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Review

Exhaled Breath Analysis (EBA): A Comprehensive Review of Non-Invasive Diagnostic Techniques for Disease Detection

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Abstract

Exhaled breath analysis (EBA) is an advanced, non-invasive diagnostic technique that utilizes volatile organic compounds (VOCs) to detect and monitor various diseases. This review examines EBA's historical development and current status as a promising diagnostic tool. It highlights the significant contributions of modern methods such as gas chromatography–mass spectrometry (GC-MS), ion mobility spectrometry (IMS), and electronic noses in enhancing the sensitivity and specificity of EBA. Furthermore, it emphasizes the transformative role of nanotechnology and machine learning in improving the diagnostic accuracy of EBA. Despite challenges such as standardization and environmental factors, which must be addressed for the widespread adoption of this technique, EBA shows excellent potential for early disease detection and personalized medicine. The review also highlights the potential of photonic crystal fiber (PCF) sensors, known for their superior sensitivity, in the field of EBA.

Keywords: exhaled breath analysis; volatile organic compounds; gas chromatography–mass spectrometry; electronic noses; photonic crystal fiber; non-invasive diagnostics; disease biomarkers

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1. Introduction

Exhaled breath analysis (EBA) has emerged as a groundbreaking non-invasive diagnostic technique, offering notable advantages over conventional methods such as blood tests and biopsies [1,2]. This technique leverages the analysis of volatile organic compounds (VOCs) present in exhaled breath, which allows the identification of biomarkers associated with various diseases, thereby facilitating early diagnosis and monitoring of disease progression [3]. Although volatile organic compounds (VOCs) are central to modern breath analysis, the diagnostic potential of exhaled breath extends beyond this single class of molecules. The intricate biomolecular composition of exhaled breath includes a wide range of biomarkers, such as inorganic gases and non-volatile substances, which provide a comprehensive overview of an individual's metabolic state. For instance, endogenous inorganic gases serve as critical indicators: nitric oxide (NO) is an established biomarker for airway inflammation in asthma; ammonia (NH_3) has been linked to renal and liver disorders; hydrogen (H_2) and methane (CH_4) are routinely measured to diagnose gastrointestinal conditions; and carbon dioxide (CO_2) dynamics can also be indicative of pulmonary diseases. Additionally, analyzing non-volatile compounds—such as proteins, cytokines, and lipids—captured in exhaled breath condensate (EBC) offers a distinct yet complementary diagnostic window for pulmonary and systemic inflammation [4].

The historical origins of breath analysis can be traced back to ancient Egypt, where physicians diagnosed diseases based on breath odors. They associated specific odors with certain conditions, such as a sweet scent with diabetes mellitus, a fishy odor with liver disease, and a urine-like smell with kidney disease [5]. While using breath as a diagnostic tool is not a novel concept, its evolution into a sophisticated, scientifically driven practice is more recent. In contemporary times, the adoption of advanced analytical techniques, such as gas chromatography–mass spectrometry (GC-MS), ion mobility spectrometry (IMS), and electronic noses, has greatly enhanced the accuracy and reliability of EBA [6]. These technologies enable the detection of VOCs at extremely low concentrations, which is critical for detecting subtle metabolic changes that may signal disease.

The journey of exhaled breath research began with pioneers such as Linus Pauling, who employed gas chromatography to demonstrate the presence of numerous volatile compounds in breath samples [7]. This seminal work paved the way for contemporary research linking specific VOCs to various health conditions. Today, nanotechnology and sensor design advancements have significantly improved the sensitivity and specificity of breath analysis, making it a powerful tool in modern medicine [8].

One of the main advantages of EBA is its non-invasive nature. In contrast to blood tests and biopsies, which require the extraction of bodily fluids or tissues, breath analysis can be performed quickly and painlessly, making it more acceptable to patients [9]. The non-invasive nature of EBA is also advantageous for monitoring chronic diseases and managing critically ill patients, as it reduces infection risks and enables frequent testing [10–12]. In recent years, EBA has demonstrated promise in diagnosing a wide range of diseases, including respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), metabolic disorders like diabetes, and even cancer [13]. EBA has shown potential for early and non-invasive cancer detection by analyzing VOC patterns in breath, particularly in lung cancer [14] and head and neck cancers [15]. Similarly, breath tests have been developed to monitor glucose levels in patients with diabetes, offering a convenient alternative to traditional blood glucose testing [16].

The underlying principle of EBA is that metabolic processes produce specific VOCs exhaled in breath. These VOCs can serve as biomarkers for various physiological and pathological states. For example, isoprene, acetone, and ethane are VOCs associated with oxidative stress and lipid peroxidation, which are common in many diseases [17]. The systemic pathway by which VOCs originate from tissues and are transported via the bloodstream before being expelled in breath is illustrated in Figure 1. By analyzing the concentrations and patterns of these compounds, insights can be gained into a person's health status.

Technological innovations have been crucial in advancing exhaled breath analysis (EBA), improving its sensitivity, accuracy, and potential for clinical applications. Integrating machine learning algorithms with analytical techniques has enhanced the ability to interpret complex breath data. Machine learning models can analyze large datasets to uncover hidden patterns and correlations that traditional statistical techniques might overlook, enhancing diagnostic accuracy. This has led to the development of predictive models for disease detection and progression, increasing the clinical utility of EBA. Machine learning algorithms can identify subtle changes in VOC patterns that may indicate disease, further improving the accuracy and reliability of EBA. Despite its promise, EBA still faces several challenges that must be addressed. One of the main issues is the standardization of breath sampling and analysis procedures. Variability in sampling methods, environmental factors, and individual differences can affect the reproducibility and accuracy of results [18].

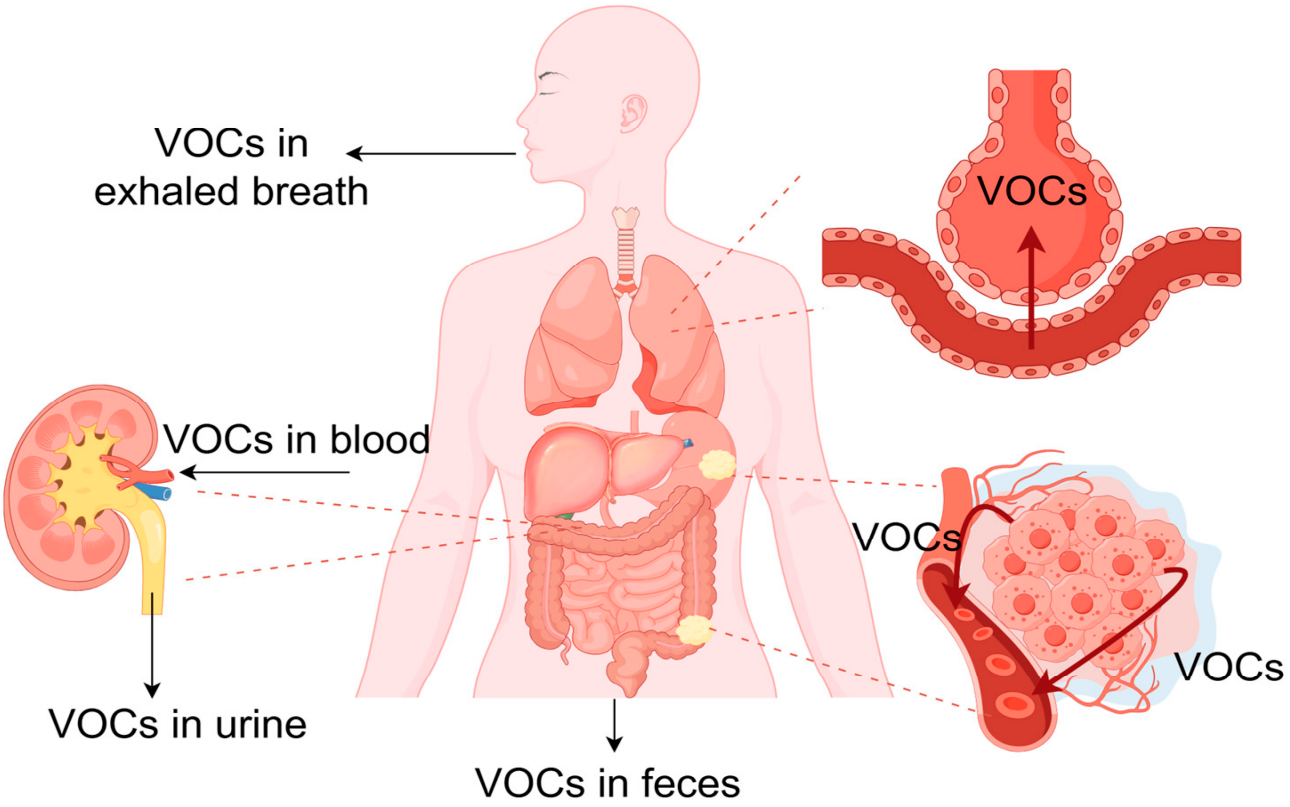


Figure 1. This figure illustrates the systemic dispersal of volatile organic compounds (VOCs) originating from gastrointestinal tumor tissues to various regions within the body [19].

Numerous reviews have been published on EBA, covering various aspects from biomarker discovery to specific sensor types. However, this review provides a unique added value by bridging the gap between established analytical techniques (like GC-MS and electronic noses) and the cutting-edge developments in photonic crystal fiber (PCF) sensor technology. While other reviews may mention PCF sensors in passing, this work focuses on them, providing a detailed overview of their operational principles and recent applications. By systematically comparing the advantages and disadvantages of PCF sensors with other prominent technologies, this review offers a forward-looking perspective on how photonics is poised to overcome key challenges in the field, paving the way for the next generation of non-invasive diagnostic tools.

In conclusion, exhaled breath analysis represents a promising non-invasive diagnostic tool with significant potential to revolutionize healthcare. Its ability to detect VOCs associated with various diseases offers a valuable means for early diagnosis and monitoring of disease progression. However, further research and technological advancements are necessary to overcome the existing challenges and fully realize the potential of this innovative diagnostic approach. EBA techniques' continued development and validation promise to improve patient outcomes and advance personalized medicine. The potential of EBA in customized medicine is vast. By analyzing an individual's unique VOC profile, EBA can provide tailored diagnostic and treatment strategies, leading to more effective and efficient healthcare. Additionally, developing portable and user-friendly devices for breath analysis is crucial for the widespread adoption of EBA in clinical practice.

2. Methodology: A Systematic Approach to Literature Synthesis

The foundation of this comprehensive review rests upon a rigorous and systematic interrogation of the scientific literature, designed to capture the breadth and depth of research in exhaled breath analysis (EBA). Our search strategy was executed across a curated selection of premier academic databases, including the interdisciplinary archives of Web of Science and Scopus, the biomedical-centric repository of PubMed, and the engineering and technology-focused collections within IEEE Xplore and SpringerLink. Google Scholar was used as a supplementary tool to identify additional relevant publications and gray literature. The search, encompassing literature published up to early 2025, was not static but an iterative process. It employed a multi-tiered query strategy combining MeSH (Medical Subject Headings) terms with a spectrum of keywords, evolving from broad concepts to specific technologies: *("exhaled breath analysis" OR "breathomics") AND ("volatile organic compounds" OR "VOCs" OR "breath biomarkers") AND ("gas sensor" OR "electronic nose" OR "GC-MS" OR "non-invasive diagnosis") AND ("photonic crystal fiber" OR "PCF")*.

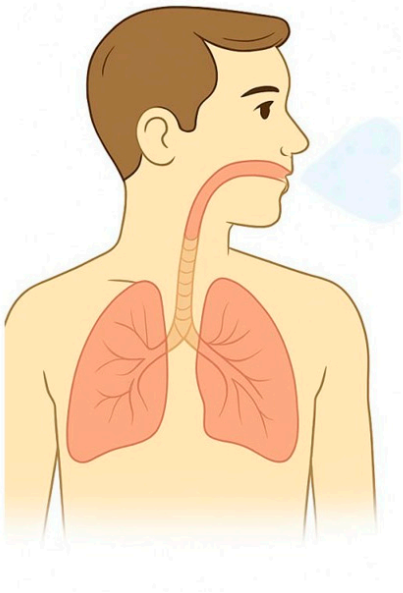
A stringent set of inclusion and exclusion criteria was applied to sculpt a focused and relevant narrative from the vast body of resulting literature. We prioritized peer-reviewed original research articles and authoritative reviews that form the intellectual bedrock of the field. The scope was intentionally confined to studies published in English, centering on human breath analysis for disease diagnosis or biomarker discovery and detailing the principles or applications of sensor technologies in EBA. Conversely, we systematically excluded non-human (animal) studies, ephemeral communications such as editorials or conference abstracts lacking a full paper, and articles where breath analysis was not the primary diagnostic modality, ensuring the integrity and focus of our review.

This multi-stage selection process was a meticulous exercise in intellectual distillation. The initial pool of several thousand articles was screened by title and abstract to filter for relevance. The remaining publications underwent a full-text assessment against the established criteria. This was not merely a filtering task but a synthesis process, where we sought to weave disparate research threads into a coherent and insightful tapestry. The ultimate goal was to construct a review that not only summarizes the state of the art but also illuminates the trajectory of the field, highlighting the critical transition from established methods to the next frontier of photonic-based diagnostics.

3. Common Diseases Diagnosed by Breath Analysis

Breath analysis is emerging as a critical, non-invasive diagnostic method with significant potential for the early identification and monitoring of various illnesses. This approach involves analyzing exhaled breath for volatile organic compounds (VOCs) and other markers indicative of specific diseases. The non-invasive nature of breath analysis enhances its appeal, as it reduces patient discomfort and the need for more invasive procedures, such as biopsies or blood tests. Furthermore, its ability to provide immediate results makes it a highly effective tool in clinical settings.

This section explores the application of breath analysis in diagnosing several prevalent diseases by examining their specific biomarkers in exhaled breath. A comprehensive discussion of these diseases follows. Table 1 details the biomarkers identified for each disease, explains their diagnostic use, cites relevant studies, and lists any FDA-approved markers. To complement this, Figure 2 offers a visual summary of prominent diseases and their associated breath biomarkers.



BREATH BIOMARKERS	
Name of the Disease	**Biomarker**
Lung Cancer	VOCs such as alkanes and benzene derivatives
Asthma	Nitric oxide (NO)
Chronic Obstructive Pulmonary Disease (COPD)	Carbon dioxide (CO_2), methane, pentane
Diabetes Mellitus	Acetone
Helicobacter pylori Infection	Carbon-13 (^{13}C)
Liver disease	Ammonia
Gastrointestinal	Carbon monoxide
Alcohol Consumption	Ethanol

Figure 2. Volatile organic compounds (VOCs) in exhaled breath as non-invasive biomarkers. This figure shows the respiratory system and lists prominent VOCs that can be detected in breath, along with their potential diagnostic utility for a range of diseases and conditions.

Table 1. Diseases diagnosed by breath analysis.

Name of the Disease	Exhaled Biomarker	Description	References of Studies	FDA-Approved Biomarkers for Disease Diagnosis
Lung Cancer	VOCs such as alkanes, benzene derivatives, aldehydes	Breath analysis for lung cancer involves detecting specific VOCs produced by cancerous cells. Elevated levels of n-pentane and isoprene are commonly observed.	[20,21]	None
Asthma	Nitric oxide (NO)	Elevated levels of NO in exhaled breath indicate airway inflammation, which is a hallmark of asthma.	[22,23]	Fractional exhaled nitric oxide (FeNO)
Chronic Obstructive Pulmonary Disease (COPD)	Carbon dioxide (CO_2), methane (CH_4), ethane	COPD diagnosis through breath analysis involves detecting elevated levels of specific gases such as ethane and pentane.	[24,25]	None
Diabetes Mellitus	Acetone	Elevated levels of acetone in breath correlate with blood glucose levels, indicating diabetes.	[1,26]	None
Helicobacter pylori Infection	Carbon-13 (^{13}C) urea	The urea breath test (UBT) detects H. pylori infection by measuring labeled CO2 after ingestion of 13C-urea.	[24,27]	13C-urea
Liver Disease	Ammonia, acetone	Elevated levels of ammonia and acetone indicate impaired liver function.	[28,29]	None
Neonatal Jaundice	Carbon monoxide (CO)	CO breath test detects elevated levels of CO, indicating jaundice in newborns.	[30,31]	Carbon monoxide test

Table 1. *Cont.*

Name of the Disease	Exhaled Biomarker	Description	References of Studies	FDA-Approved Biomarkers for Disease Diagnosis
Gastrointestinal Disorders	Hydrogen (H_2), methane (CH_4)	Breath tests for hydrogen and methane are used to diagnose conditions like fructose and lactose malabsorption and bacterial overgrowth.	[32,33]	Hydrogen and methane breath tests
Alcohol Consumption	Ethanol	Ethanol breath test measures blood alcohol levels.	[34]	Ethanol test

4. Sensors Used in Exhaled Breath Analysis

Exhaled breath analysis is a promising non-invasive diagnostic tool that detects volatile organic compounds (VOCs) to identify various diseases. The development and application of sensors in this field have significantly advanced our ability to diagnose and monitor health conditions through breath analysis. Various types of sensors, including metal oxide gas, chemiresistive, and mid-infrared tunable laser spectroscopic, are crucial in detecting biomarkers in exhaled breath. The following section will introduce the sensors in this field for detecting gases. An overview of the various sensor technologies employed in EBA is presented in Figure 3. The general principle involves the interaction of exhaled biomarkers with a sensor, which generates a detectable signal that is subsequently amplified and analyzed, as shown schematically in Figure 4.

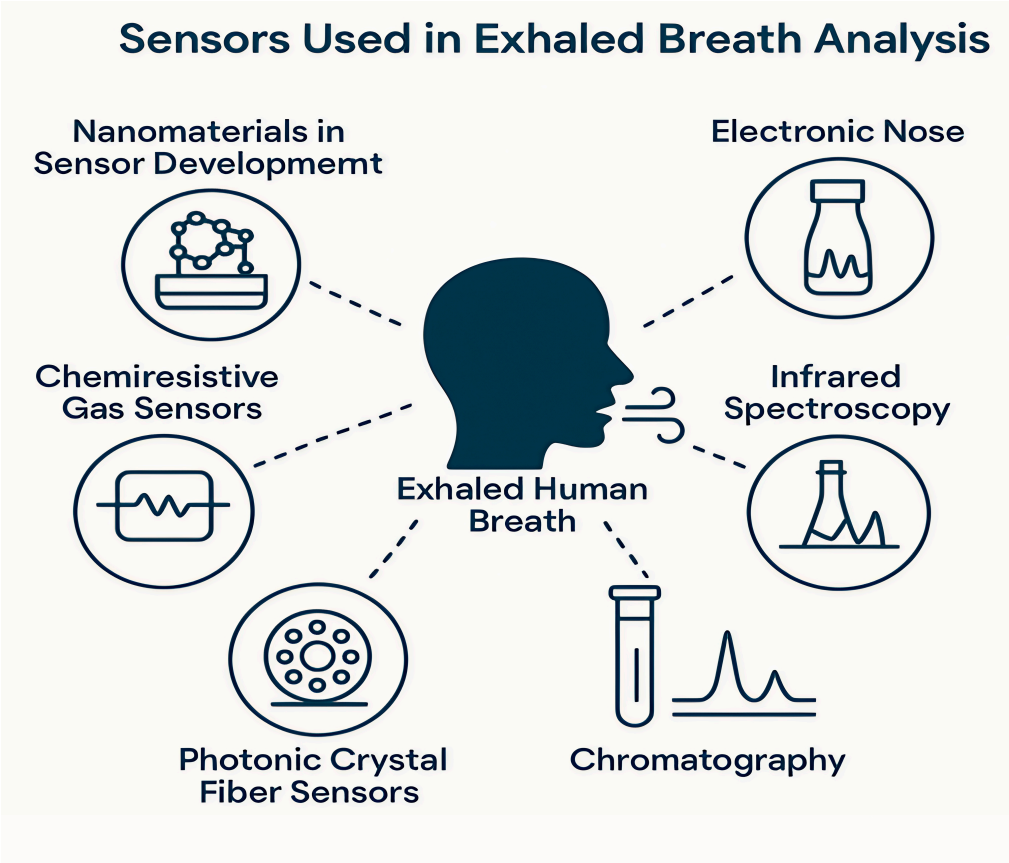


Figure 3. Schematic overview of various sensor technologies utilized in exhaled breath analysis.

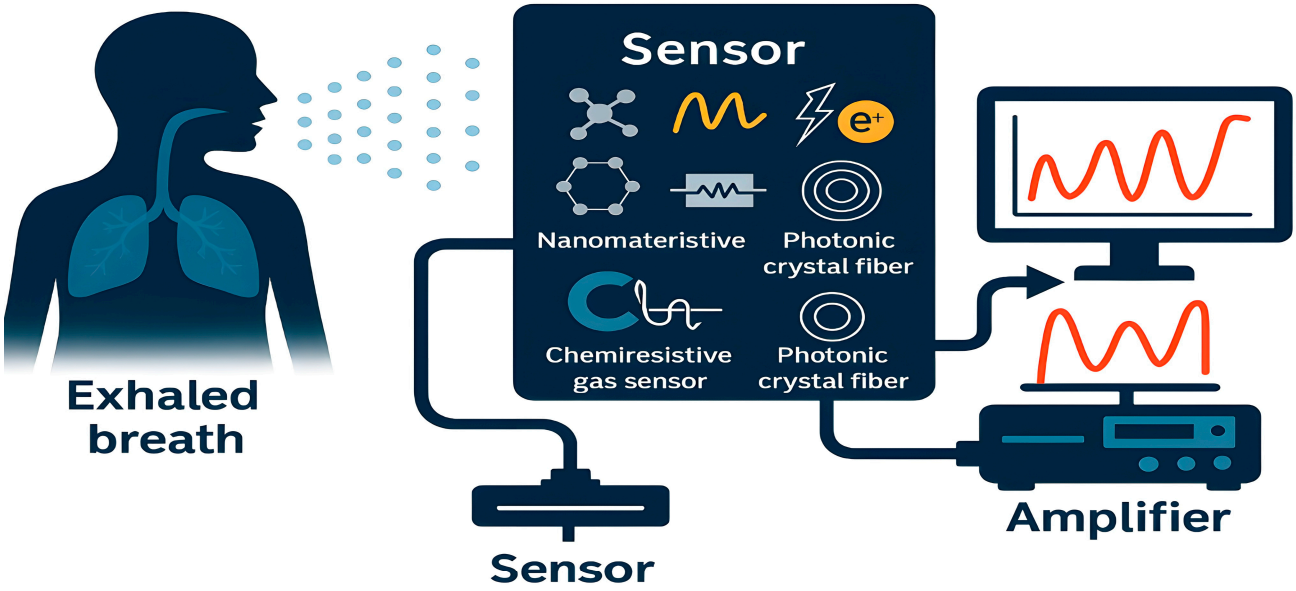


Figure 4. Exhaled breath analysis: VOC interaction with the sensor generates an electrical signal, which is amplified and displayed for biomarker detection.

4.1. Role of Nanomaterials in Sensor Development

Nanomaterials, such as carbon nanotubes, graphene, and metal oxides, provide unique properties that enhance sensor performance. Their high surface area/volume ratio increases the active sites available for gas interaction, improving sensitivity. For example, single-walled carbon nanotubes (SWNTs) functionalized with specific chemical groups have shown high sensitivity to nitric oxide (NO), a significant marker in breath analysis for respiratory diseases [35]. This high sensitivity to NO is particularly crucial for clinical applications, as it allows for the non-invasive monitoring of asthma control and patient response to anti-inflammatory therapy.

Graphene and its derivatives are also notable for their exceptional electrical properties, which enhance the response of gas sensors. Graphene-based sensors can detect minute changes in electrical conductivity when VOCs are adsorbed on their surface. This property is beneficial for detecting acetone, a biomarker for diabetes [36]. The ability to detect acetone with such precision is a significant step towards developing a convenient, pain-free daily monitoring tool for diabetic patients, replacing the need for frequent blood tests.

The incorporation of nanomaterials not only improves sensitivity but also reduces sensors' response and recovery times. Metal oxide nanomaterials, such as ZnO and SnO_2, exhibit rapid response times when exposed to VOCs due to their excellent electron mobility and surface reaction kinetics. These materials have shown significant improvements in detecting low concentrations of gases, such as isopropanol, indicative of lung cancer [37].

Additionally, the stability of nanomaterial-based sensors is a critical factor for their practical application. ZnO-Bi_2O_3 nanosheets grown on hollow-core fibers have demonstrated exceptional stability and repeatability in detecting acetone at room temperature, making them suitable for long-term breath analysis [38]. Such exceptional stability at room temperature addresses a key challenge for practical sensors—long-term reliability—making these devices more suitable for real-world clinical and point-of-care settings.

Nanomaterials offer tunable chemical and physical properties, allowing for the customization of sensors to target specific VOCs. This versatility is crucial for developing selective sensors that distinguish between different gas analytes. For instance, ZnO nanostructures can be doped with various metals to enhance their selectivity for particular VOCs. Fe-doped ZnO nanoneedles have been shown to selectively detect isopropanol,

a potential biomarker for lung diseases, at very low concentrations [37]. The chemical versatility of carbon-based nanomaterials also makes them ideal for constructing flexible and wearable sensors. This property is particularly advantageous for developing portable diagnostic devices that can provide real-time monitoring of VOCs in exhaled breath [39]. The development of advanced fabrication techniques has enabled the precise integration of nanomaterials into sensor platforms, enhancing their performance. For example, using horizontal vapor-phase crystal growth to synthesize ZnO and SnO_2 nanomaterials has resulted in sensors with rapid response times and high sensitivity to VOCs [40]. Moreover, microfabrication and microfluidic technologies have facilitated the miniaturization of gas sensors, making them more compact and portable. This advancement is essential for creating point-of-care devices that can be used for early disease detection in clinical settings. Several studies have demonstrated the practical application of nanomaterial-based sensors in detecting disease biomarkers. For instance, a smartphone-based resistive gas sensor employing ZnO nanosheets in exhaled breath has shown high sensitivity to lung cancer-related VOCs, such as diethyl ketone and acetone. This innovative approach combines the advantages of nanomaterials with the accessibility of smartphone technology, providing a cost-effective solution for early disease diagnosis [41]. Another notable application is the use of polymer-modified quartz tuning forks embedded with nanomaterials to detect low concentrations of VOCs. This method has proven effective in distinguishing between healthy and VOC-spiked breath samples, showcasing its potential as a non-invasive diagnostic tool [42]. While nanomaterial-based sensors have shown significant promise, challenges remain to be overcome. One major issue is the selectivity of sensors in the presence of multiple interfering gases. Researchers are exploring strategies to improve selectivity, such as functionalizing nanomaterials with specific chemical groups or combining different nanomaterials to create composite sensors [43].

Additionally, incorporating advanced signal processing methods and machine learning algorithms can improve the precision and dependability of breath analysis results. These technologies can help in the real-time analysis of complex VOC profiles, providing more precise diagnostic information [44]. Incorporating nanomaterials into sensor technology has revolutionized the field of exhaled breath analysis. Their unique properties enhance sensors' sensitivity, selectivity, and overall performance, making them invaluable tools for non-invasive disease diagnosis. Recent advancements in nanomaterial-based sensors, summarizing the applications and target gases discussed in this section, are presented in Table 2.

Table 2. Recent advancements in nanomaterial-based sensors.

Application	Sensor Type	Nanomaterials	Target Gas	Key Features	References
Early-stage disease diagnosis	Chemoresistive VOC sensors	Nanomaterials (general)	VOCs	High sensitivity, real-time, non-invasive diagnosis	[45]
Lung cancer detection	Resistive gas sensor	ZnO nanosheets	Diethyl ketone, acetone, isopropanol	High sensitivity, smartphone integration	[41]
Diabetes diagnosis	Chemiresistive sensors	ZnO-Bi_2O_3 nanosheets	Acetone	High sensitivity and selectivity	[38]
General disease diagnosis	Various sensor technologies	Nanomaterials (general)	VOCs	Non-invasive, highly selective, sensitive, robust sensors	[46]
Non-invasive medical diagnostics	Metal oxide semiconductor sensors	WO_3 nanowires	VOCs	Enhanced response with UV-light irradiation, selective towards VOCs	[47]

Table 2. *Cont.*

Application	Sensor Type	Nanomaterials	Target Gas	Key Features	References
VOC detection for health and environmental applications	Gas sensors	Ag-doped ZnO	Propanol, acetone, methane	High sensitivity at low operating temperatures	[48]
Diabetic diagnosis via exhaled breath	Gas sensors	Zn_2SnO_4 nanoparticles	Acetone	High sensitivity, good selectivity, and stability	[49]
General disease diagnosis via breath analysis	NM-based gas sensors	Nanomaterials (general)	VOCs	High surface-to-volume ratio, controllable morphology, potential for miniaturization	[43]
Early and non-invasive disease diagnosis	Gas sensors	Nanomaterials (general)	VOCs	Accurate detection, potential for commercial use as disease self-test kits	[50]
VOC detection in human breath for diabetes and respiratory diseases	Binary nanocompos-ites	Reduced graphene oxide/SnO_2	Acetone	Enhanced acetone sensing performance distinguishes between healthy and diabetic subjects	[51]
Portable, low-cost sensors for environmental and health applications	Hybrid nanomaterial sensors	Conducting polymers, metal oxides, graphenes	VOCs	Superior sensitivity, low detection limits, potential for miniaturization, and versatility	[52]

4.2. Chemiresistive Gas Sensors

Chemiresistive gas sensors are crucial for medical diagnostics and environmental monitoring to detect exhaled gases. The principle of chemiresistive gas sensors involves a change in electrical resistance when exposed to target gas molecules. The sensor, typically composed of a sensitive material like metal oxides, interacts with gas molecules in the breath. These molecules adsorb onto the surface, altering charge carrier density and leading to a measurable change in resistance correlated to gas concentration, enabling the detection and quantification of various biomarkers in exhaled breath [53,54]. This technology is widely used for gas detection due to its simplicity, low cost, and high sensitivity, playing a significant role in monitoring exhaled gases for health condition biomarkers [55]. Gas molecules either donate or withdraw electrons from the sensor material, affecting its resistance. A typical sensor has a sensing layer on an insulating substrate with electrodes for measuring resistance changes [56]. This layer can be optimized for sensitivity and selectivity to specific gases. Exhaled breath contains VOC biomarkers detectable by these sensors, enabling non-invasive diagnostics [57]. Humidity and other gases in exhaled breath can interfere with sensor readings, leading to false positives or inaccurate measurements. Research focuses on integrating humidity-resistant materials and advanced sensor designs to mitigate this issue [58]. Over time, chemiresistive sensors may experience drift in their baseline resistance, affecting their long-term stability and reliability. Efforts are being made to improve the material properties and sensor designs to enhance stability and reduce drift [59].

Accurately quantifying biomarker concentrations in exhaled breath is challenging due to the low concentrations and the presence of interfering substances. Developing highly sensitive and selective sensors is crucial for accurate quantification [60]. Current sensors may not be capable of simultaneously detecting a broad spectrum of biomarkers. This limitation is being addressed by developing sensor arrays and multifunctional sensors that can detect multiple biomarkers simultaneously [61]. Sensors based on nanoparticle-structured interfaces have been designed to detect lung cancer biomarkers in human breath with high sensitivity and a limit of detection as low as six ppb [62]. An ultrasensitive chemiresistive

sensor based on γ-Bi_2MoO_6-CuO heterostructure can detect H2S, a biomarker for asthma, with a detection limit of 5 ppb. This sensor helps distinguish between asthmatic patients and healthy individuals and can monitor the severity of asthma [63].

4.3. Electronic Nose Technology

Electronic nose (eNose) technology, modeled after the mammalian sense of smell, has become a promising non-invasive tool for disease diagnosis by detecting volatile organic compounds (VOCs) in breath [64]. VOCs are organic chemicals with high vapor pressure at room temperature, and their analysis in exhaled breath can indicate the presence of different diseases such as cancer, lung conditions, and infections [65,66]. An eNose system typically comprises three main components: a sensor array, a signal processing circuit, and a pattern recognition system [64]. The sensor array is the heart of the eNose, consisting of multiple chemical sensors with varying sensitivity and selectivity to different VOCs [67]. These sensors can be categorized based on their transduction mechanisms, including:

- **Metal Oxide Sensors (MOSs):** These sensors rely on the change in electrical conductivity of a metal oxide semiconductor upon interaction with VOCs. When VOC molecules adsorb onto the sensor surface, they change the electron density, resulting in a detectable variation in resistance [67]. MOSs are among the most widely used sensors in eNose technology due to their high sensitivity, fast response times, and relatively low cost [68]. These sensors are based on a semiconducting metal oxide layer (e.g., tin dioxide and zinc oxide) deposited on a substrate. The gas molecules adsorb onto the sensor surface upon exposure to VOCs, changing the metal oxide's electrical conductivity. This change in conductivity is directly proportional to the concentration of the VOCs and can be measured as a change in resistance. The selectivity of MOSs can be tuned by adjusting the operating temperature, the type of metal oxide, and the addition of dopants or catalysts [69].
- **Conducting Polymer (CP) Sensors:** Similar to MOSs, CP sensors also exhibit changes in electrical conductivity upon exposure to VOCs. The interaction of VOCs with the polymer matrix causes swelling or contraction, resulting in a change in resistance. CP sensors offer an alternative approach to VOC detection, leveraging changes in the electrical conductivity of a polymer film upon interaction with VOCs. These sensors often comprise a polymer matrix (e.g., polypyrrole and polyaniline) embedded with conductive particles (e.g., carbon black). The adsorption of VOCs onto the polymer matrix can cause it to swell or contract, resulting in a change in the distance between the conductive particles and, consequently, a change in resistance. CP sensors are known for their flexibility in design, ease of fabrication, and potential for miniaturization [70].
- **Quartz Crystal Microbalance (QCM) Sensors:** These sensors utilize the piezoelectric effect of a quartz crystal resonator. When VOCs adsorb onto the crystal surface, the mass of the crystal changes, leading to a shift in its resonant frequency. This frequency shift is proportional to the mass of the adsorbed VOCs [71]. QCM sensors exploit the piezoelectric properties of quartz crystals to detect VOCs. These sensors consist of a quartz crystal resonator coated with a selective material that adsorbs specific VOCs. The adsorption of VOCs onto the crystal surface increases its mass, causing a decrease in the crystal's resonant frequency. This frequency shift is proportional to the mass of the adsorbed VOCs and can be used to quantify their concentration. QCM sensors are highly sensitive and can detect even trace amounts of VOCs [72].
- **Mass Spectrometry (MS) Sensors:** MS sensors ionize VOC molecules and separate them according to their mass-to-charge ratio, producing a mass spectrum that serves as a unique fingerprint for identifying the VOCs in the sample [73]. While not as common as MOS, CP sensors, or QCM sensors, MS sensors offer unparalleled selectivity and

sensitivity in VOC detection. In MS sensors, VOCs are ionized and separated based on their mass-to-charge ratio. The resulting mass spectrum provides a unique fingerprint of the VOCs present in the sample. However, MS sensors are typically bulky, expensive, and require complex operation, limiting their widespread adoption in eNose technology [74]. A comparative summary of these sensor technologies, highlighting their principles of operation, advantages, and disadvantages, is provided in Table 3.

Table 3. Comparison of sensor technologies in eNose applications.

Sensor Type	Principle of Operation	Advantages	Disadvantages	References
Metal Oxide Sensor (MOS)	Change in electrical conductivity upon VOC adsorption	High sensitivity, fast response, low cost, mature technology	Limited selectivity, cross-sensitivity, susceptibility to humidity and temperature variations	[68,69]
Conducting Polymer (CP) Sensor	Change in electrical conductivity upon VOC adsorption	Flexibility in design, ease of fabrication, miniaturization potential	Low sensitivity compared to MOSs, potential for drift and aging	[70]
Quartz Crystal Microbalance (QCM) Sensor	Change in resonant frequency due to mass change upon VOC adsorption	High sensitivity, ability to detect trace amounts of VOCs	Requires selective coatings, susceptibility to interference from other gases	[72]
Mass Spectrometry (MS) Sensor	Ionization and separation of VOCs based on mass-to-charge ratio	Unparalleled selectivity and sensitivity	Bulky, expensive, complex operation	[74]

The signal processing circuit collects the signals generated by the sensor array, amplifies them, filters out noise, and converts them into digital data. This data is then fed into the pattern recognition system, which employs machine learning algorithms to identify patterns and correlations within the sensor responses. By comparing these patterns to a database of known VOC profiles, the eNose can identify and quantify the VOCs in the exhaled breath, thus aiding in disease diagnosis. Despite its potential, eNose technology faces several challenges, including sensor limitations in sensitivity and selectivity, interference from environmental factors such as humidity and temperature, and the complexity of data analysis [75,76]. However, ongoing research and development efforts are focused on overcoming these challenges by developing more sensitive and selective sensors, robust algorithms for data analysis, and portable and affordable eNose devices [77]. With continued advancements, eNose technology is promising to revolutionize disease diagnosis and personalized medicine.

4.4. Chromatography

Chromatography operates on the principle of differential partitioning, where analytes distribute themselves between a stationary phase and a mobile phase based on their affinity for each phase. The stationary phase can be solid, liquid, or gel, while the mobile phase is typically a gas (in GC) or liquid (in LC). The analytes' unique interactions with both phases result in their separation as they travel through the chromatographic system. This principle is fundamental to all chromatographic techniques used in breath gas analysis [78].

- **Gas Chromatography (GC):** GC is the workhorse of breath gas analysis, separating volatile organic compounds (VOCs) based on their boiling points and polarity. The sample is vaporized and carried through a column by an inert carrier gas. Different VOCs interact differently with the column's stationary phase, leading to separation.

This method is frequently combined with mass spectrometry (GC-MS) and offers excellent sensitivity and specificity for detecting and measuring VOCs [79].

- **Liquid Chromatography (LC):** LC is used for less volatile or polar analytes, such as metabolites. In this process, the sample is dissolved in a liquid mobile phase and then injected into a column containing a solid stationary phase. Separation occurs due to differences in the analytes' affinity for the stationary and mobile phases. LC-MS is a powerful combination for analyzing complex biological samples [80].
- **Ion Mobility Spectrometry (IMS):** IMS is a rapid technique where ionized gas-phase molecules are separated based on their size, shape, and charge in an electric field. IMS is becoming increasingly popular for its speed, portability, and sensitivity in detecting VOCs, including those in exhaled breath [81].

Challenges and Limitations

- **Gas Chromatography (GC)**

Despite its advantages, GC faces several challenges. The requirement for sample pre-treatment and derivatization can be time-consuming and introduce variability. Additionally, the high cost of equipment and maintenance limits its widespread clinical application [81].

- **Liquid Chromatography (LC)**

LC also has its limitations, including the complexity of the system and the need for extensive method development to optimize separation conditions. The lower sensitivity compared to GC-MS can be a drawback for detecting low-abundance metabolites [81].

- **Ion Mobility Spectrometry (IMS)**

While advantageous for its rapid analysis and portability, IMS suffers from lower resolution compared to traditional chromatographic methods. This may hinder its capacity to differentiate between compounds with comparable structures. Furthermore, environmental factors like humidity and temperature can impact IMS measurements, potentially reducing accuracy [81].

4.5. Infrared Spectroscopy

Mid-infrared spectroscopy, including photoacoustic spectroscopy, is highly sensitive to detecting specific biomarkers in breath samples. It is also non-invasive and provides real-time results [82]. The technique uses mid-infrared laser absorption to identify various gas molecules in exhaled breath, making it highly specific and sensitive [83].

Measurement Process

1. **Sample Collection:**

Exhaled breath is collected non-invasively using sampling bags or direct breath capture systems. These systems ensure that the breath sample is uncontaminated and accurately represents the gases present in the respiratory tract [84].

2. **Mid-Infrared Laser Source:**

A mid-infrared laser, typically a quantum cascade laser (QCL), emits light at specific wavelengths that correspond to the absorption peaks of the target gas molecules. This light is directed through the breath sample [85].

3. **Photoacoustic Effect:**

The light absorbed by the gas molecules in the sample causes them to heat up and expand, creating pressure or sound waves. This is known as the photoacoustic effect. The intensity of these sound waves is proportional to the concentration of the gas molecules [86].

4. **Detection:**

The generated sound waves are detected using sensitive microphones or acoustic sensors. The signals are then processed and analyzed to determine the concentration of specific gases in the breath sample [87]. A key advantage of mid-infrared spectroscopy is its capability to deliver real-time results, which is essential for applications such as medical diagnostics requiring immediate analysis. Additionally, the non-invasive nature of the method makes it suitable for continuous monitoring without patient discomfort [85]. Despite its advantages, mid-infrared spectroscopy has certain limitations. One major drawback is the requirement for high precision in instrument calibration and maintenance to ensure accurate measurements. Moreover, the initial cost and complexity of the equipment can hinder its widespread adoption in clinical settings [84]. In conclusion, while mid-infrared spectroscopy, including photoacoustic spectroscopy, offers high sensitivity and non-invasive, real-time analysis of breath biomarkers, its high costs and stringent calibration requirements may limit its broader application [82].

4.6. Photonic Crystal Fiber Sensors

Photonic crystal fiber (PCF) sensors direct light through a microstructured optical fiber featuring a periodic pattern of air holes along its length. The key mechanism that enables high sensitivity in PCF sensors is the interaction between the light and the target gas within the fiber's hollow core. This interaction is enhanced by the large surface area and the specific geometrical configuration of the PCF, which maximizes the overlap between the light field and the gas molecules [88]. The hollow-core design allows the light to be confined in the core while interacting with the gas molecules. This interaction leads to a change in the light's properties, such as its intensity or wavelength, which can be measured to determine the concentration of the gas [89]. The evanescent field, which extends into the hollow core, enhances the sensitivity by increasing the light-gas interaction length [90]. A typical experimental configuration for performing such gas sensing measurements is illustrated in Figure 5.

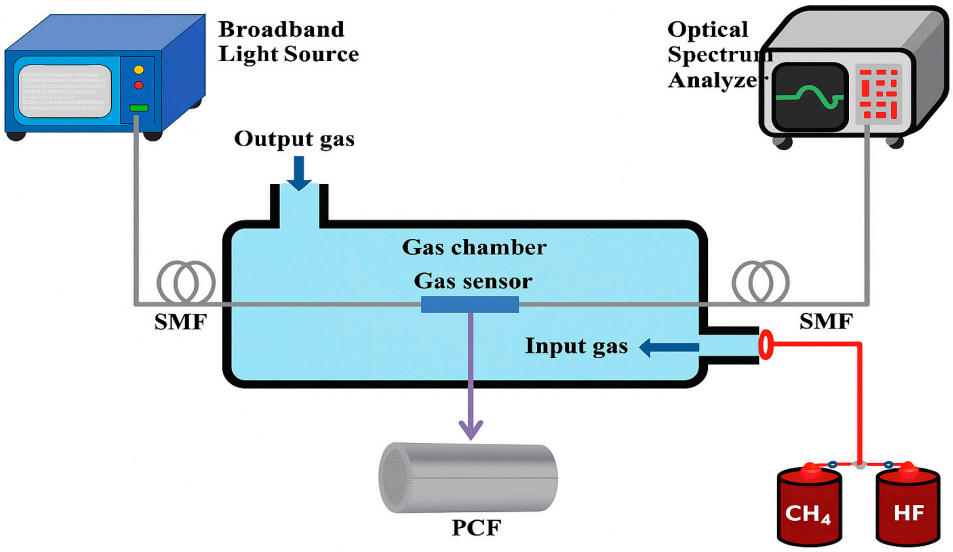


Figure 5. Diagram illustrating the suggested experimental configuration for gas sensing with the PCF [91].

Differential Optical Absorption Spectroscopy (DOAS): This technique involves measuring the absorption of specific wavelengths of light that correspond to the absorption lines of the target gas. The hollow-core PCF acts as a gas cell where the light travels through the gas, allowing precise gas concentration measurement based on absorption characteris-

tics [92]. Geometrical Configuration: By optimizing the size, shape, and arrangement of the air holes in the PCF, the sensitivity and detection limits can be significantly enhanced. Different designs, such as spiral porous cores and triangular structures, have been shown to provide high sensitivity [93]. Material Selection: The choice of materials for the core and cladding can also impact the performance. For example, using materials with high refractive indices can improve the confinement of light within the core, enhancing the sensor's sensitivity.

Outstanding Features of PCF Sensors

1. **High Sensitivity:** PCF sensors can detect very low concentrations of gases due to their enhanced light-gas interaction. Sensitivities as high as 75% have been reported, making them suitable for detecting trace amounts of gases such as ammonia, hydrogen, and methane [94].
2. **Fast Response Time:** The design of PCF sensors ensures rapid response to changes in gas concentration, which is critical for real-time monitoring and breath analysis applications. The fast response is due to the efficient gas diffusion within the hollow core and the swift interaction with the guided light [95].
3. **Compact and Lightweight:** PCF sensors are inherently compact and lightweight, which makes them easy to integrate into portable devices for on-site and real-time gas monitoring. This compactness is advantageous for applications in medical diagnostics, environmental monitoring, and industrial safety [96].
4. **Wide Wavelength Range:** These sensors can operate over a wide range of wavelengths, from ultraviolet to infrared, allowing the detection of various gases with different absorption characteristics. This versatility makes PCF sensors suitable for multiple applications [97].
5. **Robustness and Durability:** PCF sensors are engineered for durability and robustness, allowing them to perform reliably even under harsh environmental conditions. Their structural integrity ensures long-term reliability and consistent performance, essential for continuous monitoring applications [98]. A comprehensive comparison of these sensor technologies, outlining their respective advantages, disadvantages, and operational features, is presented in Table 4.

Table 4. Comparison of sensor technologies.

Sensor Type	Advantages	Disadvantages	Cost	Features	Gas Detection	Limitations	Response Time	Sensitivity	References
Nanomaterial-Based	High sensitivity and selectivity, low cost, portable, non-invasive, low power consumption	Sensitive to humidity, may require pre-treatment, stability issues	Low	Uses metal oxides, carbon nanotubes, graphene; can be miniaturized	NO, NH_3, H2S, acetone, other VOCs	Humidity sensitivity, stability issues in varying conditions	Seconds to minutes	High sensitivity (ppb level)	[99]
Chemiresistive Gas	High sensitivity, capable of detecting multiple gases, pattern recognition, portable	May require calibration, influenced by environmental conditions, moderate cost	Moderate	Uses an array of sensors integrated with AI and pattern recognition systems	H2S, NH_3, NO, VOCs	Environmental sensitivity, potential need for recalibration	Seconds to minutes	High sensitivity (ppb level)	[100,101]
Electronic Nose (E-nose)	High sensitivity, can detect multiple gases, pattern recognition, portable	May require calibration, influenced by environmental conditions, moderate cost	Moderate	Uses an array of sensors integrated with AI and pattern recognition systems	H2S, NH_3, NO, VOCs	Environmental sensitivity, potential need for recalibration	Seconds to minutes	High sensitivity (ppb level)	[100,101]

Table 4. *Cont.*

Sensor Type	Advantages	Disadvantages	Cost	Features	Gas Detection	Limitations	Response Time	Sensitivity	References
Infrared Spectroscopy	High precision and accuracy, can detect a wide range of gases, non-invasive	Expensive, requires skilled operation, large equipment	Very high	High precision, capable of detecting a wide range of gases	Multiple VOCs, CO_2, CH_4	Expensive, not easily portable	Seconds to minutes	High sensitivity (ppb to ppm level)	[102]
Chromatography	High accuracy, can detect very low concentrations of gases, gold standard for analysis	Expensive, time-consuming, requires skilled operation, non-portable	Very high	High accuracy and sensitivity, capable of comprehensive gas analysis	Wide range of VOCs	Expensive, non-portable, requires skilled operation	Minutes to hours	Very high sensitivity (ppb level)	[103]
Photonic Crystal Fiber	High sensitivity, selectivity, low interference from humidity, non-invasive, highly stable	High cost, requires specialized equipment and knowledge for operation	Moderate	Uses photonic crystals, highly selective and stable, less affected by humidity	Multiple VOCs, NOx	High cost, requires specialized operation	Seconds to minutes	Very high sensitivity (ppb level)	[43]

Photonic crystal fiber (PCF) sensors leverage advanced optical and structural properties to provide high sensitivity, fast response times, and robust performance for gas detection. Despite their complex manufacturing requirements and sensitivity to environmental factors, these features make them highly effective for applications such as breath analysis, environmental monitoring, and industrial safety. Photonic crystal fiber sensors are highly effective for detecting gases in exhaled breath because of their exceptional sensitivity, selectivity, stability, and resistance to humidity interference. These advanced qualities make them particularly suitable for non-invasive disease diagnosis via breath analysis.

5. PCF Sensors in EBA

Photonic crystal fiber (PCF) sensors have emerged as a significant advancement in the field of exhaled breath analysis (EBA). These sensors utilize distinctive optical characteristics to identify and measure volatile organic compounds (VOCs) as well as additional biomarkers present in exhaled breath. The core principle of PCF sensors is based on guiding light through a microstructured optical fiber with a periodic arrangement of air holes running along its length. This design allows a high degree of interaction between the light and the target gas molecules, thereby enhancing the sensitivity and selectivity of the sensors [104].

PCF sensors operate either by confining light within a hollow core or by utilizing the evanescent field effect, in which the light interacts with the gas molecules in the air holes [105]. The alteration of the light's properties—such as intensity or wavelength—when interacting with gas molecules is measured to quantify the concentration of the target analytes [106]. The hollow-core PCF design, in particular, maximizes the overlap between the light field and the gas molecules, thereby significantly enhancing the sensor's performance [107].

Types of Photonic Crystal Fiber Sensors

1. **Hollow-Core PCF Sensors:** These sensors confine the light within a hollow core surrounded by a microstructured cladding. The interaction between light and gas molecules takes place within the hollow core, resulting in enhanced sensitivity and swift response times [108].
2. **Solid-Core PCF Sensors:** These sensors use the evanescent field that extends into the microstructured cladding filled with gas. Although they generally have lower sensitivity than hollow-core PCFs, they are more straightforward to fabricate and highly effective for specific applications [109].

PCF sensors have shown great promise in detecting various biomarkers in exhaled breath, such as nitric oxide (NO), ammonia (NH3), acetone, and other VOCs associated with diseases like asthma, diabetes, and lung cancer [104]. PCF sensors' high sensitivity and specificity make them suitable for early diagnosis and monitoring of these conditions [110]. For instance, ammonia detection using PCFs is crucial for early diagnosis of renal diseases, as elevated ammonia levels in breath indicate kidney dysfunction [104]. Additionally, detecting biomarkers like acetone is essential for monitoring diabetes, as acetone levels correlate with blood glucose levels [111]. PCF sensors have also been employed to detect hydrogen and methane, biomarkers for gastrointestinal diseases, enhancing non-invasive diagnostic capabilities [107]. A summary of various PCF sensors developed for detecting specific biomarkers associated with different diseases is presented in Table 5.

Table 5. PCF sensors for disease detection using EBA.

Title	Gas/Analyte	Disease Diagnosed	Sensitivity	Advantages & Features	Wavelength/Band	References
Ammonia Measurement via PCF	Ammonia	Kidney disease	63.18%	Moisture-resistant, FEM-optimized	1.544 µm	[104]
CO Detection via Hollow-Core PCF	Carbon monoxide (CO)	Hyperbilirubinemia	64.28%	Early jaundice detection	1.567 µm	[108]
Isoprene Detection via PC	Isoprene	Liver fibrosis	0.321 nm/ppm	Tamm plasmon-based, non-invasive	Visible-NIR	[112]
Liquid Crystal PCF Sensor	Acetone	Diabetes	65 ppm (LOD)	Compact, temp-compensated	N/A	[113]
Antiresonant PCF for Respiration	Water vapor	Respiration monitoring	—	Wearable, tracks breathing	~1.5 µm	[114]
Circular PCF for IgG/IgM	Antibodies	COVID-19	High (qualitative)	Low loss, blood-serum compatible	Not stated	[115]
PCF Humidity Sensor	Humidity	Respiratory rate	−0.166 dB/%RH	Low temp cross-sensitivity	~1.55 µm	[116]
PCF Fluorescence for Lactic Acid	Lactic acid	Sepsis/cancer	0.8–9.5 µM (LOD)	Dual-channel, enzymatic	Fluorescence	[117]
Raman-Enhanced HC-PCF	VOCs (propene, H_2, CO_2)	Lung cancer	SRS-based	High enhancement, broadband	Visible–NIR	[118]
High-Performance SO_2 PCF Sensor	Sulfur dioxide	Respiratory risk	87.39%	Low loss, THz-compatible	1.8 THz	[119]
PCF Sensors for Cancer Detection (Review)	Various biomarkers	Multiple cancers	— (review)	SPR/SERS/Interferometry Overview	Various	[120]
Helically Twisted PCF Sensor	CO, NOx, SOx	Toxic gas exposure	3000 RIU^{-1}	100% relative sensitivity, simple build	0.2–3.0 THz	[121]
Trace C_2H_2 Detection via HC-PCF	Acetylene (C_2H_2)	VOCs in breath	49 ppm (LOD)	Linear response, real-time sensing	1–500 Hz	[122]

6. Challenges, Interdisciplinary Roles, and Future Perspectives

Despite the immense potential of EBA, several significant challenges must be addressed to facilitate its transition from research laboratories to routine clinical practice. Addressing these hurdles requires a concerted, interdisciplinary effort.

6.1. Standardization and Confounding Factors

A major challenge is the lack of standardization in breath sample collection and analysis protocols. Factors such as breathing rate, exhaled air volume, and the portion of breath sampled can significantly affect VOC concentrations. Furthermore, results can be

influenced by numerous confounding factors, including the patient's diet, smoking habits, medications, and environmental exposures. Establishing universal protocols is essential for ensuring the reproducibility and comparability of data across different studies.

6.2. Sensor Performance and Clinical Validation

While sensor technology has advanced rapidly, challenges related to selectivity, stability, and sensitivity in a complex and humid breath matrix persist. Sensors must be able to reliably detect ppb-level concentrations of specific biomarkers without interference from other compounds or sensor drift over time. Beyond technical performance, the most critical step involves large-scale clinical validation. Many promising biomarkers identified in small-scale studies have yet to be validated in large, diverse patient cohorts, a costly but necessary process for regulatory approval.

6.3. The Essential Role of Interdisciplinary Collaboration

The success of EBA is fundamentally dependent on collaboration between different disciplines. Physicians and clinicians are crucial for defining clinical needs, designing robust studies, and interpreting data within a pathological context. Simultaneously, engineers, chemists, and material scientists are responsible for designing novel sensor materials (such as the nanomaterials and PCFs discussed), improving sensor characteristics, and developing hardware. This synergy ensures that the technology addresses real-world health problems effectively.

6.4. Future Perspectives

The future of EBA is promising, with a clear trajectory toward portable, low-cost, point-of-care devices. Integrating artificial intelligence will enhance diagnostic accuracy and may predict disease progression or treatment response. The ultimate goal is to develop devices that can be used in a general practitioner's office or even at home, revolutionizing personalized medicine and enabling disease screening on an unprecedented scale.

7. Conclusions

Exhaled breath analysis has evolved from ancient diagnostic practices to a sophisticated, science-driven approach, offering significant advantages over traditional methods. The ability to detect VOCs at very low concentrations enables the identification of biomarkers associated with various diseases, facilitating early diagnosis and monitoring. Modern analytical techniques such as GC-MS, IMS, and electronic noses have significantly improved the accuracy and reliability of EBA. Integrating machine learning algorithms with these techniques has further enhanced their diagnostic capabilities. Among the various sensor technologies, photonic crystal fiber (PCF) sensors stand out due to their exceptional sensitivity and specificity. PCF sensors, which leverage advanced optical properties and the interaction between light and gas molecules, offer unparalleled performance in detecting VOCs in exhaled breath. These sensors have demonstrated high sensitivity in detecting biomarkers for asthma, diabetes, and lung cancer. The hollow-core PCF design, in particular, maximizes the overlap between the light field and the gas molecules, significantly enhancing the sensor's performance. The superior sensitivity of PCF sensors compared to other methods makes them particularly suitable for early disease detection. For instance, PCF sensors have shown high sensitivity in detecting acetone, a biomarker for diabetes, and ammonia, which is associated with renal diseases. The ability to detect such biomarkers at very low concentrations makes PCF sensors a powerful tool for non-invasive diagnostics. Despite the promising potential of EBA and PCF sensors, some challenges must be addressed. Standardizing breath sampling and analysis procedures is crucial to ensure reproducibility and accuracy. Additionally, environmental factors and individual differences

can affect the results, necessitating further research and technological advancements to overcome these challenges.

In summary, exhaled breath analysis, especially when utilizing photonic crystal fiber sensors, shows great promise as a non-invasive diagnostic method with the potential to significantly advance healthcare practices. The continued development and validation of EBA techniques, coupled with advancements in sensor technology, hold the promise of improving patient outcomes and advancing personalized medicine. The development of portable and user-friendly devices for breath analysis will be crucial for the widespread adoption of EBA in clinical practice.

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