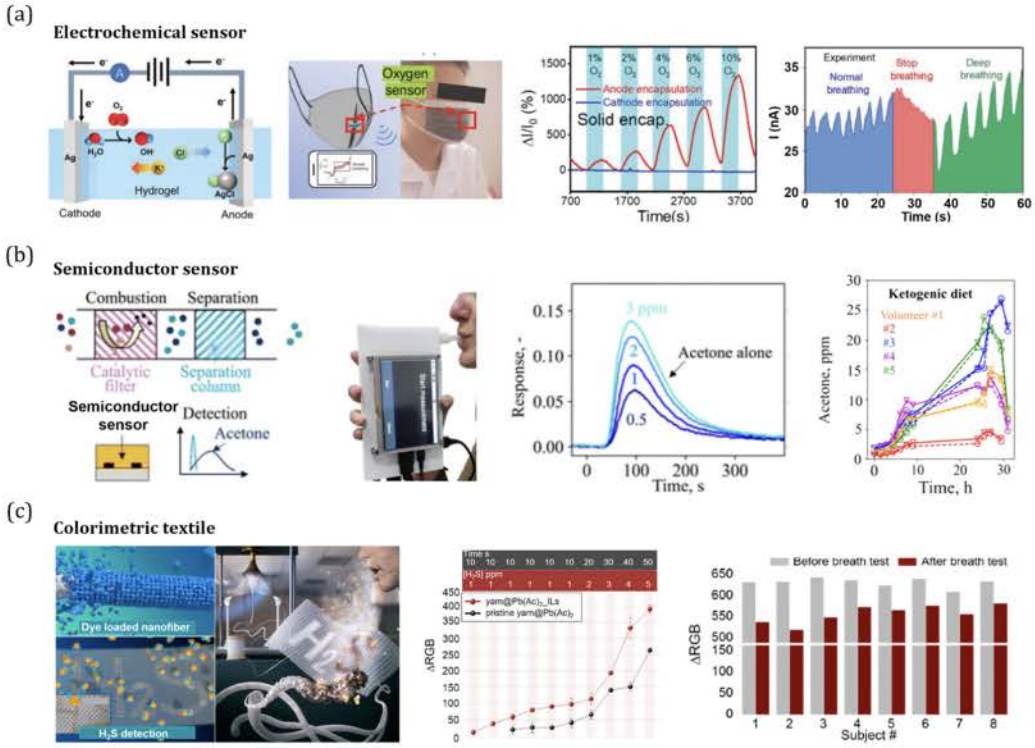

Fig. 6. Miniaturized gas sensing system development for in situ breath analysis. (a) Hydrogel material-based electrochemical oxygen sensor for breath oxygen measurement in a mask device. [165] (b) A portable semiconductor sensor based on interferon filtering and separation for exhaled acetone analysis. [188] (c) A colorimetric textile based H_2S sensor for halitosis breath detection. [127].

exhaled breath for medical diagnostics [123], [124]. However, the requirement for additional chemical substances, such as ozone, presents challenges for miniaturization.

7) Others: In addition to the aforementioned methodologies, a diverse array of techniques has been applied for exhaled gas sensing, including colorimetric methods [125], [126], [127], photoacoustic [128], [129], thermal conductivity sensors [130], and surface plasmon resonance techniques [131], [132] etc. Colorimetric methods are among the simplest and most stable sensor technologies available, making them particularly well-suited for the construction of wearable devices (Fig. 6(c)). However, their selectivity and sensitivity are relatively limited compared to other techniques.

C. Biomarkers

1) Oxygen and Carbon Dioxide: Oxygen, an essential element for sustaining life, plays a vital role in biological processes. During the respiratory cycle, atmospheric oxygen enters the pulmonary system, diffusing across the alveolar-capillary membrane into the circulatory bloodstream. Here, it binds to erythrocyte hemoglobin, forming oxyhemoglobin, which transports oxygen to various tissues and organs. Within these tissues, oxygen dissociates from hemoglobin and participates in cellular respiration, acting as the terminal electron acceptor in the mitochondrial electron transport chain. This process culminates in the production of adenosine triphosphate (ATP), the primary energy currency of cells, powering diverse cellular functions. [133].

Oxygen uptake (VO_2) is a critical measure, reflecting the amount of oxygen absorbed and utilized by the body. In exercise physiology, VO_2 reflects the consumption of oxygen by exercising muscles. By analyzing the oxygen content in inhaled and exhaled air, researchers can quantify VO_2, providing insights into exercise capacity and metabolic capabilities. Within seconds to minutes after the onset of intense exercise, VO_2 may rise rapidly from about 0.25 L/min at rest to an individual maximum that may exceed 5 to 6 L/min, known as maximal oxygen uptake (VO_{2max}) [134], [135]. VO_{2max} has a close correlation with exercise and metabolic capacity [136], [137]. The kinetics of VO_2 changes are also commonly used to analyze cardiopulmonary function in patients with pathologically slowed VO_2 kinetics, such as those with COPD and other obstructive lung diseases [138].

While oxygen is essential for cellular respiration, it also gives rise to a metabolic waste product: carbon dioxide. After carbon dioxide is produced during cellular metabolism, it needs to be transported through the bloodstream to the lungs for removal. Carbon dioxide is transported in the blood in three main forms: dissolved in plasma, combined with hemoglobin to form carbaminohemoglobin, or converted to bicarbonate. In the capillaries, carbon dioxide diffuses into the erythrocytes, where it partially combines with water to form carbonic acid, which rapidly dissociates into hydrogen ions and bicarbonate by the enzyme carbonic anhydrase. This process plays a key role in maintaining acid-base balance and metabolic homeostasis [139]. Eventually, carbon dioxide is re-released in the alveolar

capillaries, diffuses from the blood into the alveoli, and is expelled from the body through exhalation.

Oxygenation and ventilation are independent physiological processes, and monitoring oxygenation alone, such as through pulse oximetry, is insufficient for assessing ventilatory function. Carbon dioxide levels, on the other hand, provide a more accurate reflection of ventilation [140]. The study of carbon dioxide is particularly relevant in the context of hypoventilation due to lung diseases, such as hypercapnia resulting from delayed carbon dioxide removal [141] or hypocapnia caused by hyperventilation [142]. Exhaled carbon dioxide monitoring has important clinical applications, including confirming endotracheal intubation and recognizing the serious consequences of mistaken esophageal intubation [143]. Additionally, it plays a vital role in diagnosing obstructive sleep apnea syndrome (OSAS), enabling timely intervention. Another significant medical application is the breath $^{13}CO_2$ test. This technology involves administering a substance labeled with a stable isotope of carbon (^{13}C) to the subject, which, upon metabolism, produces $^{13}CO_2$. The ratio of $^{13}CO_2$ to $^{12}CO_2$ in the exhaled breath is then measured, providing valuable information about metabolic processes in the body [144]. For instance, the Breath $^{13}CO_2$ test can be used to assess liver function [145], diagnose Helicobacter pylori (HP) infections [146], and monitor metabolic disorders [147]. Furthermore, synergistic research on oxygen and carbon dioxide, exemplified by indirect calorimetry, estimates energy metabolism and receptor utilization, offering a profound understanding of human metabolic dynamics and their impact on overall health [148]. Thus, carbon dioxide monitoring stands as a cornerstone in gaining insights into the patient's respiratory and metabolic state.

Four prevalent clinical monitoring methods are employed for the in vivo assessment of oxygen and carbon dioxide: 1) arterial blood gas analysis (PaO_2, $PaCO_2$), 2) end-tidal breath analysis ($PetO_2$ $PetCO_2$), 3) pulse oximetry (SaO_2), and 4) transcutaneous gas analysis ($PtcO_2$, $PtcCO_2$). Blood gas analysis serves as the gold standard for evaluating respiratory function and blood acid-base balance, but its invasive nature presents challenges for continuous monitoring [149], [150]. The other three non-invasive methods as alternatives can reflect blood gas parameters under certain conditions [151]. End-tidal analysis directly analyzes exhaled gas composition, offering superior real-time capabilities, albeit requiring cumbersome equipment. Pulse oximetry is a non-invasive method that measures the oxygen saturation ratio in arterial blood by analyzing light absorption changes during pulsatile blood flow. Although it is convenient, it can be affected by factors like low perfusion, leading to potential inaccuracies [152]. Transcutaneous gas measurements provide a more comprehensive assessment of tissue gas content. This technique involves locally heating the skin to induce vasodilation and enhance gas diffusion. By doing so, it more accurately reflects blood gas values, including not only oxygen but also carbon dioxide levels. Consequently, transcutaneous gas monitoring offers broader applicability in clinical settings, enabling continuous assessment of both ventilation efficiency and tissue oxygenation status. [153].

Clinical oxygen and carbon dioxide sensing systems typically consist of sampling devices and sensing units. Sampling devices can be categorized based on medical applications and wear locations, including blood gas analyzers [154], Douglas bags [155], respiratory masks [156], transdermal patches [157], and indirect calorimetry hoods [156], among others. Regarding gas sensing units, current CO_2 sensors for respiratory gas analysis are based on Non-dispersive infrared (NDIR) principles [158], offering rapid response but requiring gas chamber and air pump systems for gas renewal. For blood gas and transcutaneous analysis of dissolved gases and miniaturized devices, CO_2 analysis techniques rely on electrochemical technology using Severinghaus electrodes [159]. Oxygen analysis across various forms is based on electrochemical Clark electrodes [160].

Recent research has focused on wearable analytical devices, such as NDIR-based masks and skin electronic systems for CO_2 concentration measurement [161], [162]. Wearable oxygen sensing devices utilize colorimetric [163], [164] or electrochemical methods [165], offering miniaturization and integration potential. However, practical performance still needs improvement in terms of response speed, measurement accuracy, calibration frequency, membrane replacement, and duration. From systematic perspective, minimizing the size of wearable sensors while maintaining measurement precision is crucial for realizing the full potential of this field.

2) Nitric Oxide: Fractional exhaled nitric oxide (FeNO) is an important biomarker in diagnosing and managing airway inflammation. Nitric oxide is a gas molecule produced by airway epithelial cells under the influence of specific enzymes such as inducible nitric oxide synthase (iNOS). Its concentration accurately reflects the inflammatory level of the airways, providing clinicians with a non-invasive, rapid, and reliable assessment method to diagnose and treat airway inflammation, like asthma. Specifically, due to chronic airway inflammation, asthma patients typically have higher FeNO levels than healthy individuals. Through regular FeNO measurements, doctors can dynamically assess the severity of airway inflammation and adjust treatment plans accordingly, particularly the dosage of anti-inflammatory treatments like inhaled corticosteroids. [166]. Besides asthma, FeNO measurement is also applicable to other eosinophil-related inflammatory airway diseases such as COPD, allergic rhinitis, and eosinophilic bronchitis [167]. In these conditions, changes in FeNO levels can reflect disease states and treatment efficacy, providing an important reference for clinical decision-making.

Two main methods are used to detect exhaled nitric oxide: the ozone chemiluminescence method, considered the gold standard, and electrochemical devices suitable for portable applications. In the chemiluminescence method, ozone (O_3) reacts with nitric oxide (NO) to produce nitrogen dioxide (NO_2) and oxygen (O_2). During the formation of nitrogen dioxide, some NO_2 molecules are in an excited state (NO_{2*}). As these excited NO_2 molecules return to their ground state, they emit photons (i.e., luminescence) [168]. This principle is used in commercial instruments, like the model 280i by Sievers. With electrochemical technological advancements, FeNO measuring devices (such as NIOX MINO) are becoming more portable and suitable for a broader range of clinical and home environments, making personal, independent measurements possible [169].

These devices measure NO concentration by oxidizing NO at a platinum electrode at 0.8 V, correlating the oxidation current with NO concentration after removing interfering gases and other components [170]. However, NO concentrations obtained through commercial electrochemical devices are generally slightly lower than those from chemiluminescence devices [171].

3) Ammonia: Ammonia in exhaled breath is closely related to protein metabolism in the body, primarily originating from the breakdown of proteins, amino acids, and urea. The metabolism and excretion of ammonia is a physiological process involving the coordinated action of multiple organ systems [172], [173], with the oral cavity being a significant source of ammonia in exhaled breath. Urea in saliva is broken down by urease produced by oral bacteria, generating substantial amounts of ammonia, which helps neutralize acidic substances, protecting the oral mucosa and teeth from acid erosion [174]. This natural buffering mechanism plays a crucial role in maintaining oral health. In certain disease states, the concentration of ammonia in exhaled breath can change significantly, thus holding potential diagnostic value. For instance, patients with renal insufficiency have markedly elevated urea levels in blood and saliva due to impaired urea excretion. This leads to the production of large amounts of ammonia in the oral cavity, giving the patients' breath a characteristic ammoniacal odor. This phenomenon is not only a clinical manifestation of renal insufficiency but also offers possibilities for non-invasive kidney function assessment [175]. Furthermore, the levels of exhaled ammonia are also associated with HP infection in the stomach. Studies have shown that without urea ingestion, HP-positive individuals have lower exhaled ammonia levels compared to normal subjects. However, upon urea ingestion, HP-positive individuals exhibit a notable increase in ammonia levels due to the urease produced by HP in the stomach, which breaks down urea into ammonia. This ammonia is then absorbed into the bloodstream and exhaled through the lungs. In contrast, normal individuals show minimal change in ammonia levels [176]. This difference provides a theoretical basis for developing HP infection diagnostic methods based on exhaled ammonia detection [177].

For the detection of breath ammonia, a crucial point to consider is that ammonia is highly soluble in water. Therefore, humidity measurement or dehumidification is necessary before detecting gaseous ammonia. Numerous methods can achieve breath ammonia detection [178]. However, most methods rely on complex systems and are not suitable for daily monitoring. Despite the development of wearable devices based on chemiresistive [179] and colorimetric [180] principles for ammonia detection, these devices have not yet provided in situ quantitative measurement data.

4) Acetone: Acetone, a prominent gas molecule in biological analysis, is primarily produced through fat metabolism in the body. When carbohydrate supply is insufficient, the body turns to fat reserves for energy, generating ketone bodies like acetone during ketogenesis. Acetone is released into the bloodstream and expelled through breath [181]. In specific conditions, such as in diabetic ketoacidosis, prolonged fasting, or ketogenic diets, the concentration of acetone in exhaled breath can increase significantly [182]. In healthy individuals, the concentration of exhaled acetone is relatively low, typically ranging from 0.1 to 2 ppm. Mild fasting or low-carbohydrate diets may elevate acetone concentrations to between 2 and 10 ppm, while in cases of diabetic ketoacidosis or strict ketogenic diets, the concentration of acetone in exhaled breath may exceed 100 ppm, demonstrating a wide range of concentrations [183]. Due to this variability, breath acetone analysis shows great promise in the fields of diabetes management [184], metabolic nutrition [185], and liver function assessment [186].

For offline measurement of exhaled acetone content, GC-MS is considered the gold standard. From the perspective of portable, wearable online measurements, chemiresistive and electrochemical sensors are popular research areas [183]. Chemiresistive sensors utilize nanomaterials to enhance sensitivity and selectivity for acetone gas, but have difficulty eliminating interference from other gases. Consequently, some research focuses on preprocessing breath gas to remove interfering components [187], [188]. Electrochemical sensors face challenges in constructing the chemical reaction system, with approaches based on enzyme systems requiring further evaluation of selectivity [189], [190]. Other sensors are based on strong acid electrolytes, which significantly limit their potential for wearable applications [191], [192].

5) Hydrogen and Methanol: Hydrogen-producing bacteria, especially anaerobic bacteria, are present in the intestines of both healthy people and patients suffering from lactulose intolerance or small intestinal bacterial overgrowth. These bacteria produce hydrogen by fermenting unabsorbed carbohydrates. When small intestinal carbohydrates are malabsorbed or small intestinal bacteria are overpopulated, large amounts of unabsorbed carbohydrates reach the colon, leading to significant hydrogen production. The hydrogen is absorbed into the circulation and eventually released through expiration [193]. Although the sensitivity of the hydrogen breath test is only 30-40%, it is popular due to its non-invasiveness [194].

Measurements of methane are closely related to hydrogen concentrations. Approximately 15-30% of the human intestinal flora contains *Pseudomonas smithi*, a bacterium that converts four hydrogen atoms into one methane molecule [195]. In addition, studies have shown that methane concentration is positively correlated with the constipation severity, providing new insights for the diagnosis of intestinal dysfunction [196], [197]. Thus, combined measurements of hydrogen and methane can significantly improve diagnostic accuracy for malabsorption syndromes and small intestinal bacterial overgrowth [198].

Electrochemical [199] and chemiresistive [200] sensing technologies have made hydrogen testing equipment more affordable, increasing the popularity of non-invasive breath hydrogen tests. Some sensors based on thermal conductivity measurements are also commonly used for hydrogen detection due to the significant difference in thermal conductivity between hydrogen and other gases [201]. Additionally, sensors utilizing the Seebeck effect, where trace hydrogen undergoes combustion reactions, raising the temperature at the reaction interface, can assess hydrogen content. [202], [203]. Methane monitoring is

primarily based on optical methods, such as photoacoustic and optical absorption [204], [205].

6) Ethanol and Acetaldehyde: Breath ethanol testing has proven to be a remarkable success in the field of breath analysis, establishing itself as a reliable gold standard for alcohol detection. The strong linear relationship between breath and blood ethanol levels has made it an indispensable tool in legal and medical settings [206]. Recent research has unveiled an intriguing phenomenon: the production of ethanol in the intestines, even without alcohol consumption, suggesting a potential link to obesity and fatty liver disease. This finding offers a novel perspective on obesity-related disorders [207], [208]. Acetaldehyde, the first metabolite of ethanol, is primarily produced in the liver. The concentration of acetaldehyde in exhaled breath is typically lower than that of ethanol and can be used to assess alcohol metabolism status [209]. Furthermore, as an aldehyde, endogenous acetaldehyde is also important in cancer metabolism research [210].

Breath Alcohol Concentration (BrAC) measurement has advanced significantly, with electrochemical methods leading the way. Electrochemical fuel cell-based sensors, widely used in commercial breathalyzers, have become prevalent due to their simplicity, portability, cost-effectiveness, rapid detection, acceptable accuracy, data linearity, sensitivity, and alcohol selectivity. These attributes facilitate real-time measurements, handheld device applications, and overall efficacy in both research and practical BrAC assessment scenarios [211]. Enzymatic alcohol sensors present a promising alternative for BrAC measurement. Sensors utilizing alcohol oxidase (AOx) and alcohol dehydrogenase (ADH) enzymes provide cost-effective solutions for ethanol detection [212]. Additionally, sensors based on aldehyde dehydrogenase enzymatic reactions excel in measuring acetaldehyde, a key metabolite of ethanol [209]. These enzyme-based sensors complement existing technologies, offering advantages in terms of cost and specificity for both ethanol and its metabolites in breath analysis applications.

7) Sulfide Containing: Exhaled sulfur compounds are valuable biomarkers for oral hygiene assessment and airway inflammation detection. In oral health, bacteria in the mouth produce sulfur compounds such as hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH), and dimethyl sulfide (CH_3SCH_3) when breaking down sulfur-containing amino acids. Detection of volatile sulfur compounds (VSCs) enables evaluation of halitosis severity and periodontal disease status [213], [214]. In airway inflammation, sulfur compound detection aids in diagnosing and monitoring inflammatory conditions like asthma and COPD where elevated sulfur compound levels are observed [215].

Semiconductive chemiresistors are extensively studied for VSC detection, offering structural stability, high sensitivity, and low cost [216]. Carbon-based materials enable VSC measurements at room temperature, facilitating wearable device integration [217].

8) Carbon Monoxide: Carbon monoxide (CO) is an important biomarker for assessing smoking status [218]. Additionally, exhaled carbon monoxide (eCO) has shown potential in assessing inflammation in asthma, COPD, cystic fibrosis, and lung cancer [219], [220], [221]. Furthermore, CO is also commonly used in lung diffusion testing (DLCO) to measure the lung's capacity for oxygen absorption [222].

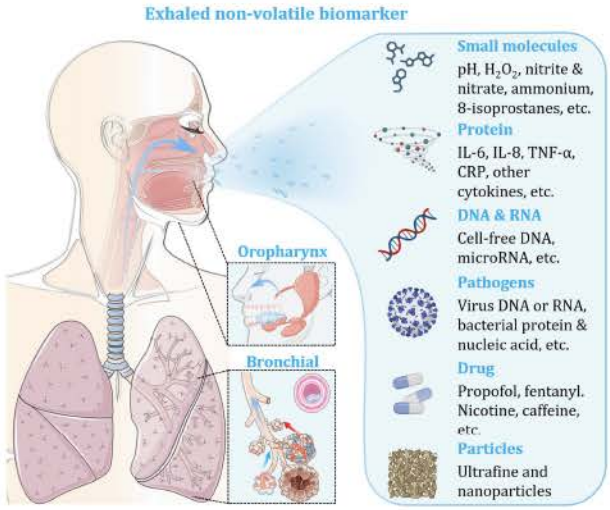

Fig. 7. Non-volatile composition in human exhaled breath.

Electrochemical sensors are the mainstream commercial devices for CO monitoring, capable of distinguishing the commonly used 6 ppm threshold for smokers [223]. However, for lower physiologically relevant endogenous CO levels, MS or NDIR methods are required for measurement [224], [225].

9) Other VOCs: The aforementioned volatile substances are relatively characteristic elements, either possessing distinct physiological properties or being present in high concentrations. However, breath still contains over 200 other VOCs of significant medical value, though clinical trial data based on these VOCs have not yet been fully integrated into our understanding of functional and mechanistic physiology [226]. Relevant medical fields include cancer [227], gastrointestinal disorders [228], pulmonary inflammation [229], cardiovascular disease [230], diabetes metabolism [231], and liver metabolism [232]. The types of compounds encompass alkanes, aldehydes, ketones, aromatics, carboxylic acids, furans, and esters. The complex interplay between these compounds and clinical physiology makes it challenging to establish a consensus on the efficacy of individual compounds in identifying specific diseases. Consequently, omics approaches are often employed to study these VOCs. For instance, furans, cyclic hydrocarbons, aromatic compounds, and benzene derivatives have been consistently identified as cancer markers. The pathophysiology of COVID-19 involves inflammatory responses characterized by oxidative stress, which is linked to aldehydes and hydrocarbons [233].

Many semiconductor-based VOC sensors, while capable of measuring the equivalent total amount of VOCs, generally lack selectivity and thus cannot be directly used for precise classification and measurement of VOCs [234]. Therefore, MS remains the primary tool for clinical detection of volatile organic compounds.

IV. Chemical Non-Volatile Substances Test

Breath non-volatile substances originate from the microdroplets of the respiratory tract. The alveolar surface is lined

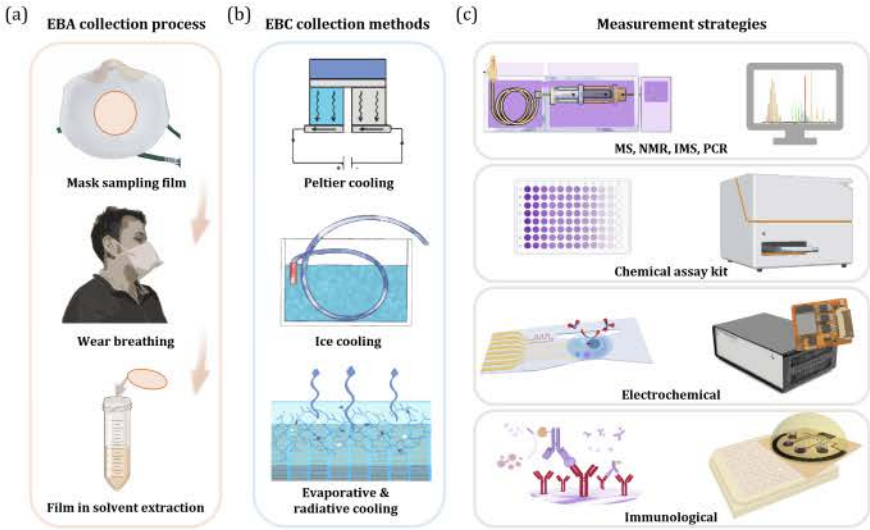

Fig. 8. Collection and detection procedures for non-volatile substances in exhaled breath analysis. (a) EBA collection process. Figures are adapted from [256] (b) EBC collection methods. (c) Measurements strategies for non-volatile substances in breath analysis. EBA, exhaled breath aerosol; EBC, exhaled breath condensate; MS, mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; IMS, ion mobility spectrometry; PCR, polymerase chain reaction.

with a surfactant and fluid layer containing various molecules. The epithelial cells lining the airways (bronchioles) are covered with airway surface liquid. During exhalation, these fluids are disturbed by airflow, forming aerosols and droplets of varying sizes. As shown in Fig. 7, these substances contain a broad range of components from small ions to macromolecules like proteins. Their composition provides valuable insights into the origin and chemical environment within the respiratory tract, making them highly promising non-invasive samples for assessing human health status.

A. Sampling Methods

Breath sampling methods for non-volatile substances offer two primary approaches: exhaled breath aerosol (EBA) and exhaled breath condensate (EBC). As illustrated in the Fig. 8(a), EBA collection utilizes collection films integrated into wearable breath platforms, such as face masks. By wearing these devices for a specified duration, sufficient EBA samples are obtained. A solvent is then added to extract and dissolve the aerosol particles, facilitating further biochemical analysis. While this method is simple and cost-effective, its reliance on external solvents can impact stability and reproducibility, limiting its use in quantitative detection and continuous monitoring.

EBC is a liquid matrix containing non-volatile substances and soluble gases. It is generated when high-temperature, high-humidity exhaled air comes into contact with a cold interface, causing breath vapor to condense into liquid while trapping aerosols and droplets. According to the Fig. 8(b), two common clinical collection methods involve using collection tubes in temporary low-temperature environments or employing thermoelectric cooling devices. While the former is simple, it has a short cooling duration and fluctuating condensation temperatures. The latter maintains stable temperatures but is energy-intensive. Both methods are bulky, hindering long-term monitoring and wearable applications. Moreover, they overemphasize extremely low temperatures ($<0\,^{\circ}C$, while the actual dew point is only about $5\,^{\circ}C$ lower than breath temperature, $\sim 30\,^{\circ}C$), resulting in excessive EBC sample production, which contradicts the current trend in microfluidic analysis. Low temperatures also result in high EBC dilution ratios and therefore lower biomarker concentrations, complicating detection. Recently, with the emergence of passive cooling technologies, hydrogel cooling and radiative cooling have been applied to the condensation process of EBC [235]. These methods are compact, energy-efficient, and suitable for wearable devices, producing desirable detection volumes and enabling continuous monitoring. Additionally, in the sampling of non-volatile substances in exhaled breath, several critical factors must be considered. Primarily, the coating material of the condensing surface at the sampling interface must possess non-adhesive properties towards biomarkers [236]. To mitigate oral saliva contamination, nasal exhaled breath collection methods can be employed, or salivary amylase tests can be utilized to verify contamination levels. Furthermore, attention must be paid to the potential degradation of active substances and dilution ratio variations of samples due to differences in temperature and humidity to ensure the accuracy and reliability of the collected data [237]. In EBC research, it is imperative to focus on collection methodologies and environmental conditions while mitigating exogenous factors that may confound experimental results.

B. Detection Method

1) Spectrometry: Spectrometric technologies, including MS [238], nuclear magnetic resonance (NMR) [239], and ion mobility spectrometry (IMS) [240] offer both offline detection and online monitoring capabilities for non-volatile breath analysis (see Fig. 8(c)). Liquid chromatography-mass spectrometry (LC-MS) systems are commonly utilized for offline analysis

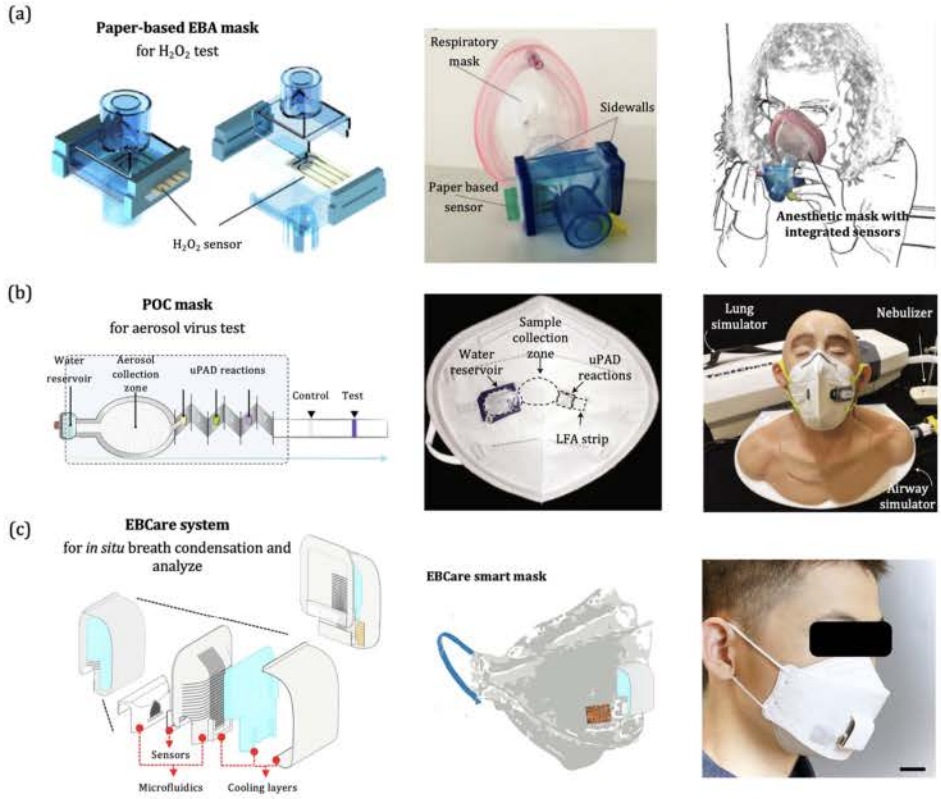

Fig. 9. Wearable smart mask system development for ***in situ*** breath aerosol and condensate analysis. (a) A paper-based electrochemical sensor in a mask for H_2O_2 detection in exhaled breath aerosol. [247] (b) A POC mask with microfluidics for COVID-19 test base crisper technology. [255] (c) A smart mask system integrated with in situ condensation, microfluidics and sensing function for real-time exhaled breath condensation analysis. [235] EBA, exhaled breath aerosol; EBC, exhaled breath condensate; POC, point of care.

of non-volatile breath metabolites and proteins. Prior to LC-MS analysis, breath analytes typically undergo preprocessing steps, including extraction, centrifugation, and concentration [241]. In contrast, online spectrometric analysis involves direct, real-time, and efficient ionization of molecules from exhaled breath. Electrospray ionization (ESI) is a common ionization technique employed in this context [242]. These spectrometric methods facilitate high-throughput and accurate measurements, often regarded as the gold standard in breath analysis. However, it is noteworthy that these systems are generally characterized by their complexity and substantial cost.

2) Electrochemical: Electrochemical sensors present a compelling option for measuring electroactive non-volatile biomarkers in breath. Their low cost, operational simplicity, and ease of integration into compact devices make them highly attractive [243]. Furthermore, their versatility allows for effective integration with other biotechnologies, such as immunological techniques [244] and aptamer-based technologies [245], resulting in sensors with multiple measurement principles. Consequently, several studies have explored EBC bioanalysis using electrochemical sensors, including the analysis of ions [246], reactive oxygen species [247] and proteins [248]. Thus, the ease of integration positions electrochemical sensors as a promising technological solution for portable and wearable devices in detecting non-volatile substances in breath.

3) Chemical Assay Kit: Chemical assay kits are widely utilized for analyzing small molecules in EBC. These kits, with their pre-formulated reagents and detailed protocols, offer a convenient and standardized approach to specific analyses. Due to the predominantly aqueous nature of EBC and the absence of significant interfering substances, pretreatment is often unnecessary, allowing for direct analysis using assay kits. The advantages of chemical assay kits lie in their convenience, consistency, and reproducibility, with many kits employing colorimetric or fluorescence detection techniques. These kits play a crucial role in simplifying experimental procedures, enhancing efficiency, and standardizing EBC analysis [249].

4) Immunology: Immunological methods are powerful tools for studying biomacromolecules in EBC. Based on the principle of specific antigen-antibody binding, these techniques enable efficient and sensitive detection and quantification of proteins [250], cytokines [251], and other biomarkers in EBC [252]. Common immunoassay techniques include enzyme-linked immunosorbent assay (ELISA), immunofluorescence, and electrochemical sensing, offering high specificity, sensitivity, and the capability for multiplexed analysis. With the advancements in microfluidic technologies and nanomaterials, novel immunosensors have shown great promise in EBC analysis, further expanding the possibilities for accurate and reliable biomarker detection [253].

C. Wearable Systems

Wearable devices are at the forefront of innovation in the analysis of non-volatile breath substances, offering a promising avenue for non-invasive, portable, and real-time monitoring of breath biomarkers. Research in this area primarily focuses on two aspects: EBA studies and EBC analysis. In EBA research, researchers are developing technologies to capture and analyze particles in exhaled breath. These particles may contain important biomarkers such as inflammation biomarkers [247] (Fig. 9(a)), viruses [254], [255] (Fig. 9(b)), or bacteria [256]. Mask-based platforms are of particular interest as they seamlessly integrate into daily life without additional burden on users, equipped with miniature sensors and sampling media for in-situ aerosol collection and analysis during wear [257], [258].

The smart mask-based EBC analysis system, depicted in Fig. 9(c) [235], integrates mini-condensers, microfluidic devices, and diverse sensing elements to detect multiple biomarkers in EBC. The primary challenge in EBC analysis revolves around the feasibility, stability, and continuous collection of EBC using wearable devices. Key factors influencing this process include the condensation of exhaled breath and the material characteristics that impact droplet nucleation and accumulation. Passive cooling methods, such as hydrogel evaporation and radiative cooling, are considered ideal solutions to overcome these challenges. Another critical aspect is the miniaturization of sensor-based devices, where electrochemical sensors excel due to their exceptional compactness. By focusing on these areas, the field of wearable EBC devices can advance significantly [259], [260]. All aforementioned technologies are characterized by low power consumption, which significantly mitigates the challenge of power supply in wearable devices.

Given the convenience and cost-effectiveness of these wearable devices, extensive clinical validation is a crucial step in the transition of novel breath analysis devices from laboratory to practical applications. This validation process aims to assess the accuracy, reliability, and practicality of these devices in diagnosing and monitoring various health conditions. With ongoing advancements in materials science, electronics, and biosensing technologies, wearable breath analysis devices show great promise in the analysis of non-volatile substances for early disease diagnosis, chronic disease management, and personalized medicine.

D. Biomarkers

1) Small Molecules:

a) pH: pH serves as a robust and reproducible biomarker in EBC, reflecting airway acidity [261]. In healthy individuals, the airways maintain a slightly alkaline environment [262]. However, in patients with obstructive airway diseases such as asthma [263], COPD [264], and cystic fibrosis [265], the airways often become acidified. This acidification process enhances the production of acidic droplets in the airway lining fluid (ALF), which are then more readily captured in the EBC, contributing to its acidic nature [261]. However, the measurement of EBC pH, while informative, presents technical challenges. It necessitates the exclusion of volatile carbon dioxide (imparting EBC carbonic acid properties), typically achieved by bubbling an inert gas (e.g., argon) through the sample or by controlling carbon dioxide partial pressure [266]. This requirement complicates in-situ pH monitoring of EBC.

b) Hydrogen peroxide: Elevated levels of H_2O_2 in EBC have been frequently observed in patients with airway inflammation [267], [268]. This increase is attributed to the activation of various cells in the respiratory system during inflammatory processes, including airway epithelial cells, endothelial cells, neutrophils, alveolar macrophages, and eosinophils. These activated cells produce superoxide radicals, which subsequently generate H_2O_2. However, the origin of H_2O_2 in EBC remains a subject of debate. Some researchers propose that water vapor might spontaneously generate hydrogen peroxide at the condensation interface, raising questions about the source of H_2O_2 in EBC samples [269], [270]. Regardless of its origin, the reactive nature of H_2O_2 necessitates immediate monitoring for optimal detection and quantification [247].

Most clinical studies rely on H_2O_2 assay kits that utilize peroxidase enzymes (such as horseradish peroxidase, HRP) to catalyze the reaction between H_2O_2 and specific substrates, producing detectable fluorescent or colored products. The intensity of these products is proportional to the H_2O_2 in the sample [271]. The advent of electrochemical sensors has enabled real-time analysis of H_2O_2 in EBC, based on the redox current of H_2O_2 at Prussian blue or platinum electrodes in microfluidics [272], [273]. However, both H_2O_2 assay kits and electrochemical sensors exhibit relatively low sensitivity, with H_2O_2 levels in EBC often approaching their lower limits of detection.

c) Nitrite/nitrate: NO_2^- and NO_3^- play dual roles as both products and precursors in the NO metabolic cycle [274]. In healthy individuals, their levels in EBC are typically low. However, these levels can increase significantly in conditions such as respiratory infections, asthma, and COPD [275], [276]. This elevation generally indicates inflammatory responses in the respiratory tract, reflecting increased NO production. Additionally, levels of NO derivatives such as S-nitrosothiols and nitrotyrosine may also be elevated in these conditions [277].

NO_2^- and NO_3^- assay kits utilize NO_3^- reductase enzymes to convert NO_3^- to NO_2^- (alternatively only NO_2^- detection without the enzyme), followed by the Griess reaction to detect total NO_2^-. This reaction produces a colored azo dye, with intensity proportional to the concentration of NO_2^- and NO_3^- in the sample [278], [279]. The advent of ion-selective or carbon-based redox electrodes has enabled real-time analysis of NO_2^- and NO_3^- in EBC, based on the potentiometric and amperometric response of these ions at specific membrane electrodes or electrode potential (~0.7 V) [246], [280].

d) Ammonium: NH_4^+ is the dominant ion in the EBC, primarily originating from the dissolution of NH_3 [281]. This relationship is governed by Henry's law for soluble gas-solution ion equilibrium, offering a potentially effective method for indirectly monitoring NH_3 gas levels in breath. The quantification of NH_4^+ in EBC presents several advantages over conventional NH_3 gas monitoring, particularly in addressing challenges such as real-time measurements and humidity interference. This

approach may prove more suitable for long-term wearable measurements in breath monitoring.

NH_4^+ assay kits typically utilize the Berthelot reaction, where NH_4^+ reacts with phenol and hypochlorite to form indophenol blue, with light intensity proportional to NH_4^+ concentration. The development of ion-selective electrodes has enabled real-time analysis of NH_4^+ in EBC, based on the potentiometric response of these ions at specific ion-selective membranes (Nonactin-based) on electrodes [282].

e) Arachidonic acid derivatives (8-isoprostane and leukotrienes): Arachidonic acid (AA), a polyunsaturated omega-6 fatty acid predominantly found in cell membrane phospholipids, serves as a precursor for various biologically active substances. Through diverse enzymatic pathways, AA is metabolized to produce compounds such as 8-isoprostane [283], prostaglandins [284], and leukotrienes (LTs) [285]. These metabolites exhibit potent inflammatory bioeffects on airway epithelial cells and other airway cells. The ALF serves as a crucial medium for these effects, containing substantial amounts of AA and its derivatives [286], [287]. EBC, being a non-invasive sample of ALF components, allows for the detection of 8-isoprostane, LTs, and prostaglandins. These compounds have emerged as important biomarkers for oxidative stress and respiratory inflammation. Most pulmonary diseases demonstrate elevated concentrations of these derivatives in EBC, reflecting oxidative stress conditions [288].

Methods for detecting AA derivatives in EBC include GC/MS, LC/MS, radioimmunoassay (RIA), and enzyme immunoassay (EIA). By integrating immunosensing techniques [289] or molecularly imprinted polymer (MIP) [290] technologies, electrochemical sensors can effectively detect biomarkers such as 8-isoprostane and leukotrienes [291].

f) Others: Electrolytes, trace metals, adenosine, glucose, and lactate represent a significant class of small molecule biomarkers that reflect the ionic balance, metabolic state, and redox environment of the respiratory tract. Electrolytes (such as sodium, potassium, and chloride) potentially indicate the dilution ratio of EBC to ALF [292]. Trace metals (like iron and zinc) are involved in the regulation of airway inflammation or serve as monitors for specific occupational environments [293]. Adenosine acts as a signaling molecule regulating airway reactivity [294], while glucose [295], [296], [297] and lactate [298], [299] reflect the glucose content and energy metabolism status of the pulmonary fluid environment. Encouragingly, several studies have reported on the quantification of glucose and lactate in EBC using electrochemical devices. This suggests the potential for continuous, wearable monitoring of these biomarkers [300], [301]. Concentration changes of these molecules may indicate various respiratory diseases, including asthma, COPD, and cystic fibrosis. These small molecules are relatively stable in EBC, easily detectable, and often respond rapidly to physiological and pathological changes. Their comprehensive analysis can provide multidimensional information about the respiratory tract microenvironment, aiding in early disease diagnosis, condition monitoring, and treatment response evaluation, thus offering crucial insights for personalized precision medicine in respiratory system diseases.

2) Proteins: EBC proteins, primarily cytokines, play a central role in the immune and inflammatory response of the host defense system. Based on their ability to either promote or inhibit inflammatory responses, these cytokines can be divided into three categories: pro-inflammatory cytokines (e.g., IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17, IFN-γ, and TNF-α), anti-inflammatory cytokines (e.g., IL-4, IL-5, IL-10, IL-13, and TGF-β), and chemokines (e.g., IL-8, MCP-1 and MIP-1ß). Systematic cytokine analysis is important for the diagnosis and treatment of airway diseases [302]. Furthermore, the C-reactive protein (CRP) content in EBC is considered to provide another useful diagnostic tool for detecting and monitoring low-grade inflammation in asthma patients [303].

Proteins in EBC can be detected by using ELISA. Studies have reported that the levels of several cytokines in EBC ranging from approximately 1-50 pg/mL [251], [304]. However, the accuracy of these values remains challenging due to cytokine levels in EBC are typically near the lower limit of the assay methodology. Combining immunological and electrochemical methods shows significant potential. This approach allows sensing elements to induce electrical signals upon capturing large target molecules like proteins [248], [305]. In addition, surface acoustic wave (SAW) sensors can be incorporated into immunosensing technologies to enable miniaturized detection of carcinoembryonic antigen (CEA) in EBCs [253].

3) DNA/RNA: Nucleic acid detection in EBC is promising in lung cancer research [306], with investigators focusing on various genetic and epigenetic markers such as mutation hotspot [307], microsatellite alterations [308], mitochondrial genes [309], cell-free DNA [310], and microRNA [311]. These genetic and epigenetic markers are utilized not only in lung cancer research but also in studies of other respiratory diseases such as COPD [312].

4) Pathogens: Respiratory infections, caused by pathogens such as viruses and bacteria, are a major global health concern. Traditional diagnostic methods like sputum culture or swabs may be limited by sample collection difficulties and sensitivity. EBC allows for non-invasive sampling, suitable for children and patients unable to provide sputum. Pathogen detection can be categorized into endogenous and exogenous biomarkers. Endogenous markers result from abnormal metabolic patterns due to infection, manifesting as changes in VOCs [313] or biomolecules [314]. Exogenous markers primarily involve detecting pathogen-specific substances [305], [314]. Analysis of EBC components using MS, immunoassays, and other techniques can identify specific pathogens. Viral pathogens such as *SARS-CoV-2* [315], [316], *Torque teno* virus [317], *H1N1* [318], and *influenza* virus [254], [319] are primarily identified by detecting viral nucleic acid. For bacterial pathogens, like *Methicillin-resistant Staphylococcus aureus* (MRSA), *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa* [320], detection methods may simultaneously target their specific proteins [305], lipids [321], and nucleic acid [320] to enhance diagnostic accuracy and reliability. This method offers the advantages of being non-invasive, simple, and high throughput, aiding in early diagnosis and control of respiratory infections.

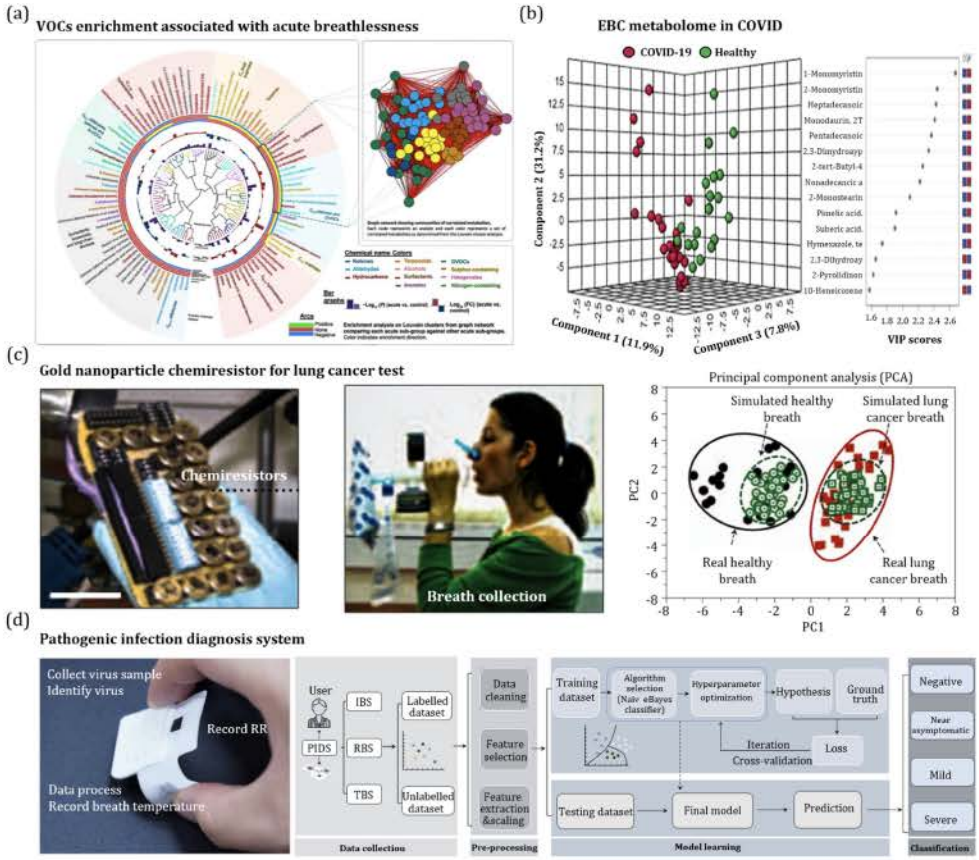

Fig. 10. Breathomics and related data processing methodologies. (a) VOCs enrichment associated with acute breathlessness. [335] (b) EBC metabolome in COVID. [339] (c) Gold nanoparticle chemiresistor array for lung cancer test. [344] (d) A pathogen infection diagnostic system integrating physical and chemical sensing elements generates multimodal data for machine learning classification of COVID conditions. [257].

Respiratory infectious diseases primarily spread through droplets or aerosols, making face masks the most effective personal protective equipment in daily life [322], [323]. The wearable, low-cost nature of masks and their direct contact with respiration make them an ideal platform for collecting and detecting respiratory pathogens [324]. Mask-based devices have shown promising applications in large-scale pathogen screening and collection in less developed regions [256], [321]. Additionally, some real-time point-of-care (POC) systems using microfluidics have enabled on-site virus screening during the COVID-19 pandemic based on immunoelectrochemical sensors or CRISPR sensing technology [255], [257]. These advancements demonstrate the significant potential of masks as tools for personal respiratory pathogen assessment.

5) Drugs: Personalized treatment is increasingly vital, with multiple factors affecting drug dosage. Therapeutic drug monitoring is crucial for narrow therapeutic range medications. Real-time breath sampling provides immediate pharmacokinetic information, particularly beneficial for emergency, anesthesia, and intensive care patients, enabling precise medication adjustments [242]. Various drugs such as propofol [325], fentanyl [326], methadone [327], nicotine [328], and caffeine [329] can be detected in breath, with some showing excellent correlation to blood concentrations. This indicates the value of investigating non-invasive monitoring of exhaled drugs through breath.

Due to low drug concentrations in EBC and complex molecular structures, detection techniques require high sensitivity and resolution. For rapid and accurate drug concentration measurement, fast, sensitive, and user-friendly instruments are needed. MS, as one of the most sensitive and versatile analytical tools, may play a crucial role in measuring levels of drugs and metabolites for future personalized patient treatment [242]. Drugs that can be recognized by immune elements may also be measured electrochemically, making at-home monitoring easier [330].

6) Exogenous Particles: Ultrafine particles and nanoparticles depositing in the deep lungs pose high health risks, potentially causing respiratory and cardiovascular diseases. While the causal link between mineral particle inhalation and pneumoconiosis is established, the role of nanoparticles in interstitial lung diseases remains unclear. Bronchoalveolar lavage fluid and EBC are important diagnostic tools for studying lung pathology. Recent studies show that EBC can assess occupational exposure and lung function impairment, but whether its particle load accurately reflects deep lung conditions requires further investigation [331], [332], [333].

V. Breathomics

As illustrated in Fig. 10(a) and (b), the bioinformation contained in breath is remarkably complex and vast, requiring

advanced data processing techniques for comprehensive analysis. While certain breath characteristics can be linked to specific health conditions, a single molecular marker may correspond to multiple physiological states, and conversely, a single state can be indicated by various molecular markers. This complexity is further compounded by individual variations in anatomical structure, leading to substantial differences in the physiological characteristics observed in breath. From a physical perspective, features such as individual breath patterns, breathing rhythms, along with temperature and humidity, are interrelated and collectively reflect the overall condition of the respiratory system [257], [334]. Chemically, exhaled breath contains between 200 and 2000 different compounds, encompassing a wide range of metabolic pathways and physiological states [335], offering valuable insights into various processes, like glucose metabolism and lipid oxidation [336], [337]. Additionally, the diversity and abundance of non-volatile components, such as various biomolecules [338], [339] and proteins [340], [341], further contribute to the complexity of breath analysis.

To effectively tackle the complexities of breath analysis, a comprehensive approach involving advanced data processing methods that can handle the high dimensionality and variability of breath data is essential. These methods are adept at identifying patterns and correlations among the diverse features found in breath samples. Supervised learning algorithms, like support vector machines [342] and random forests [82], are commonly used for classification tasks, helping to distinguish between different physiological or pathological states based on breath profiles. Unsupervised learning methods, such as principal component analysis (PCA) [343], [344] and clustering [345] techniques, are useful for dimensionality reduction and the discovery of novel breath patterns (see Fig. 10(c)).

Additionally, deep learning approaches, particularly convolutional neural networks (CNNs) [346] and recurrent neural networks (RNNs) [347], can capture complex temporal dynamics and non-linear relationships within the data, making them ideal for analyzing breath waveform and rhythm. To ensure the robustness and accuracy of these models, rigorous validation and cross-validation techniques are employed, alongside large, diverse datasets to train the algorithms effectively. Furthermore, as shown in Fig. 10(d), integrating multi-omics data, including proteomics and metabolomics, with physical analysis of breath can enhance the understanding of underlying biological processes and improve diagnostic accuracy [329]. By leveraging these advanced data processing methods, researchers can develop more precise and individualized diagnostic tools, ultimately contributing to the advancement of precision medicine.

VI. Human Machine Interaction

Breathing, a fundamental and low-energy physiological process, has recently emerged as a focal point in the development of human-machine interaction (HMI) technologies. Traditional HMI methods typically depend on mechanical, acoustic, bioelectrical, or optical inputs [348], [349]. While these established technologies offer reliable performance, they often entail significant motion consumption and visibility, which can constrain their practical applications and user comfort. In contrast, breathing input technology capitalizes on the natural patterns of nasal and oral breath, enhanced by the integration of accelerometers and advanced sensors, to provide a novel interaction mode characterized by minimal energy expenditure and inherent naturalness. By capturing variations in breath rate and pressure, this approach facilitates the implementation of continuous and discrete input patterns, thereby offering a more efficient and user-friendly solution for HMI applications [350], [351].

Moreover, the use of machine learning algorithms to interpret non-vocalized breath patterns has the potential to revolutionize fields such as speech recognition and control systems [352]. By training models to recognize and respond to specific breathing patterns, this technology could enable new forms of interaction that are less reliant on traditional voice commands. The advantages of breathing input are underscored by its low visibility and its capacity to protect user privacy, coupled with its broad applicability across various user demographics and environmental contexts. This technology is particularly promising for users with physical disabilities and diverse settings where conventional input methods may be less effective or practical.

The potential applications of breathing input technology extend to smart hospital environments, where breathing input could provide intuitive control mechanisms that adapt to user needs with minimal physical effort [353]. Additionally, in virtual and augmented reality settings, breathing-based interactions could enhance immersion and user engagement by integrating a natural and seamless mode of control. As technological advancements continue to evolve, the integration of breathing input into HMI systems is expected to significantly enhance user experiences, making interactions more natural, efficient, and accessible [354], [355].

VII. Outlook and Conclusion

In the wake of the five-year global COVID-19 pandemic, breath research has emerged as a critical focus across physiology, medicine, and engineering. Respiratory science, an ancient discipline, has been propelled forward in recent decades by advanced technologies such as CT and magnetic resonance imaging (MRI); sampling techniques including sputum, nasopharyngeal swabs, bronchoscopy, and exhaled breath analysis; along with MS and nucleic acid detection methods. The field of breath analysis still faces numerous pressing challenges and promising research frontiers. These include:

1) The clinical implementation and standardization of non-invasive breath analysis across diverse demographics to establish a robust diagnostic database.
2) The exploration of chemical information in breath to uncover novel biomarkers linked to physiological states necessitates the development of advanced analytical devices, requiring significant enhancements in selectivity and sensitivity to accurately detect and quantify diverse breath constituents at ultra-low concentrations.
3) Advanced data processing technologies, particularly machine learning, are transforming breath health analysis

through large-scale omics data. This transformation encompasses raw data preprocessing, health status inference from biomarker distributions, and the establishment of comprehensive breathomics. This multifaceted approach integrates diverse data types, enabling personalized diagnostics and treatment strategies in pulmonary medicine.; and

4) The integration of emerging wearable technologies with real-time sampling and detection techniques promises to revolutionize precision and personalized medicine. Advancements in device miniaturization and wireless connectivity enable seamless, unobtrusive continuous respiratory monitoring in everyday settings. This breakthrough facilitates long-term monitoring across diverse physiological states, offering rich, individualized data on health trajectories and responses to various stimuli. Additionally, the development of cost-effective point-of-care solutions expands the applicability of these technologies, particularly in areas such as infectious disease management, making healthcare more accessible and responsive.

These directions hold the promise to provide more accurate data support for early diagnosis and tailored treatments, opening vast horizons for breath-related medical research and clinical applications. The future of breath analysis hinges on interdisciplinary collaboration. The synergistic application of engineering, material science, computer science, and biology are poised to catapult breath analysis and monitoring to unprecedented heights, ushering in a new era of breath health and personalized precision medicine.

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