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ENose: a new frontier for non-invasive cancer detection and monitoring

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Abstract

Electronic Nose (ENose) technology has emerged as a transformative tool in medical diagnostics, leveraging sensor arrays that mimic the human olfactory system to detect odors and volatile organic compounds (VOCs) in various biological samples. ENose systems utilize a range of sensor types, such as metal oxide semiconductors and conducting polymers, to generate unique "smell fingerprints" through pattern recognition algorithms. These systems have shown promise in diagnosing various medical conditions, including respiratory diseases, infectious diseases, metabolic disorders, and neurological conditions. Notably, ENose technology holds significant promise in cancer diagnostics, offering a non-invasive, cost-effective, and rapid approach to early detection and monitoring. It has demonstrated impressive accuracy (85%-95%) in detecting cancers and monitoring complications. However, challenges remain, including issues with standardization, sensor sensitivity, and data interpretation. Despite these hurdles, ENose technology's market growth is fueled by the increasing prevalence of chronic diseases. Recent developments in Artificial Intelligence (AI), particularly machine learning techniques like deep learning, have enhanced the diagnostic accuracy and robustness of ENose devices. This paper explores the evolution, core principles, applications, challenges, and future potential of ENose technology, with particular emphasis on integrating recent advancements in AI for enhanced detection and interpretation. Future research and collaboration across sectors are essential to overcome existing challenges and integrate ENose into mainstream healthcare.

Keywords: Electronic nose, volatile organic compound, ENose in healthcare, pattern recognition algorithms, cancer, diagnosis

INTRODUCTION

Electronic Nose (ENose) technology is an intriguing topic that emulates the sense of smell in electronic gadgets. Like the human olfactory system, these technologies detect and recognize odors or volatile chemicals. ENose systems operate based on pattern recognition. They are made up of a series of sensors that detect various volatile substances in the air. Each sensor responds uniquely to different odors, resulting in a distinct "smell fingerprint" for each molecule[1]. When exposed to a sample, the sensors emit signals, which are then processed and analyzed to identify and categorize the odor based on its distinct pattern. An ENose is often made up of a sensor array comprising a variety of sensors, including Metal Oxide Sensors (MOS) and conducting polymers. These sensors sense volatile chemicals and send signals. A data collection system captures and processes these signals, while pattern recognition algorithms use the data to detect and categorize odors. The data are then shown through an output interface, giving real-time feedback on odor detection[2-4].

In this review, we aimed to give an in-depth assessment of ENose technology, with an emphasis on its current and future applications for cancer diagnostics. We explored the underlying concepts of ENose technology, charting its evolution from early industrial prototypes to its critical role in medical diagnostics, focusing on the detection of disorders via breath Volatile Organic Compounds (VOCs). The article emphasizes the benefits of ENose in oncology, including early cancer identification, increased patient comfort, faster findings for timely therapies, preventative tactics, lower risk of complications, affordability, and remote monitoring of patients. Furthermore, new trends and future directions in ENose technology are described, highlighting the ability for integration into wearable devices, applications in precision oncology, and greater clinical acceptability, as well as the existing hurdles and prospects for additional study.

The remainder of the paper is structured as follows: After the introduction, Section 1 provides a comprehensive overview of the history and development of ENose technology in medical applications. Section 2 highlights the importance of rapid, non-invasive diagnostic tools in healthcare and explores the principles of ENose technology, focusing on sensor arrays and detection mechanisms. Section 3 delves into the applications of ENose in cancer diagnostics, examining its role in detecting various cancers, including lung, breast, gastrointestinal, prostate, head and neck, and bladder cancers. Section 4 addresses the challenges associated with ENose technology in medical diagnostics. Section 5 explores future directions and opportunities, including ENose's potential in remote cancer monitoring and telemedicine, the significance of collaborative and interdisciplinary research, and its clinical implementation. Finally, the paper concludes in section 5.

The history of ENose in medical applications and cancer detection

The history of ENose technology in medicine, particularly in cancer detection, reflects a journey of innovation, from its early conceptualization to its current integration of Artificial Intelligence (AI)-driven advancements in clinical applications. Originally developed in the late 20th century for industrial and environmental purposes, ENose technology began to transition into medical research in the 1990s, with a focus on disease diagnosis through the detection of VOCs in breath [Figure 1]. During this period, the development of sensor arrays using metal oxide semiconductors and conducting polymers initiated the exploration of using ENose for detecting diseases via breath VOCs[5]. By the 2000s, advancements in sensor technology and algorithms significantly enhanced the accuracy of ENose devices. This period saw the first clinical trials applying ENose technology to detect various illnesses, including lung cancer and diabetes. The use of breath analysis to identify VOCs linked to cancer began to show real promise, particularly for lung

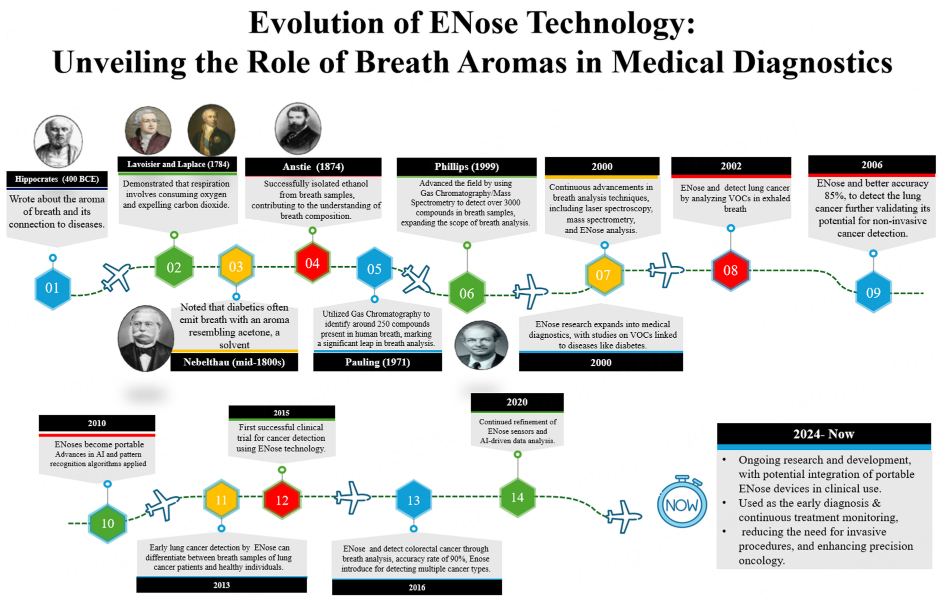

Figure 1. History of ENose in Medicines with respect to breath aromas and cancer. ENose: Electronic nose.

cancer detection[6]. A significant milestone occurred in 2002 when researchers demonstrated that ENose technology could detect lung cancer by analyzing VOCs in exhaled breath. This study marked one of the first major successes in applying ENose to cancer diagnostics[7]. By 2006, researchers at St. George's University Hospitals NHS Trust in London successfully used an ENose to differentiate breath samples from lung cancer patients and healthy individuals. This study achieved an accuracy rate of around 85%, further confirming the potential of ENose for non-invasive cancer detection[8]. The 2010s saw significant advancements in miniaturization, making ENoses portable and more suitable for point-of-care (POC) applications. These developments paved the way for the technology's increased use in personalized medicine, allowing for real-time disease monitoring. ENoses became essential for identifying respiratory conditions, malignancies, infections, and metabolic abnormalities, and for monitoring organ transplants. During this decade, the integration of AI and machine learning algorithms greatly improved the accuracy, specificity, and reliability of cancer detection. AI-driven pattern recognition systems enabled ENoses to identify biomarkers linked to specific cancer types, such as lung and breast cancers, facilitating their use in precision oncology[9].

In 2013, researchers at the University of Manchester demonstrated the potential of ENose technology to differentiate between breath samples from lung cancer patients and healthy controls, offering promising results for early lung cancer detection (van de Goor *et al.*, 2018). This study marked another important step in validating ENose as a tool for cancer diagnosis[10]. A breakthrough occurred in 2015, when clinical trials using ENose technology for cancer detection, specifically lung cancer, demonstrated successful results by analyzing VOCs in exhaled breath. This success paved the way for further exploration of ENose technology in early cancer detection, with a particular emphasis on non-invasive diagnostic methods[11]. Another major milestone was achieved in 2016 by researchers at the University of California, Berkeley, who used an ENose to detect colorectal cancer through breath analysis. The ENose was able to identify cancer-specific VOCs with an impressive accuracy rate of 90%, further broadening the scope of ENose applications in cancer diagnostics[12]. As we move into the 2020s, ENose technology continues to evolve with further improvements in sensors and enhanced AI algorithms that drive more accurate data interpretation. Its integration into clinical settings is expanding, not only for cancer detection but also for monitoring treatment effectiveness and detecting recurrence, particularly in cancers such as colorectal and gastric cancers[13]. Looking ahead, 2024 marks an exciting milestone as portable ENose devices are being developed for real-time, non-invasive cancer monitoring. These advancements are enhancing precision oncology by enabling early diagnosis and continuous monitoring of treatment responses, thereby improving patient outcomes while reducing the need for invasive tests. Ongoing research and development in this field hold the potential to revolutionize cancer care by providing early detection and more effective disease management strategies[14].

IMPORTANCE OF RAPID AND NON-INVASIVE DIAGNOSTIC TOOLS IN HEALTHCARE

Rapid and non-invasive diagnostic tools play a crucial role in healthcare for several reasons. They facilitate the early detection of diseases, enabling prompt interventions and treatments that enhance patient outcomes while reducing healthcare expenses. Non-invasive tools eliminate the need for invasive procedures or sample collection methods, improving the overall patient experience and encouraging adherence to healthcare protocols[15]. This seems particularly evident in cancer diagnostics, since a prompt intervention can dramatically impact patient outcomes. The rapid and non-invasive diagnostic tools that can be used in healthcare are shown in Figure 2.

Rapid diagnostic tools deliver quick results, aiding healthcare providers in making informed and timely decisions about patient care, particularly relevant in oncology, which is characterized by time-sensitive treatments. These tools bolster preventive healthcare efforts by enabling early detection, identifying risk factors, and preventing disease progression or complications. Non-invasive diagnostic tools lower the risk of healthcare-associated infections (HAIs) from invasive procedures, enhancing patient safety and reducing strain on healthcare systems. Most often, they serve as screening tests and only when positive, followed by more accurate analysis; this makes them available for large fractions of patients in a time a cost-effective way. In fact, financial savings result from reducing the need for multiple tests, hospital stays, and invasive procedures, making healthcare more efficient and accessible. Remote patient monitoring using non-invasive tools allows healthcare providers to track disease progression, assess treatment efficacy, and intervene as needed without frequent in-person visits. Patients benefit from quick access to diagnostic information, which promotes active participation in healthcare decisions and enhances overall engagement with healthcare services[16-18].

Principles of ENose technology

ENose technology operates on several underlying principles and utilizes a sensor array that responds to VOCs or odors, generating unique electrical signals known as "smell fingerprints"[19]. These signals are processed through pattern recognition algorithms, often employing machine learning techniques for odor identification. Calibration ensures accurate odor recognition, with results presented through an output interface for real-time feedback, enabling applications in medical diagnostics, environmental monitoring, and security, as shown in Figure 3.

Briefly, ENose works through these different steps[20]:

Sensor array: An ENose typically consists of an array of chemical sensors, each designed to respond to different VOCs or odors. These sensors may include MOS, conducting polymers, Quartz Crystal Microbalances (QCM), and Surface Acoustic Wave (SAW) sensors.

Pattern recognition: When exposed to a sample containing VOCs, the sensors generate electrical signals based on their interactions with the compounds. The pattern of these signals, often referred to as the "smell

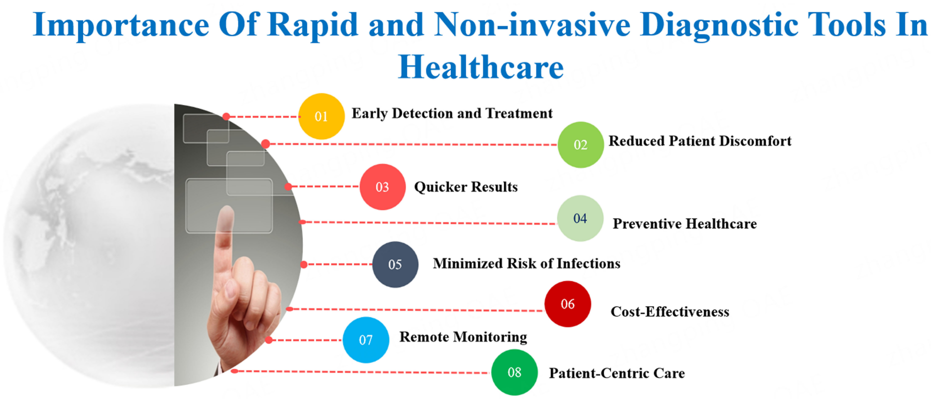

Figure 2. Importance of rapid and non-invasive tools in healthcare.

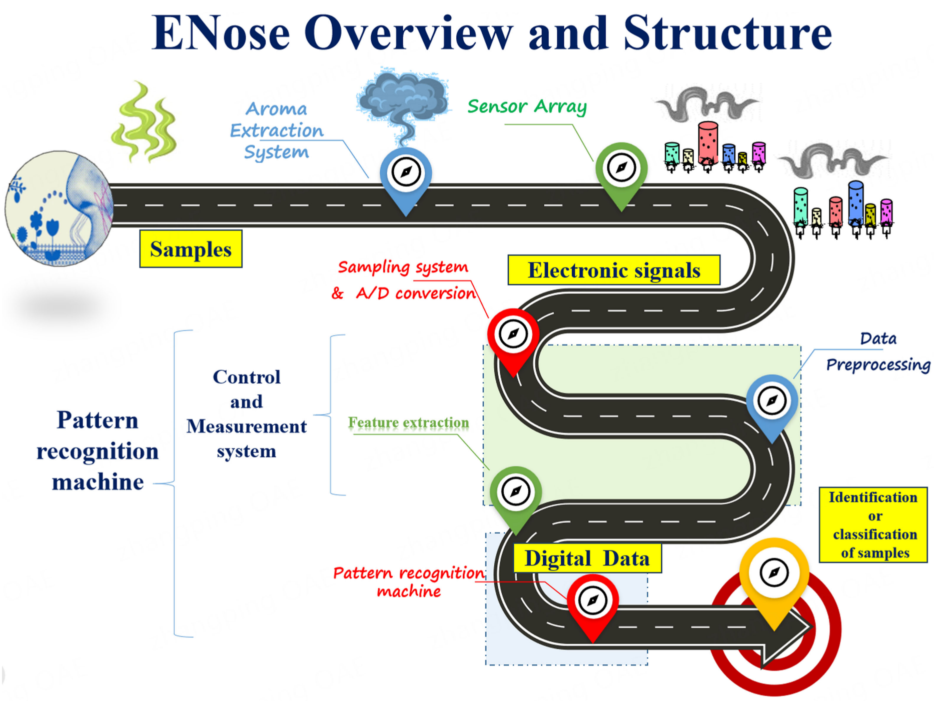

Figure 3. ENose overview and structure. ENose: Electronic nose.

fingerprint", is unique for each VOC.

Data acquisition: The signals from the sensor array are collected using a data acquisition system. This system digitizes the analog signals for further processing.

Pattern recognition algorithms: Advanced algorithms process digitized sensor data to identify patterns and distinguish between different odors. Machine learning techniques, such as neural networks or support vector machines, are commonly used for this purpose.

Calibration: ENose requires calibration to establish baseline responses for various odors. This calibration ensures accurate and consistent odor recognition over time.

Response analysis: The processed data are analyzed to identify and classify the detected odor based on its unique pattern. This analysis may involve comparing the sensor response pattern to a database of known odor patterns or using statistical methods to determine similarity scores.

Output interface: The results of the odor analysis are typically presented through an output interface, such as a graphical display or numerical output. This interface provides real-time feedback on the detected odor and its concentration or classification.

By combining sensor technology, pattern recognition algorithms, and data analysis techniques, ENose technology can effectively mimic the human olfactory system and detect a wide range of odors or VOCs in various applications, including medical diagnostics, environmental monitoring, quality control, and security[21].

Sensor arrays and detection mechanisms

ENose sensor arrays contain a variety of sensor types, including MOS, conducting polymers, QCM, SAW sensors, optical sensors, and capacitive sensors. These sensors detect VOCs via a variety of processes, including changes in electrical conductivity, mass shifts on quartz crystals, changes in acoustic wave propagation, differences in optical characteristics, and capacitance changes. The combined reactions of these sensors provide a unique "smell fingerprint", which is analyzed using pattern recognition algorithms to identify and categorize odors, improving sensitivity and selectivity in odor identification. These sensors' detection processes use physical or chemical interactions between VOCs and sensor surfaces, which cause detectable changes in electrical, acoustic, optical, and mechanical characteristics.

The sensor array's combined reaction to numerous VOCs creates this "smell fingerprint", which pattern recognition algorithms use to reliably detect and categorize odors. Integrating several sensor types into an array enhances the sensitivity, selectivity, and overall capabilities of ENose systems for detecting odors[22-24].

Applications of ENose in cancer diagnostics

ENose technology is used in medical diagnostics to diagnose a wide range of conditions via non-invasive breath analysis, including respiratory diseases, malignancies, infectious agents, and metabolic problems [Figure 4]. It also helps to monitor organ transplants, measure wound healing, identify narcotics and alcohol, and enable personalized medication[25,26]. As far as cancer is concerned, new methods for early-stage detection are under investigation. A few of them, including those using gas chromatography (GC) and mass spectrometry (MS), are based on gaseous sample analysis. These devices are expensive, difficult to use in daily medical practice, and have limited portability, making them only suitable for organized laboratory environments. By contrast, cheaper portable ENose instruments can detect very low amounts of molecules, distinguishing between volatile metabolites in complex mixtures[27].

Therefore, so far, breath analysis is one of the most promising uses for ENose technology. Cancer cells produce distinct metabolic byproducts, which can be identified as particular VOCs in the breath. In addition, urine and perspiration contain VOCs that can be used as cancer biomarkers. The ENose detects these chemicals with excellent sensitivity, adding another non-invasive tool for early cancer detection.

According to the most recent studies, ENose can distinguish with high accuracy between healthy people's breath patterns and those with cancers such as lung, breast, and colorectal cancer[28,29]. The most frequently analyzed type of cancer is certainly lung cancer; however, different tumors are also considered in studies using ENose technology.

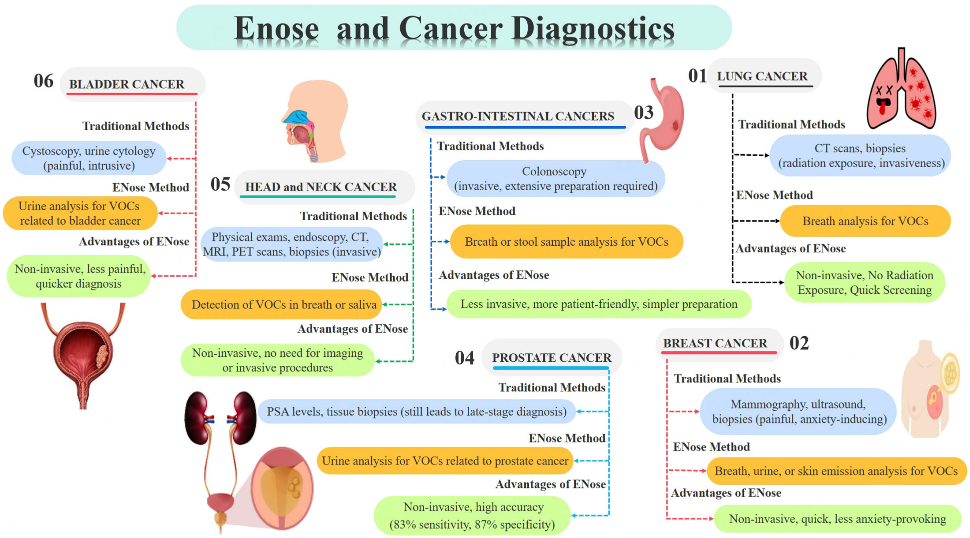

Figure 4. Various uses of ENose in medical research and Cancer diagnosis. ENose: Electronic nose; VOCs: volatile organic compounds; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

ENose vs. lung cancer

Lung cancer is one of the most common causes of cancer-related death worldwide. Early detection dramatically increases survival rates. Traditional procedures, such as CT scans and biopsies, are only partially successful, and have drawbacks such as radiation exposure and invasiveness[30]. The ENose is a non-invasive alternative that analyzes breath samples for VOCs related to lung cancer. Research has shown that ENose can detect lung cancer with high sensitivity and specificity, making them useful tools for early detection. Most studies using ENose technology achieved satisfactory sensitivity, specificity, and accuracy (An accuracy of over 80% in differentiating between lung cancer (LC) and controls, as well as between LC and other cancer types), despite the low specificity of ENose systems in general. Particularly, a recent study by Rocco et al. indicated an 86% sensitivity and 95% specificity compared to histopathology[31]. In addition, a multicentric study showed an Area Under the Curve (AUC) of 95% when an appropriate AI algorithm was applied[32]. On the other hand, a certain degree of heterogeneity in cancer detection can be due to (1) signal acquisition protocols, (2) the device used, and (3) the studied population (in terms of both size and pre-test disease probability). As far as devices are concerned, the most used nanosensors are either integrated into commercial devices like the Cyranose 320 (Sensigent, Baldwin Park, CA, USA) or as non-commercial products and prototypes. Nanosensors provide numerous advantages over traditional sensors, including fast response times, adequate detection limits, great portability and scalability, good sensitivity and resolution, and high selectivity[33]. Machado *et al.* published a study in 2005[34] that used a portable chemical vapor detector with 32 composite carbon black-polymer sensors (Cyranose 320) to distinguish between patients affected by lung cancer and controls. VOCs in exhaled air attach to polymers, causing a reversible change in the electrical resistance of sensors. This system showed a sensitivity of 71.4% and a specificity of 91.9%. Di Natale *et al.*[35] used aniline, alkanes, and benzene derivatives, while D'Amico *et al.* and Tran *et al.*[36,37] used aniline, o-toluidine, and cyclopentane, and Peng *et al.*[38] used isoprene, alkanes, methyl alkanes, and benzene derivatives as disease biomarkers. Remarkably, as technology advanced, nanosensors produced increasingly accurate readings. Bikov *et al.*[39] found poor performance and difficult airflow control in evaluating VOCs using Principal Component Analysis (PCA) for discriminating between classes, with only 40% specificity in distinguishing between lung cancer patients and healthy smokers. Hubers *et al.*[40] also found poor specificity in discriminating between patients. The characteristics were reduced using a PCA with six components. PCA performed better in discriminating categories; therefore, it was utilized to create a Receiver Operating Characteristic (ROC) curve to calculate sensitivity and specificity. Sensigent developers have then improved their product's performance through feedback from trials and technological advancements, as evidenced by large-scale research published by Tirzïte *et al*. in 2017 and 2019[41,42]. The Cyranose 320 accurately distinguishes between lung cancer patients and controls, as well as different stages of lung cancer, utilizing Support Vector Machine (SVM) and Logistic Regression Analysis (LRA). Future improvements to Cyranose 320 performance should focus on improving specificity and lowering false positives. Huang *et al.*[43] found that when using Linear Discrimination Analysis (LDA) and SVM for classification, it is important to keep temperature and humidity stable in the testing environment.

MOS sensors have been widely utilized in ENose applications for lung cancer discrimination and continue to be a leading technology in the sector after many years of application. MOS devices offer several advantages, including a wide range of responses, high sensitivity, low cost, fast response time, small size, easy fabrication, long-lasting life, and a wide temperature range. However, controlling these variables is crucial due to their high selectivity, high power consumption, instability, and sensitivity to external changes[44]. Several other studies have followed[45], and overall, the use of ENose systems for lung cancer detection has shown promising results. Numerous studies have demonstrated the effectiveness of ENose technology in detecting the disease, suggesting its potential for broader use, even in clinical practice. However, further technological advancements are necessary to enhance the performance of these systems, along with properly designed diagnostic accuracy studies.

ENose vs. breast cancer

Breast cancer is often detected using mammography, ultrasound, and biopsies. While successful, these procedures can be painful and cause worry in patients[46]. The ENose can detect VOCs in the breath, urine or even skin emissions that are symptomatic of breast cancer, providing a non-invasive and quick screening tool. Early studies have yielded promising findings, indicating that ENoses could supplement established diagnostic approaches, particularly in resource-limited situations. Specifically, when VOCs from urine were assessed, the system achieved an overall accuracy of 75%, with a sensitivity of 100% and a specificity of 50%[47].

ENose vs. gastrointestinal cancers

Colorectal cancer screening frequently relies on colonoscopy, an invasive procedure that necessitates extensive preparation[48]. The ENose analyzes breath or stool samples for VOCs associated with colorectal cancer, providing a less invasive and more patient-friendly screening procedure. Early detection with non-invasive methods can motivate more people to have frequent screenings, potentially lowering mortality rates. Using neural networks, a portable ENose was capable of an overall accuracy of 81% in discriminating cancerous vs. non-cancerous patients, with high sensitivity (91%) but still suboptimal specificity (55%)[49]. In addition, ENose technology was crucial for early detection of gastric carcinoma (GC). GC is the sixth most common type of tumor, but it is third in terms of mortality rates, mainly due to late identification. ENose tools have been studied using nanosensors in three out of five published studies. Capelli *et al*. applied ENose to classify breath samples from 16 GC patients and 28 controls. The ROC curve showed 81% sensitivity and 71% specificity, but limitations were noted due to the small sample size and specificities of the Chinese population. Future studies should focus on early GC tumor identification and evaluate their effectiveness and potential practical application[50].

ENose vs. prostate cancer

Despite the availability of screening procedures based on Prostate-Specific Antigen (PSA) levels and tissue biopsies, a significant number of patients still present with advanced prostate cancer. Protocols to detect

VOCs in the urine of patients affected by prostate cancers have been developed, showing accuracy, sensitivity, and specificity of 83% (CI95% 77-89), 82% (CI95% 73-88), and 87% (CI95% 75-94), respectively[51].

ENose vs. head and neck cancer

The traditional methods for detecting head and neck cancer include physical examination, endoscopy, and imaging tests like Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography(PET) scans. A biopsy is often performed to confirm the presence of cancer. These methods help assess the size, location, and spread of the tumor[52].

Head and Neck cancer (HNC) has been studied in seven articles, with MOS sensors being the most commonly used due to their widespread and low cost. ENose demonstrated good sensitivity, specificity, and accuracy, comparable to that of LC. For example, van Hooren *et al.* used ENose to characterize the exhaled breath of HNC patients and differentiated between HNC and colon cancer[53]. Hakim *et al.* used commercial ENose tools to distinguish between various types of cancer. Two studies utilized nanosensors, with the ENose (NA-NOSE) device showing excellent performance. Hakim *et al.* achieved 100% sensitivity in discriminating HNC and controls, and 90% sensitivity and specificity in differentiating HNC from lung cancer[54]. Later, Gruber *et al.* distinguished between HNC and controls and different tumor sites with 90% accuracy[55].

ENose vs. bladder cancer

Bladder cancer is difficult to identify early due to the lack of particular symptoms. Traditional diagnostic procedures, such as cystoscopy and urine cytology, can be painful and intrusive[56]. ENose analyzes urine samples for VOCs linked to bladder cancer. Studies have demonstrated that ENose can distinguish urine samples from bladder cancer patients and healthy individuals with excellent accuracy. Interestingly, studies on bladder cancer also confirmed the importance of the bioinformatic tools accompanying the ENose technology. In fact, Tyagi *et al.* showed that the sensitivity and specificity of VOC detection in urine were 0.93 and 0.88, respectively, using a Sparse Logistic Regression, and 0.93 and 0.76 using a Random Forest classifier[57]. This confirmed that detection and interpretation must evolve in parallel in order to ensure an accurate diagnosis.

CHALLENGES OF ENOSE IN MEDICAL DIAGNOSTICS

ENose technology faces various challenges that need to be addressed for its successful implementation in medical diagnostics [Table 1]. One of the major hurdles is calibration and standardization, as ensuring consistent sensor responses across different ENose models is difficult, leading to variations in readings and interpretations[58,59]. Environmental odors further complicate matters, as they can interfere with detecting target odors, reducing the specificity and reliability of the system, especially in complex settings. Another challenge is the complexity of odor profiles, as medical odors often involve a wide range of VOCs in varying quantities, requiring sophisticated algorithms for accurate analysis and interpretation. The sensitivity and selectivity of sensors are critical as ENose sensors need to be finely tuned to detect low concentrations of specific VOCs while remaining selective and not confused by other odors. In addition, validation and clinical utility are key, as more studies are needed to establish the clinical efficacy and predictive value of ENose technology in comparison to traditional diagnostic methods. Proper data interpretation and analysis are also essential, as analyzing complex datasets, identifying patterns, and applying statistical models are crucial for correct diagnosis. Furthermore, cost and accessibility pose significant barriers. High initial costs, maintenance, and calibration fees can prevent widespread adoption, so making ENose systems more affordable and accessible is necessary. The integration of ENose technology into clinical workflows is

Table 1. ENose challenges and their role in cancer detection

Challenge	Description
Calibration & standardization	Calibration is essential for reliable findings; however, standardizing sensor responses between ENose models is problematic, resulting in inconsistent readings and data interpretation
Interference from environmental odors	Environmental odors can disrupt target odor detection, compromising specificity and reliability, especially in complex environments
Complexity of odor profiles	Medical odor profiles are complicated with various VOCs and changing quantities, necessitating advanced algorithms for correct analysis and interpretation
Sensor sensitivity & selectivity	ENose sensors require optimization to identify small amounts of target substances while staying selective for distinct odors
Validation & clinical utility	Validation studies are needed to prove the clinical efficacy, sensitivity, specificity, and prediction value of ENose technology compared to traditional diagnostic procedures
Data interpretation and analysis	Skill in analyzing data, pattern identification, and statistical modeling is essential for proper ENose data interpretation and diagnosis
Cost and accessibility	Adoption may be hindered by initial expenditures, maintenance, and calibration fees, necessitating efforts to make it affordable and accessible to healthcare professionals and patients
Integration with clinical workflow	Successful deployment in medical practice requires seamless integration into clinical processes, user-friendly interfaces, and compliance with EHRs
Water vapor interference	Water vapor in breath samples can interfere with ENose readings by masking or diluting VOC signals, complicating accurate disease detection, and reducing diagnostic reliability. Both endogenous and exogenous water contribute to this challenge
Biomarker overlap & influence	Some cancer biomarkers may overlap, making it difficult to distinguish between diseases. Additionally, syndromes can influence results, complicating diagnosis and increasing the challenge of accurate detection

ENose: Electronic nose; VOCs: volatile organic compounds; EHRs: electronic health records.

another challenge, requiring user-friendly interfaces and seamless compatibility with electronic health records (EHRs) to ensure smooth implementation in medical practice. Water vapor interference is another issue, as breath samples often contain moisture that can distort the readings, making it difficult to isolate VOCs and compromising diagnostic accuracy. Both endogenous and exogenous water play a role in this challenge. Finally, biomarker overlap is a concern, as some cancer biomarkers may be common across different diseases, making it challenging to distinguish between conditions. The presence of syndromes can also influence the results, further complicating diagnosis and increasing the difficulty of achieving accurate and reliable detection. Addressing these challenges will be essential for optimizing ENose technology for broader clinical use, particularly in cancer detection and monitoring[60,61].

FUTURE DIRECTIONS AND OPPORTUNITIES

Recent advancements in ENose technology include improved sensor technology and signal processing techniques, leading to more accurate and dependable ENose equipment for medical diagnosis. Integrating ENose technologies with other diagnostic modalities, such as imaging or genetic analysis, enables a more comprehensive and multi-modal approach to disease detection and monitoring. ENose technology is being applied in new areas like personalized medicine, disease phenotyping, therapeutic surveillance, and precision agriculture, demonstrating its adaptability and potential in various fields. These advancements and trends signify the ongoing evolution and maturation of ENose technology, paving the way for enhanced diagnostic capabilities, improved patient outcomes, and broader applications across different sectors. Beyond medical uses, ENose is used in the food sector for food safety and quality control, identifying spoilage, pollutants, and determining food freshness using odor profiles. These applications demonstrate the broad applicability and potential effect of ENose technology in a variety of sectors, highlighting its importance in developing diagnostics and improving patient outcomes[62-64]. Future trends in ENose technology include integration with artificial intelligence for improved diagnosis and personalized medicine. ENose has the potential to revolutionize healthcare by enabling early detection and targeted treatment strategies. Particularly, since ENose was developed for diagnosing various diseases and conditions, early cancer diagnosis is a primary purpose. It is conceivable that, based on the cancer site, different strategies might be adopted (e.g., breath for lung cancers and cancers heavily affecting metabolism like liver and kidney, bowel gas for GI tract tumors, and even blood for hematopoietic malignancies and metastasis in general). In fact, ENose has been shown to differentiate between cancer types based on VOC profiles. Furthermore, ENose might also help anticipate complications in cancer patients, such as infections, liver and kidney toxicity, or glucose level deregulation following steroid administration[65,66]. Additionally, ENose assesses exposure to environmental toxins and pollutants and detects toxins in air, water, or soil through VOC analysis. In the food and beverage industry, ENose ensures food safety and quality by detecting spoilage, contamination, and adulteration in food products and assessing the quality and authenticity of beverages based on aroma profiles. This may impact cancer epidemiology, favoring the recognition of risk factors and maybe preventing the consumption of contaminated food[67].

Role of ENose in remote cancer monitoring and telemedicine

ENoses play an important role in remote monitoring and telemedicine because they provide a non-invasive, real-time tool for detecting and analyzing VOCs in a range of clinical and environmental contexts. The use of ENoses in telemedicine allows for continuous and remote monitoring of patients' health when a direct physical examination is not possible. In these circumstances, the ENose can effectively gather diagnostic information remotely, allowing a prompt identification of treatment complications as well as cancer recurrences[68,69]. The data generated by ENoses may be securely communicated to healthcare practitioners, enabling rapid analysis and decision making even from a distance. As technology advances and ENose devices become more portable, affordable, and user-friendly, their role in remote monitoring and telemedicine is expected to grow even more, revolutionizing healthcare delivery by providing efficient, cost-effective, and patient-centered diagnostic solutions regardless of geographical distance or healthcare resource constraints[70-72].

Collaborative efforts and interdisciplinary research in advancing ENose technology

ENose technology's future includes personalized medicine and point-of-care diagnostics, leveraging advanced sensors and AI for tailored healthcare. Its role extends to remote monitoring and telemedicine, enabling real-time data transmission and enhancing patient accessibility. Collaborative interdisciplinary research is crucial for advancing ENose capabilities, driving innovation, and integrating it into clinical practice for improved patient outcomes[73-75].

Clinical implementation

Several major recommendations can help to guide future ENose technology. To begin, ENose devices must continue to be validated and standardized in clinical applications. Robust clinical trials (phase 1 to 4 diagnostic accuracy studies) are required to prove the reliability, sensitivity, and specificity of ENose technology for diverse cancer types, and for different VOC sources, hence assuring its usefulness in real-world healthcare settings[76-78]. The development of user-friendly, portable ENose devices would assist wider implementation in clinical practice, allowing for point-of-care testing and remote monitoring of patients. Miniaturization and integration with digital health platforms will improve ENose technology's accessibility and usefulness across a wide range of healthcare settings[79,80]. Collaboration among researchers, physicians, engineers, and industry partners is critical for driving innovation and optimizing ENose technology for clinical applications. This collaborative approach can hasten the translation of research results into useful diagnostic tools that enhance cancer patient care outcomes. Furthermore, regulatory agencies must provide clear norms and criteria for the use of ENose devices in medical diagnostics, ensuring that safety, reliability, and ethical concerns are addressed. Overall, future research should focus on improving ENose technology's diagnostic accuracy, accessibility, and clinical value, paving the path for wider acceptance and inclusion into standard medical practice[81,82].

DISCUSSION AND CONCLUSION

The ENose technology has developed as a potential field in medical diagnostics and uses sensor arrays that simulate the human olfactory system to detect odors and volatile organic compounds (VOCs). ENose consists of sensor arrays composed of various sensors such as metal oxides and conductive polymers, which respond differently to various VOCs. Pattern recognition algorithms use these responses to create a unique "olfactory fingerprint" to identify and classify odors. The analysis presented in this paper explores the evolution, basic concepts, advantages, challenges, and future possibilities of ENose technology in the healthcare field, with a focus on cancer diagnosis. ENose technology has diverse medical applications. Beyond oncology, ENose has widespread applications in the management of diabetes, respiratory health, and infectious disease diagnosis, including respiratory diseases [asthma, chronic obstructive pulmonary disease (COPD), respiratory infections], infectious diseases (tuberculosis, pneumonia, sepsis), metabolic disorders (diabetes, kidney disease, liver disease), and neurological disorders (Alzheimer's, Parkinson's, epilepsy). For instance, this technology can differentiate between bacterial and viral infections with 87% accuracy, which is a crucial feature during pandemics like COVID-19. ENose is also increasingly used in food safety and environmental monitoring, where it can detect pollutants and food spoilage with high accuracy, indirectly contributing to disease prevention and public health promotion. Recent years have shown that cancer diagnosis can significantly benefit from ENose technology, both in early detection and post-treatment monitoring. For example, the World Health Organization (WHO) reported 19.3 million new cancer cases in 2020 and predicts this number will rise by around 50% by 2040, highlighting the urgent need for innovative technologies like ENose for early intervention and improved patient outcomes. The global ENose market, valued at $18.4 million in 2023, is expected to grow at a compound annual growth rate (CAGR) of 12.5% from 2024 to 2030. This growth is primarily driven by the increasing prevalence of chronic diseases such as cancer, diabetes, and respiratory diseases, as well as the growing demand for advanced diagnostic tools. In this context, ENose technology offers several advantages, including non-invasive testing, rapid results, low cost, and portability, which improve early cancer detection, monitoring of residual diseases, and point-of-care testing. However, this technology faces challenges such as standardization, data interpretation complexity, sensitivity and specificity issues, and the need for clinical validation. Standard calibration protocols have been shown to reduce variability by up to 30% and improve diagnostic reliability, facilitating broader adoption in clinical settings. Ensuring consistent results to gain the trust of doctors, healthcare providers, and regulators is essential for integrating ENose technology into mainstream medicine. The sensitivity and specificity of ENose devices in detecting subtle olfactory changes associated with disease markers are crucial. Clinical trials have demonstrated accuracy rates of 85%-95% in diagnosing lung and gastrointestinal cancers, but larger studies are needed for further confirmation. ENose devices have also shown accuracy rates of over 90% in monitoring complications like infections and metabolic disorders, especially in cancer care. This capability, along with secure data transmission for remote analysis, facilitates timely interventions, reduces hospital visits, and enhances patient comfort. By overcoming these challenges and continuing to improve sensor accuracy, portability, and clinical effectiveness, ENose is well-positioned to transform diagnosis, improve patient outcomes, and expand its impact in both medical and non-medical fields. Recent studies show that 68% of healthcare professionals are ready to adopt ENose technology, provided that issues related to calibration, affordability, and regulatory compliance are addressed. This indicates a strong market readiness for ENose as a mainstream diagnostic tool. The growing demand for ENose devices highlights the need for collaboration among researchers, physicians, engineers, and industry professionals. These collaborations are key to advancing technology and ensuring its integration into modern healthcare systems. The development of user-friendly, portable, and affordable ENose devices is especially crucial for resource-limited areas where there is a high demand for point-of-care diagnostics. Future research directions should focus on clinical validations for screening the most common types of cancer, expanding detectable olfactory markers, creating user-friendly devices, and improving regulatory standards for clinical use. In summary, ENose technology has revolutionary potential in cancer diagnosis and can provide new, non-invasive, and sensitive tools for tumor detection and monitoring. Collaboration among researchers, physicians, engineers, and regulatory agencies is essential for advancing ENose technology and integrating it into routine clinical practices. Recent advancements in artificial intelligence, particularly deep learning algorithms like Convolutional Neural Network (CNNs) and Recurrent Neural Network (RNNs), have improved the accuracy of ENose systems by analyzing complex VOC patterns associated with diseases. AI-enhanced ENose systems improve data interpretation by automating analysis, providing faster and more accurate results. This integration enables the discovery of new olfactory markers and expands disease detection capabilities. AI also plays a significant role in precision oncology, helping identify cancer-specific markers in breath or bodily fluids. These AI-powered ENose systems enable personalized treatments and effective monitoring. The combination of AI and ENose promises to enhance disease detection and treatment. With continued interdisciplinary collaborations and a focus on overcoming existing limitations, ENose technology is poised to play a central role in shaping the future of personalized medicine, telemedicine, and global public health initiatives, transforming disease management and patient care with innovative, non-invasive, and diagnostic solutions.

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Conceptualization: Moshayedi AJ, Chen M, Piccaluga PP
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Conflicts of interest

Piccaluga PP is an Editorial Board member of *Journal of Cancer Metastasis and Treatment*. Piccaluga PP was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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