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Advances in Early Lung Cancer Detection Through Sensor Array-Based VOC Analysis of Exhaled Breath

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This review focuses on the emerging role of sensor array-based VOC analysis of exhaled breath, particularly using electronic nose (e-nose) technology, for the early detection of lung cancer. Given the critical importance of early diagnosis in improving lung cancer outcomes, this review emphasizes studies that target Stage I and Stage II lung cancer. Traditional diagnostic methods often fall short in identifying lung cancer at its earliest, most treatable stages, leading to high mortality rates. E-nose technology, inspired by the human olfactory system, offers a non-invasive, rapid, and potentially cost-effective approach to detecting volatile organic compounds (VOCs) in exhaled breath, which serve as biomarkers for lung cancer. Through a systematic review of the literature, we initially identified 193 studies related to e-nose-based breath analysis for lung cancer detection. After applying rigorous selection criteria, focusing specifically on studies involving early-stage lung cancer and excluding those using alternative VOC analysis methods, 12 studies were deemed eligible for inclusion. These studies demonstrate the significant potential of e-nose technology in detecting subtle changes in VOC profiles associated with early-stage lung cancer. This review synthesizes the current state of knowledge, highlights recent advancements, and discusses the challenges and future directions of integrating e-nose technology into clinical practice for early lung cancer detection. The findings underscore the promise of e-nose technology as a valuable tool in the ongoing effort to reduce lung cancer mortality through earlier diagnosis.

Keywords: Lung cancer, volatile organic compounds, electronic nose, sensor array, breath analysis.

1. Introduction

Lung cancer is a major challenge in global healthcare, heavily impacting individuals, families, and healthcare systems worldwide. Despite advances in treatments and growing awareness of risk factors, lung cancer remains a leading cause of death, largely due to late-stage diagnoses [1-3]. The prognosis for lung cancer patients is often poor, with many cases not being detected until the disease has progressed significantly [4,5]. Early detection is crucial for improving patient outcomes, but current diagnostic methods often fail to identify lung cancer in its early stages. This gap highlights the need for more effective screening techniques and earlier interventions, which could significantly reduce mortality rates and improve the quality of life for those affected by lung cancer. As research continues, the focus remains on finding better ways to detect lung cancer earlier and to provide more effective treatments for those diagnosed [6-10].

The urgency to address the significant health problem posed by lung cancer has spurred the development of innovative diagnostic technologies aimed at detecting the disease in its earliest and most treatable stages. Among these emerging approaches, exhaled breath analysis using electronic nose (e-nose) technology has gained considerable attention. This method offers a non-invasive, rapid, and potentially cost-effective way to identify volatile organic compounds (VOCs) that serve as potential biomarkers for lung cancer diagnosis [11,12]. Human breath is a complex mixture containing thousands of volatile and semi-volatile compounds, which reflect the metabolic processes occurring within the body. When these metabolic pathways are disrupted, as in the case of pathological conditions like cancer, the composition of exhaled breath changes. These alterations in VOC profiles can provide valuable insights into the presence of lung cancer, even at an early stage. The e-nose technology leverages its sensitivity and selectivity to detect these subtle changes in VOCs, allowing for the early identification of lung cancer with remarkable accuracy [13-16]. By capturing and analyzing these volatile compounds, e-nose devices can potentially distinguish between healthy individuals and those with lung cancer, offering a promising tool for early detection. This technology not only holds the potential to improve patient outcomes by enabling earlier diagnosis and treatment but also presents a less invasive and more accessible option compared to traditional diagnostic methods. As research in this area continues, e-nose technology could become a vital component in the fight against lung cancer, contributing to better survival rates and reducing the burden on healthcare systems [17, 18].

E-nose technology is inspired by the human sense of smell, which can detect a wide range of odors with remarkable accuracy [19]. This technology mimics the intricate sensory mechanism of our olfactory system by using an array of chemical gas sensors, each designed to respond to specific volatile organic compounds present in exhaled breath. By utilizing pattern recognition algorithms and multivariate analysis techniques, e-nose systems can identify unique VOC signatures associated with different physiological and pathological states, including lung cancer with the help of sensor arrays [20-25]. The structure of the sensor array based breath analysis system is depicted in figure 1. The development of e-nose technology has seen significant advancements from its initial conceptualization to its current potential for clinical application. Early versions of electronic noses were primarily designed for basic odor discrimination tasks, serving as proof-of-concept models in controlled laboratory environments. These early devices demonstrated the possibility of distinguishing between different smells but were limited in their practical applications [26,27].

However, as sensor technology and computational algorithms have advanced, modern e-nose platforms have evolved significantly. These techniques are also widely applied in various other fields, including food and beverage quality analysis, agriculture for crop monitoring, and chemical analysis, showcasing their versatility and broad utility [28-31]. They now exhibit enhanced sensitivity, specificity, and portability, making them more suitable for integration into clinical diagnostic workflows. These improvements have transformed e-nose technology from a laboratory curiosity into a promising tool for real-world applications. Today, e-nose devices are capable of detecting subtle changes in VOC profiles, offering a non-invasive, rapid, and potentially cost-effective method for diagnosing conditions like lung cancer. As research continues, the integration of e-nose technology into clinical settings could revolutionize early detection and diagnosis, leading to better patient outcomes and a significant impact on global healthcare [32,33].

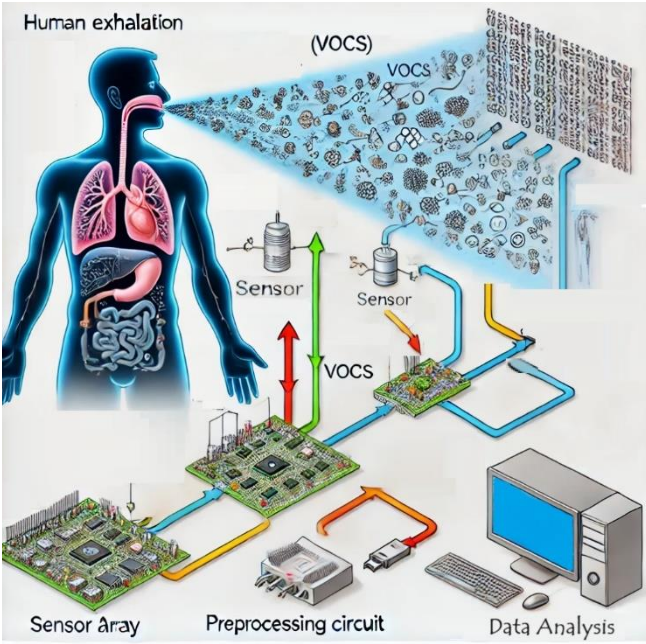

Figure 1. Sensor array-based breath VOC analysis

The purpose of this review is to critically evaluate the emerging role of sensor array-based VOC analysis, specifically using e-nose technology, in the early detection of lung cancer. By focusing on studies targeting Stage I and Stage II lung cancer, this review aims to highlight the potential of e-nose technology as a non-invasive, rapid, and cost-effective diagnostic tool that could significantly improve early detection rates and, consequently, patient outcomes. Traditional diagnostic methods often fail to identify lung cancer at these early stages, where treatment is most effective. Therefore, this review seeks to synthesize current research findings, assess the effectiveness and reliability of e-nose technology in detecting early-stage lung cancer, and identify the challenges and opportunities for its integration into clinical practice. In this comprehensive review, we undertake an in-depth exploration of the role of e-nose technology in revolutionizing lung cancer diagnosis. Specifically, we concentrate on the potential of sensor array-based breath analysis techniques for early-stage lung cancer screening, rather than covering all studies related to lung cancer detection through breath analysis. By focusing on this critical aspect, we aim to synthesize the collective knowledge and highlight recent advancements in e-nose technology as it pertains to early detection. This review seeks to provide a thorough roadmap for researchers, clinicians, and industry stakeholders, offering insights into the current state of the field, challenges, and future directions. Ultimately, our goal is to contribute to the ongoing efforts to improve early lung cancer diagnosis and patient outcomes.

2. Materials and Methods

To comprehensively explore the e-nose-based exhaled breath analysis for early lung cancer detection, a systematic search was conducted until December 2023 across multiple electronic databases and scholarly sources. The search encompassed renowned databases such as EMBASE, PubMed, Google Scholar, as well as general web searches via Google. Specific keywords and phrases, including "electronic nose," "lung cancer," "breath analysis," "biomarkers," and related terms, were employed to identify relevant literature in the field. The search strategy was meticulously crafted to ensure inclusivity while maintaining relevance to the research focus. The keywords were strategically combined using Boolean operators to enhance search precision and capture a broad spectrum of relevant publications. Synonyms and related terms were also incorporated to account for variations in terminology across different studies. Figure 2 provides a schematic representation of the method utilized for article selection.

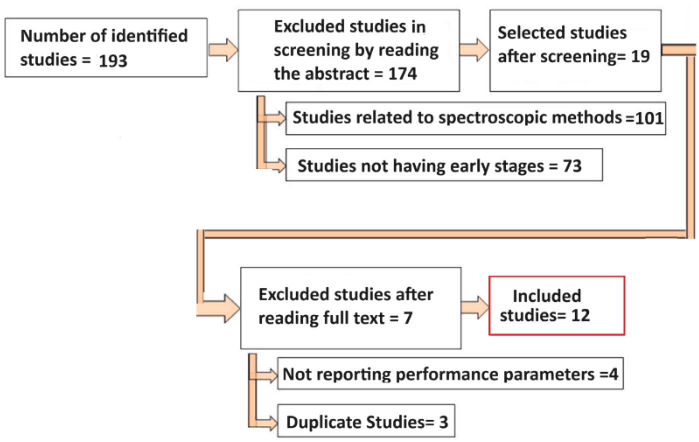

Figure 2.Articles selection Process

The inclusion criteria were meticulously predefined to ensure the selection of studies that align with the primary objective of detecting VOC biomarkers for early-stage lung cancer using e-nose technology. To be included, studies had to explicitly report on e-nose-based breath analysis methods that were specifically designed to identify VOC biomarkers associated with early-stage lung cancer. This focus on early-stage detection is critical, given that timely identification of lung cancer significantly improves treatment outcomes and survival rates. Moreover, to maintain the rigor and reliability of the review, only studies published in English and available as peer-reviewed articles were considered. This criterion was established to ensure that the included research met a high standard of scientific credibility and could be reliably compared and synthesized. Conversely, studies were excluded based on several stringent criteria to avoid any potential biases or inconsistencies in the review. Firstly, studies that failed to provide essential performance of at least accuracy, sensitivity, or specificity metrics, were excluded, as these parameters are fundamental for evaluating the diagnostic efficacy of e-nose-based detection methods. Without knowing any of these parameters, it would be challenging to assess the true potential of e-nose technology in detecting early-stage lung cancer. Additionally, studies that focused on diseases other than lung cancer were excluded to maintain the specificity of the review's objective. Similarly, studies that did not specifically target early-stage lung cancer detection were omitted, as the focus of the review is on the potential of e-nose technology in identifying cancer at the most treatable stages. Lastly, any studies employing VOC analysis techniques unrelated to e-nose technology were also excluded, as the review aims to provide a clear and focused analysis of e-nose applications in this context. These comprehensive inclusion and exclusion criteria were designed to ensure that the review encompasses only the most relevant and high-quality studies, providing a robust analysis of the potential of e-nose technology in early lung cancer detection.

Upon identification of relevant studies, their references were meticulously reviewed to identify additional original works that met the inclusion criteria. This approach ensured a comprehensive coverage of the existing literature and minimized the risk of overlooking pertinent studies. Data extraction was conducted systematically from the selected studies, encompassing various key elements essential for under-standing and evaluating the methodologies employed. This included author names, publication year, country of origin, sample size, details of breath sample collection methods, VOC detection techniques, data analysis methodologies, and performance parameters such as accuracy, sensitivity, and specificity. The collected data were synthesized and organized to facilitate a structured analysis of the methodologies employed across different studies. This process involved categorizing studies based on commonalities in their approach to breath sample collection, VOC detection, and data analysis. Discrepancies or variations in methodologies were noted, allowing for a critical evaluation of their potential impact on study outcomes and conclusions. Overall, the methodology adopted in this review adhered to rigorous systematic principles to ensure the comprehensive identification, selection, and analysis of relevant literature pertaining to e-nose-based exhaled breath analysis for early lung cancer detection.

3. Results and Discussion

A systematic review of the literature on e-nose-based exhaled breath analysis for lung cancer detection initially identified a total of 193 studies. Of these, 174 studies were excluded as shown in Figure 1. The exclusions were primarily based on the use of other methods for VOC analysis and the focus on later stages of the disease rather than early-stage detection. From the remaining 19 studies, an additional 7 were eliminated due to the absence of crucial accuracy parameters and the presence of duplicate studies. The focus was specifically on studies that included a higher number of Stage I and Stage II lung cancer cases, as early detection is critical for improving patient outcomes. After a thorough and rigorous assessment, 12 studies were ultimately deemed eligible for inclusion in this systematic review. These selected studies provide valuable insights into the potential of e-nose technology for the early detection of lung cancer, particularly in its initial stages. The selected studies exhibited varying sample sizes, e-nose technologies employed, and performance metrics, providing a diverse array of insights into the utility of e-nose technology for lung cancer diagnosis. Table 1 displays the major findings from the 12 reviewed papers.

Cyranose 320 e-nose, colorimetric sensors-based e-nose, and metal oxide gas sensors-based e-nose are majorly utilized for sensor array-based VOC analysis in early lung cancer detection. The Cyranose 320 is a portable e-nose device used for detecting and identifying VOCs in various environments, including medical diagnostics. It operates by analyzing the chemical signature of VOCs through a sensor array composed of polymer composite sensors [14, 34, 35]. These sensors respond to different chemical vapors, producing a unique pattern or "smellprint" that can be used to differentiate between samples. In medical applications, the Cyranose 320 has been particularly valuable in analyzing exhaled breath for early disease detection, such as lung cancer, due to its ability to detect subtle changes in VOC profiles associated with different health conditions. Colorimetric sensor-based e-noses utilize color-changing chemical indicators to detect and analyze VOCs in various samples, including exhaled breath. These sensors consist of chemically responsive dyes that undergo visible color changes when exposed to specific VOCs [7, 36]. The array of colorimetric sensors creates a distinct pattern or "color fingerprint" that can be captured and analyzed using imaging techniques. The color changes in the sensors correspond to the presence and concentration of specific VOCs in the breath, enabling the identification of disease-specific patterns. This method is favored for its simplicity, cost-effectiveness, and the ability to provide rapid results without the need for complex instrumentation. SpiroNose is a sophisticated e-nose device designed for respiratory diagnostics, specifically tailored for the detection and monitoring of respiratory diseases through exhaled breath analysis [37-39]. Unlike traditional e-nose devices, SpiroNose integrates spirometry, a standard lung function test with VOC detection, allowing for a comprehensive assessment of a patient’s respiratory health. The device works by capturing the exhaled breath and analyzing the VOCs present, which are indicative of metabolic processes within the body. By combining spirometry with VOC analysis, SpiroNose offers a more complete picture of lung function and potential disease states.

Most studies have predominantly utilized metal oxide gas sensor-based electronic noses for detecting and analyzing volatile organic compounds in various applications, particularly in medical diagnostics [4, 5, 8, 11, 13, 16, 19]. Metal oxide gas sensor-based e-noses are devices that utilize metal oxide semiconductors (MOS) to detect and analyze VOCs in the air. These sensors operate by measuring the changes in electrical resistance that occur when VOC molecules interact with the surface of the metal oxide material, such as tin oxide (SnO_2). When VOCs come into contact with the sensor, they either donate or accept electrons, altering the conductivity of the metal oxide layer, which is then measured and interpreted as a specific chemical response. Metal oxide gas sensors are widely used in e-nose technology due to their high sensitivity, fast response times, and ability to detect a broad range of VOCs at low concentrations. In medical applications, these sensors are valuable for analyzing exhaled breath to detect diseases such as lung cancer, where specific VOCs serve as biomarkers. The patterns of resistance changes across an array of metal oxide sensors create a unique "smellprint" that can be used to differentiate between healthy individuals and those with specific diseases. These e-noses are particularly advantageous in applications requiring robust, portable, and relatively inexpensive sensing solutions, making them suitable for both clinical and research settings focused on non-invasive diagnostics.

Among the included studies, Mazzone et al. conducted a study involving 229 subjects utilizing colorimetric sensors based e-nose technology, achieving an accuracy of 81%, sensitivity of 70%, and specificity of 86% [7]. Similarly, Chen et al. reported on a study involving 235 subjects, employing metal oxide, hot wire, and electrochemical gas sensors based e-nose, achieving remarkable accuracy (94%), sensitivity (96%), and specificity (91%) [11]. Li et al. contributed two studies to the review, one involving 52 subjects with an accuracy, sensitivity, and specificity of 92% each, and another involving 268 subjects with an accuracy of 86% [13]. Chang et al. examined the utility of metal oxide gas sensors in a study comprising 85 subjects, achieving an accuracy of 75%, sensitivity of 79%, and specificity of 72% [4]. Gasparri et al. focused on QMB sensors based e-nose technology in a study involving 146 subjects, achieving a sensitivity of 81% and specificity of 91% [24]. Tirzīte et al. investigated Cyranose 320 e-nose in a study comprising 335 subjects, achieving an accuracy of 87%, sensitivity of 87%, and specificity of 90% [34].

Table 1. Studies with e-nose based early-stage lung cancer detection

Subjects	Accuracy (%)	Sensitivity (%)	Specificity (%)	E-nose used	Reference
229	81.1	70	86	Colorimetric sensors based e-nose	7
235	93.59	95.6	91.09	Metal oxide, Hot wire, and Electrochemical gas sensors based e-nose	11
52	91.59	91.58	91.72	Metal oxide, Hot wire, and Electrochemical gas sensors based e-nose	13
85	75	79	72	Metal oxide gas sensors	4
268	86.42	87.85	82.31	Metal oxide, Hot wire, and Electrochemical gas sensors based e-nose	16
146	Not reported	81	91	QMB sensors based eNose	24
87	94.25	97.83	90.24	Metal oxide, Hot wire, and Electrochemical gas sensors based e-nose	33
335	87.3	87.3	71.2	Cyranose 320	34
191	84.65	88	81.3	Cyranose 320	14
682	87	86	89	SpiroNose	37
261	91.67	88.89	93.75	Metal oxide gas sensors based e-nose	40
137	94.16	96.34	90.91	Metal oxide gas sensors based e-nose	41

Notably, Liu et al. reported particularly promising results in their study involving 87 subjects, where metal oxide, hot wire, and electrochemical gas sensors based e-nose technology yielded impressive accuracy (94%), sensitivity (97%), and specificity (71%) [33]. These findings underscore the potential of e-nose technology in facilitating accurate and reliable early detection of lung cancer, thereby offering opportunities for timely intervention and improved patient outcomes. The observed variations in performance metrics across studies can be attributed to several factors, including differences in sample populations, e-nose technologies utilized, breath sample collection protocols, and data analysis methodologies. Furthermore, the heterogeneity in study designs and diagnostic criteria may have contributed to disparities in reported accuracy, sensitivity, and specificity values.

From the 12 studies in this review reveals a consistent and promising trend in the application of e-nose technology for the early detection of lung cancer. In these studies, the reported accuracy, sensitivity, and specificity rates exceed 85%, underscoring the reliability and effectiveness of e-nose devices in identifying early-stage lung cancer through VOC analysis. Figure 3 shows the maximum accuracy, sensitivity, and specificity for different e-nose technologies. This high level of diagnostic performance suggests that e-nose technology is capable of distinguishing between healthy individuals and those with early-stage lung cancer with a considerable degree of precision. The consistency of these results across multiple studies highlights the potential of e-nose technology as a valuable diagnostic tool that could complement or even enhance existing lung cancer screening methods. These findings reinforce the importance of further research and clinical trials to validate e-nose technology and explore its integration into routine clinical practice, with the goal of improving early detection rates and ultimately reducing lung cancer mortality.

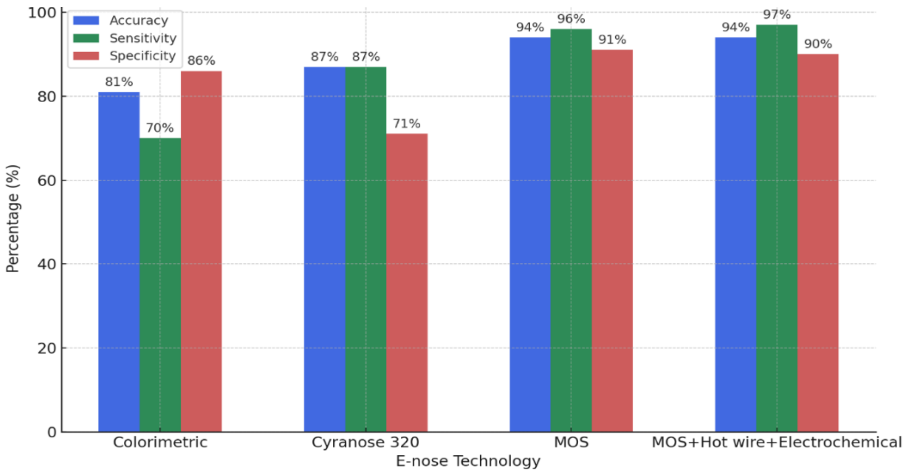

Figure 2. Maximum accuracy, sensitivity, and specificity for different e-noses from studies

The comparison of four different electronic nose technologies such as Colorimetric sensors-based e-nose, Cyranose 320, MOS based e-nose, and MOS combined with Hot Wire and Electrochemical sensors-based e-nose—reveals significant differences in their diagnostic performance for early lung cancer detection. The Colorimetric sensors-based e-nose, with a maximum accuracy of 81%, sensitivity of 70%, and specificity of 86%, demonstrates moderate effectiveness, particularly in distinguishing true negatives. Cyranose 320 performs better overall, achieving a maximum accuracy and sensitivity of 87%, though its specificity is lower at 71%, indicating a higher rate of false positives. The MOS-based e-nose stands out with the highest accuracy of 94%, a near-perfect sensitivity of 96%, and a high specificity of 91%, making it the most reliable technology for correctly identifying both true positives and negatives. Similarly, the combination of MOS, Hot Wire, and Electrochemical sensors-based e-nose also achieves a maximum accuracy of 94%, with the highest sensitivity at 97% and a strong specificity of 90%. These findings suggest that while all the technologies have potential in lung cancer detection, the MOS-based and the combined MOS, Hot Wire, and

Electrochemical sensors-based e-noses are particularly promising for clinical application due to their superior accuracy, sensitivity, and specificity. Their ability to detect early-stage lung cancer with high precision makes them valuable tools in improving early diagnosis and patient outcomes.

Despite the promising results reported by several studies, it is essential to acknowledge the limitations and challenges associated with e-nose-based breath analysis for lung cancer detection [42-45]. These include the need for standardized protocols, validation in larger and more diverse patient cohorts, and addressing confounding factors that may influence VOC profiles, such as smoking history, comorbidities, and environmental exposures [46, 47]. Furthermore, future research efforts should focus on elucidating the biological basis of VOC biomarkers associated with lung cancer pathogenesis, refining e-nose technologies to enhance sensitivity and specificity, and establishing robust diagnostic algorithms for clinical implementation. Collaborative initiatives involving multidisciplinary teams comprising clinicians, engineers, and data scientists are essential to drive innovation and translation of e-nose technology into routine clinical practice [48,49].

In our study, we looked at how well e-nose technology could help find lung cancer early. We found that it shows promise in this area. First, we found that using e-nose technology to analyze breath samples could help detect lung cancer in its early stages. This is important because screening cancer early makes it easier to treat. E-nose technology works by detecting certain chemicals in breath that could be linked to lung cancer. Our study adds to the growing evidence that e-nose could be a valuable tool in diagnosing lung cancer early. Our findings are in line with previous research that has shown the potential of e-nose technology in detecting various diseases, including lung cancer. This suggests that e-nose could be a versatile tool in healthcare, helping doctors diagnose different illnesses quickly and accurately.

However, our study also revealed some challenges and limitations with using e-nose technology for lung cancer detection. For example, we found that the accuracy of e-nose varies between different studies. Some studies showed very high accuracy rates, while others were less accurate. This could be due to differences in the types of e-nose sensors used, how breath samples were collected, or other factors. Another challenge is that e-nose technology is still relatively new, and more research is needed to fully understand its capabilities and limitations. Additionally, more research is needed to determine the best way to use e-nose technology in clinical practice, such as how often to use it and who should be tested. Despite these challenges, our study high-lights the potential of e-nose technology in improving lung cancer diagnosis. If further research confirms our findings, e-nose could become a valuable tool for doctors in the fight against lung cancer. It could help identify patients who need further testing or treatment, leading to better outcomes for patients.

The major findings from this systematic review underscore the potential of e-nose-based breath analysis as a promising approach for early detection of lung cancer. While significant progress has been made, further research is warranted to address existing challenges and realize the full clinical utility of e-nose technology in revolutionizing lung cancer diagnosis and management.

4. Conclusion

In conclusion, the utilization of e-nose technology for exhaled breath analysis holds promising potential in the early detection of lung cancer by identifying volatile organic compounds as biomarkers. The comprehensive review conducted underscores the significance of this innovative approach, as evidenced by the diverse array of studies demonstrating varying levels of accuracy, sensitivity, and specificity. Despite encountering some limitations and challenges, such as the need for standardized protocol and validation in larger patient cohorts, the collective findings accentuate the importance of continued research and development in this field. Moving forward, it is imperative to address these challenges and refine e-nose technology to realize its full diagnostic capabilities in lung cancer detection. Collaboration among multidisciplinary teams, including clinicians, engineers, data scientists, and industry stakeholders, is crucial for driving innovation and translating research findings into clinical practice. By advancing e-nose technology and overcoming existing limitations, we can significantly contribute to improved patient outcomes and healthcare practices in the realm of lung cancer diagnosis. The potential of e-nose technology extends beyond early detection to facilitate personalized treatment strategies and ultimately reduce the burden of lung cancer on individuals and society. Therefore, continued investment in research and development efforts is paramount to realizing the transformative impact of e-nose technology in revolutionizing lung cancer diagnosis and management.

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