Review Article

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Diagnosis of pathological conditions through electronic nose analysis of urine samples: a systematic review and meta-analysis

Helga A.S. Afonso[a], Mariana V. Farraia[b,c,d], Mónica A. Vieira[a], João Cavaleiro Rufo[b,c,*]

Abstract

Currently available urinalysis methods are often applied for screening and monitoring of several pathologies. However, traditionally analyzed biomarkers in urinalysis still lack sensitivity and specificity to accurately diagnose some diseases. Several studies have proposed the use of electronic noses (eNoses) for the analysis of volatile organic compounds in urine samples that may, directly or indirectly, correlate with certain pathologies. Hence, the aim of this study was to perform a systematic review and meta-analysis of studies concerning the use of portable electronic noses for diagnosis or monitoring of pathologies through analysis of urine samples. A systematic review of the literature was held according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Twenty-four articles met the inclusion criteria and were included in the analysis. The results of the revised studies showed that there are various volatile organic compound profiles, identified through eNose analysis, that may be applied for diagnosis or monitoring of several diseases, such as diabetes, urinary tract infection, inflammatory bowel disease, and kidney disease. A meta-analysis was conducted taking into consideration the data of 10 of the initial 24 articles. The pooled sensitivity, specificity, and diagnostic odds ratio were 84% (95% CI, 0.72–0.92), 85% (95% CI, 0.75–0.91), and 24.17 (95% CI: 7.85–74.41), respectively. The area under the receiver operating characteristic curve was 0.897. These results suggest that eNose technology has adequate diagnostic accuracy for several pathologies and could be a promising screening tool for clinical settings. However, more studies are needed to reduce heterogeneity between results.

Keywords: diagnosis, electronic nose, urine, volatile organic compounds

Introduction

The first laboratory test performed in medicine was urinalysis. Nowadays, it plays a paramount role in obtaining information for diagnosis in medicine.[1] Urinalysis is a simple and affordable method that provides a wide range of information about the patient's health regarding renal function, urological and liver disease, diabetes mellitus, urinary tract infection (UTI), and general hydration.[2–5] Urinalysis is also used to detect compounds not usually present in urine, such as nitrate, blood, glucose, and leucocytes.[6]

The analysis of urine is still one of the most performed diagnostic tests. Normal urine is usually slightly acidic; thus, the determination of urine pH is useful in the diagnosis and treatment of UTI and renal calculi.[7] Abnormal urine color can occur because of food, medication, metabolic products, or infection.[8] Precipitated phosphate crystals in alkaline urine cause a cloudy appearance, as well as the presence of white cells. However, sediment analysis techniques have revealed significant errors, associated with centrifugation, optics, and stains after microscopy, and false positive and false negative results may also take place in dipstick urinalysis.[9] In view of the poor analytical performance in traditional urinalysis, alternative diagnostic approaches have become a widely discussed research topic.

Recently, volatile organic compounds (VOCs) have been proposed as potentially effective biomarkers for disease diagnosis.[10] The human body releases VOCs according to each individual condition, with either physiological or pathophysiological origins. For instance, a patient with a carcinoma may produce a specific profile of VOCs released from mutated cells.[11] On the other hand, a patient with an infection may present a distinct VOC profile because of the compounds released from the infectious agent itself.[12] These distinct VOC patterns may be valuable for the rapid screening of diseases. In addition, these compounds are easily accessible and might be analyzed through different biological matrices such as urine. Urine collection is fast, and it can be easily stored and may be useful in providing valuable information.

There are several methods to analyze VOC patterns in different biological samples. However, portable electronic nose (or eNose) instruments provide several advantages in VOC analysis, especially when it concerns clinical screening.[11] eNose devices can be developed for specific applications using sensor arrays, which should be able to detect the volatile components as a whole or individually and ultimately evaluate VOC profiles that might be distinguishable according to the disease, severity, or

[a] Escola Superior de Saúde, Instituto Politécnico do Porto, Porto, Portugal, [b] EPIUnit—Institute of Public Health, University of Porto, Porto, Portugal, [c] Laboratory for Integrative and Translational Research in Population Health (ITR), Porto, Portugal, [d] Basic and Clinical Immunology Unit, Department of Pathology, Faculty of Medicine, University of Porto, Porto, Portugal

* Corresponding author. Laboratory for Integrative and Translational Research in Population Health, Instituto de Saúde Pública da Universidade do Porto, Rua das Taipas no 135, 4050-600 Porto, Portugal. E-mail address: jcrufo@gmail.com (João Cavaleiro Rufo).

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symptomatology.[13] The main advantage of these portable gaseous chemical sensing devices when compared with other techniques is its simple use at the point of care. The disadvantage is that it offers only a collective answer of sensors to the analytes being analyzed in a mixture without identifying specific chemical compounds.[14] Despite this limitation, eNose measurements are acquired from multiple sensors and provide sufficient data that are analyzed through machine learning or multivariate analysis, promoting an accurate separation of patients with different conditions.

There are several eNose devices in the market, mostly used for scientific use only. However, recent generations of these devices have already been conceived with clinical applications in mind.[10,15]

Hence, we aimed to perform a systematic review and meta-analysis of studies concerning the use of portable eNoses for diagnosis or monitoring of pathologies through the analysis of urine samples.

Methods

Systematic review

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[16] the systematic search was performed until May 9, 2021, using the following keyword combinations: *electronic nose* or *e-nose* combined with any term derived from *urine* [("electronic nose") OR (e-nose) OR (enose)) AND (urin*)] on PubMed (MEDLINE), Cochrane Library, and IEEE. Published peer-reviewed articles written in English, focusing on the diagnosis or monitoring of pathology in humans and analyzing biomarkers in urine samples through electronic nose, were taken into consideration. The inclusion criteria were (a) articles in English, (b) studies focused on the diagnosis or monitoring of a pathology, (c) measurement or detection of biomarkers in urine samples through electronic nose, and (d) studies performed on humans. Studies that did not fulfill these criteria were excluded. Nonoriginal articles, such as reviews, were not included in the qualitative or quantitative analysis. Articles focused on synthetic urine samples were also excluded. Finally, studies solely using nonportable eNose instruments were excluded. For the purpose of the present review, nonportable eNose systems may refer to any technology that needs a dedicated laboratory for operation, such as gas chromatography coupled to mass spectrometry. Moreover, data regarding publication year, studied pathology, eNose model, objectives, main results, and diagnostic test accuracy (DTA) were collected.

Quality assessment

The quality assessment of the selected studies was conducted following the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool.[17] This tool allowed the evaluation of the quality of each study according to four domains, namely patient selection, index test(s), reference standard, and flow and timing. For each quality parameter, the article was rated as "yes," "no," "unclear," "high," or "low." The quality score was calculated considering the number of questions assigned as "yes." The score varies between 0 and 9.

Meta-analysis

This meta-analysis was conducted in R, following the guidelines proposed by Shim et al[18] for DTA meta-analysis in R. Effect estimates were calculated based on true positive, false negative, true negative, and false positive counts provided in each included study. Whenever these variables were not disclaimed by the studies, data were extrapolated from sensitivity and specificity values, if available. Otherwise, articles were excluded from quantitative analysis because of insufficient test data.

Univariate analysis of metadata was performed using "meta" and "metagen" packages[19] to estimate pooled sensitivity, specificity, and diagnostic odds ratio (DOR). Bivariate analysis and receiver operating characteristic (ROC) curve were performed using the "mada" package. Forest plots were constructed to illustrate the results.

To mitigate the effect of eventual heterogeneity of the studies in the meta-analysis, random effects models were used to estimate pooled sensitivity and specificity, and the interstudy heterogeneity was studied with the DerSimonian–Laird method and Cochrane Q test.[19]

Aiming to investigate publication bias, the Begg funnel plot was constructed and the Egger test was performed.[20,21] The Duval & Tweedie trim-and-fill method[22] was performed, and a corrected funnel with three simulated studies was constructed.

Results

Included studies

The flowchart of studies selection is shown in Fig. 1. By searching through the 3 databases, we found 123 studies, including three duplicates. Of the 120 screened articles, 81 were not included after a careful verification of content according to the inclusion and exclusion criteria. From the 39 remaining studies, 14 were review articles. In the end, a total of 24 studies were eligible for qualitative analysis (Fig. 1). A summary table of the included studies, as well as their specific objectives, is provided in the supplementary material (Table S1, Supplemental Digital Content 5, http://links.lww.com/PBJ/A17).

The articles included in this systematic review were published between 1999 and 2020. In addition, the covered pathologies included diabetes, cancer, urinary tract infections, kidney diseases, bowel diseases, pulmonary tuberculosis, Crohn disease, inflammatory bowel disease (IBD), bile acid diarrhea (BAD), and gastrointestinal and respiratory infections. The eNose devices used in the studies varied substantially, with a total of 15 different models being referred. However, the most common devices were Cyranose 320 (Sensigent, Irwindale, CA) and BH-114 eNose.

The quality of the 24 studies was scored according to the QUADAS-2 guidelines (Table S2, Supplemental Digital Content 5, http://links.lww.com/PBJ/A17). In all the articles, there was a consecutive or random sample of patients enrolled, and most of the studies were performed without knowing the results of the reference study. On the other hand, most studies were unclear on the use of an appropriate interval between index test and reference standard. The average (±standard deviation) quality score of the reviewed studies was 7.06 (±1.28).

Meta-analysis

The inclusion criteria for the studies considered in this meta-analysis were based on the Cochrane norms for systematic reviews of interventions.[17] Of the 24 studies included in the qualitative review, only 10 studies presented sufficient data according to the quantitative analysis criteria. All DTA results associated with eNose analysis of urine samples were included in

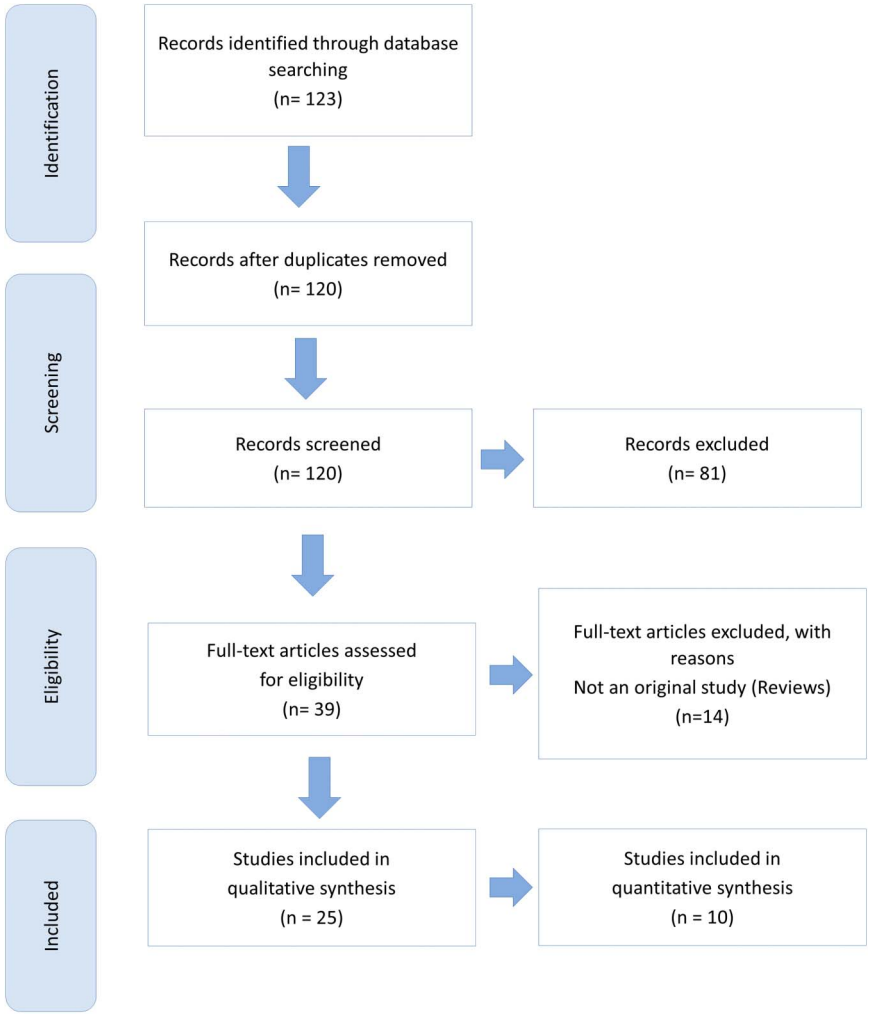

Figure 1. Summary of the literature search based on the PRISMA flowchart.[16]

the meta-analysis, if data were available. Studies containing multiple conditions were repeatedly included for each output, whenever the inclusion criteria were met.

To standardize comparisons across the studies and to guarantee the highest efficacy scenario reported for diagnosing conditions using the eNose, the most accurate iteration of the test was selected. For instance, in studies testing multiple algorithms for the diagnosis of the same condition, only data referring to the more accurate algorithm were included. Table 1 presents the studies included in the meta-analysis and the data retrieved for the meta-analysis. The articles were categorized according to pathology; therefore, there were seven groups of articles: diabetes, cancer, urinary tract infections, IBD, tuberculosis, kidney disease, and multiple pathologies. The last group contemplated articles comparing different pathologies.

On sensitivity analysis (Fig. S1, Supplemental Digital Content 1, http://links.lww.com/PBJ/A13), the studies conducted on patients with cancer presented the lowest heterogeneity, as suggested by the low percentage of interstudy variability ($I^2 = 0\%$) and low variation among observed effects ($\tau^2 = 0$). On the contrary, the group of studies evaluating urinary tract infection showed higher heterogeneity ($I^2 = 82\%$, $\tau^2 = 2.4482$, Cochrane Q test: $P < .01$). Regarding specificity (Fig. S2, Supplemental Digital Content 2, http://links.lww.com/PBJ/A14), the studies focused on diabetes presented low heterogeneity ($I^2 = 0\%$, $\tau^2 = 0$). On the other hand, studies related to tuberculosis had the highest heterogeneity (I^2 of 89%, τ^2 of 1.6366).

The regression models showed a pooled sensitivity of 84% (95% CI, 72%–92%) (Fig. S1, Supplemental Digital Content 1, http://links.lww.com/PBJ/A13) and a pooled specificity of 85% (95% CI, 75%–91%) (Fig. S2, Supplemental Digital Content 2, http://links.lww.com/PBJ/A14). However, pooled sensitivity and specificity values should not be considered separately because both contribute to the overall accuracy of the test. Hence, both variables were used to estimate the pooled DOR using a random effects model (Fig. 2).

Regarding DOR, studies related to tuberculosis presented the highest heterogeneity ($I^2 = 89\%$, $\tau^2 = 3.9209$). On the contrary, studies on diabetes were less heterogeneous. The overall DOR was 24.17 (95% CI, 7.85–74.41).

Bivariate analysis was then performed to plot the summary receiver operating characteristic curve (Fig. S3, Supplemental Digital Content 3, http://links.lww.com/PBJ/A15). The area under the curve referring to the 11 studies was 0.897, suggesting a high diagnostic accuracy. The partial AUC (area between t0 and t1) was 0.812. The sensitivity ROC parameters θ, λ, and β were -0.127, 3.186, and -0.105, respectively.

The funnel plot in Figure S4 (Supplemental Digital Content 4, http://links.lww.com/PBJ/A16) and the Egger test do not indicate strong dissimilarities, and most of the studies are within the funnel

Table 1

Studies included in the quantitative analysis

Study	Condition	eNose	Reference group	Index group	Total	TP	FP	FN	TN
Esfahani et al[28]	Diabetes (patients aged 0–4 years)	Fox 4000	73	67	140	52	11	15	62
Esfahani et al[28]	Diabetes (patients aged younger than 18 months)	Fox 4000	73	67	140	60	8	7	65
Matsumoto et al[32]	Cancer	R integral	27	36	63	22	13	14	14
Matsumoto et al[32]	Urolithiasis	R integral	27	29	56	13	9	16	18
Matsumoto et al[32]	UTI	R integral	27	10	37	6	3	4	24
Westenbrink et al[34]	Cancer	Wolf system	18	39	92	30	4	9	14
Roine et al[30]	Cancer	ChemPro 100	50	24	74	19	17	5	34
Horstmann et al[31]	Cancer	MOS-sensor	21	15	36	11	3	4	18
Visser et al[39]	UTI	Cyranose 320	27	12	39	8	8	4	19
Visser et al[39]	UTI	Cyranose 320	14	12	26	9	4	3	11
Roine et al[38]	UTI	ChemPro 100	21	80	101	78	1	2	20
Kodogiannis et al[37]	UTI	BH-114	15	30	45	30	0	0	15
Mohamed et al[42]	Tuberculosis	PEN3	240	260	500	256	4	4	236
Lim et al[41]	Tuberculosis	CSA	41	22	63	19	8	3	33

Repeated study references refer to different eligible pathologies or populations reported in the same publication.
BH, bloodhound; CSA, colorimetric sensor array; FN, false negative; FP, false positive; TN, true negative; TP, true positive; UTI, urinary tract infection.

area delimited by the confidence interval, suggesting low small-study bias.[2,3] Because the funnel plot shows some asymmetry, we performed the trim-and-fill method that estimated a corrected DOR of 6.62 (1.87–23.41) (Fig. 3).

Discussion

The present review covered studies using different eNose systems to measure the urine volatilome, with the purpose of screening or monitoring diseases with greater accuracy than traditional methods.

Diabetes

Diabetes was the most frequently targeted pathology, being mentioned in seven studies. In 2002, Linder et al[24] compared urine samples from patients with type II diabetes and healthy volunteers using an eNose system. The authors evaluated the application of data classification methods, such as self-learning

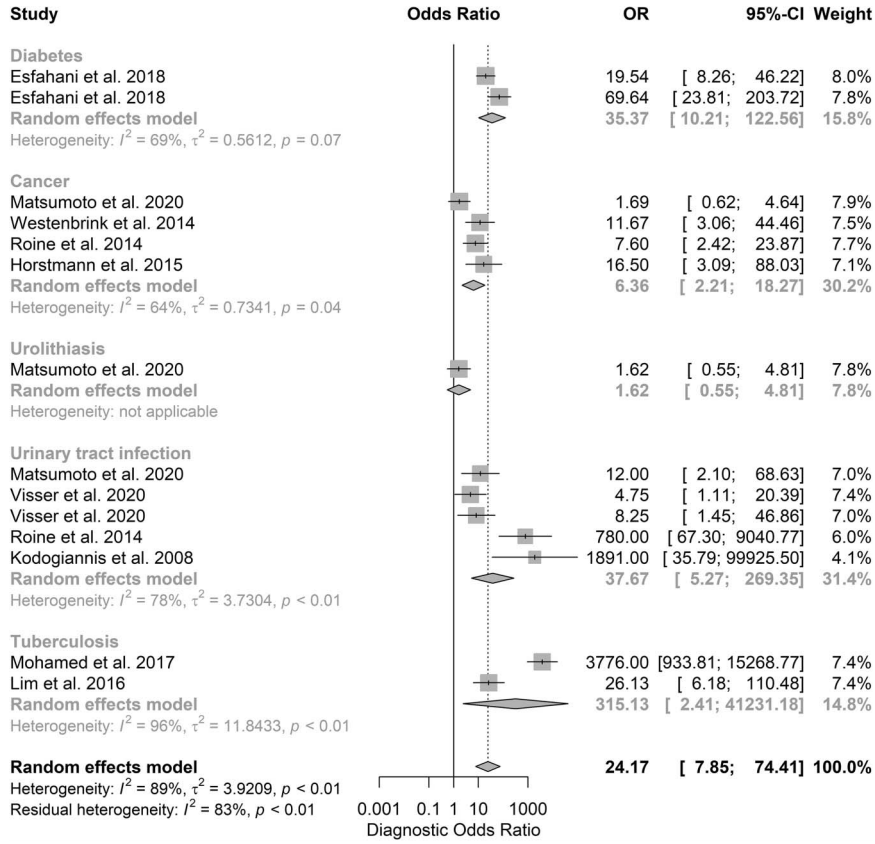

Figure 2. Forest plot showing the diagnostic odds ratio and respective confidence interval (OR [95% CI]) calculated for all studies included in the meta-analysis. The diamonds represent the pooled OR for each category of diseases. OR, odds ratio.

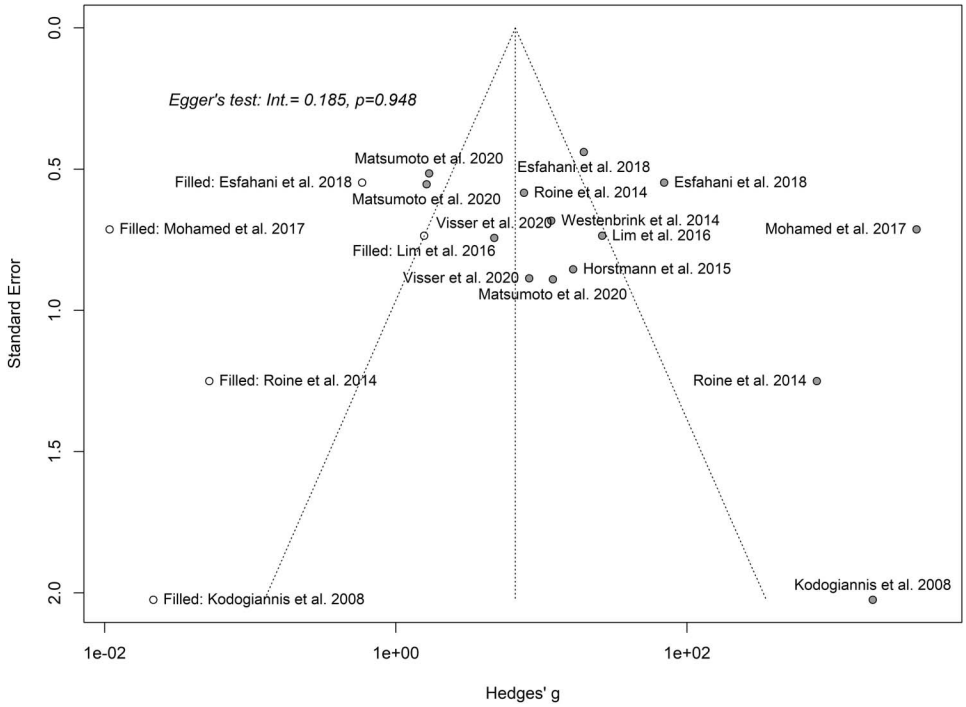

Figure 3. Begg funnel plot with Egger test after applying the Duval and Tweedie trim-and-fill method.

artificial neural networks, logistic regression (LR), and principal components analysis (PCA). The PCA correctly identified all patients except one, which indicates a successful classification rate of 96%. The artificial neural network analysis and LR analysis distinguished healthy and diseased patients with classification rates of 92% and 88%, respectively.

A decade later, a study held in Thailand produced diabetic urine obtained by adding glucose to samples of urine obtained from people with standard levels of glucose. The authors used a laboratory-made eNose for sample discrimination based on commercially available sensors and PCA, and cluster analysis methods were used for data analysis. The eNose was able to measure ammonia gas at different substrate temperatures, suggesting its potential use for diabetes diagnosis.[25] In 2016, the same institution reported a self-monitoring system to detect specific sweet-smelling urine odor known as a hand-held eNose.[26] A pattern of six volatile compounds was used: ammonia, ethyl methyl ketone, butyric acid, acetic acid, acetone, and water. These biomarkers intended to mimic the urine of patients with diabetes. This device was effective in classifying 99.5% specific urine odors, consequently pointing its convenience in real-time self-monitoring of patients with diabetes. A year later, Choden et al[27] detected five compounds commonly found in urine and then used chemiresistive gas sensors to analyze the volatiles in real urine samples using PCA and cluster analysis methods. The sensors detected VOCs distinctively. For instance, one sensor had a better response to toluene, while other detected dimethyl sulfide. These two sensors were able to differentiate diabetic from healthy urine. The remaining sensors showed poor results.

Esfahani et al evaluated urinary samples collected throughout four years using the Fox 4000 eNose (AlphaM.O.S, Toulouse, France). The analysis of all samples using the Field Asymmetric Ion Mobility Spectrometer (FAIMS) presented an AUC of 88%, sensitivity of 87%, and specificity of 82%, while the samples from the first year performed an AUC of 94%, sensitivity of 92%, and specificity of 100%. The same samples analyzed with Fox 4000 eNose achieved an AUC of 85%, sensitivity of 77%, and specificity of 85%. Samples with less than 18 months had an AUC of 94%, sensitivity of 90%, and specificity of 89%.[28] The latest study suggested the use of a Neuro-fuzzy Inference System (ANFIS) algorithm to monitor the diabetic ketones in urine through the smell of acetone.[29] The eNose consisted of four metal oxide gas sensors, instead of the five used on the previously mentioned study. The patients were required to fast for better results of detection. Using this process, it was possible to achieve a detection of 93%.[29]

The six contemplated articles showed high sensitivity and specificity values for the detection of diabetes, suggesting that the clinical screening of this disease may be a potential application of eNose technology in the near future.

Cancer

In 2014, a study evaluated the efficacy of the ChemPro 100-eNose in distinguishing prostate cancer from benign prostatic hyperplasia using urine headspace. The method resulted in a sensitivity of 78%, specificity of 67%, and AUC of 0.77.[30] Horstmann et al[31] used urine samples from patients with a suspicion of bladder cancer and healthy controls. The results showed a sensitivity of 75% and a specificity of 86% using an eNose composed by a metal oxide sensor chip with three thin oxide layers. Later, a study with a similar purpose used a commercial eNose model, made of two angled sensors.[32] The angle between sensors changed according to the chemical substances. This study contemplated 36 patients with untreated bladder cancer, 29 with urolithiasis, and 10 with urinary tract infection, and 27 were healthy. For the angles of 49, 48, and 55, the values of sensitivity, specificity, and AUC were obtained. Sensitivity values for the different angles were 61.4%, 45.6%, and 60.8%, respectively. Specificity values were 52.8%, 68.4%,

and 90.2%, respectively. The AUC values were 0.565, 0.548, and 0.909, respectively. However, the soundness of the obtained results was limited due to the number of subjects involved in this study.

Gut et al[33] measured urine headspace of patients with confirmed transitional carcinoma and healthy controls with the Cyranose 320. The device was used to perform two measurements at different storage temperatures (−20°C and −80°C), being the sensitivity values of 93.3% for both temperatures and the specificity of 86.7% for −20°C and 93.3% for −80°C. The University of Warwick in the United Kingdom developed an eNose to measure the volatile content of urine headspace based on commercial electrochemical and optical sensors.[34] The experiment contemplated urine samples from patients with colorectal cancer, irritable bowel syndrome, and controls, reporting a sensitivity and specificity of 78% and 79%, respectively. These results support the need to continue investigating the use of VOC biomarkers in clinical practice.

The five articles of this section were heterogeneous in their conclusions because of the small sample size in some of the studies. However, results for sensitivity and specificity were promising.

Urinary tract infections

For the detection of bacterial contaminants in urine, a group from the United Kingdom analyzed samples from patients divided into two groups using the BH114-Bloodhound (Leeds, United Kingdom) eNose, composed by fourteen conducting polymer sensors.[35] The analysis of the first patient group, diagnosed with urinary tract infection, was performed using a neural network algorithm, which was able to identify all but one correctly. In a second group, which included a random sample of patients attending the outpatient public health laboratory, the results were maintained. Kodogiannis and Wadge used the same eNose to detect UTI in suspected cases. The 45 samples were analyzed under the same circumstances as the aforementioned study; however, the data analysis used an Extended Normalized Radial Basis Function network. The adopted concept of fusion of the outputs of multiple classifiers dedicated to specific feature parameters was shown to be improved when compared with the normally used method based on averaging. This study showed the potential of the used system for early detection of UTIs.[36]

Later, an eNose was used to detect UTI from 45 suspected cases.[37] The aim was to study the implementation of an advanced neural network and the fusion of multiple classifiers dedicated to specific feature parameters. A total of 13 of 14 patients with UTI were correctly identified.

A proof-of-principle study in Tampere, Finland, displayed the applicability of an ion mobility spectrometry (IMS)–based eNose to discriminate the most common UTI pathogens.[38] A certain number of culture samples containing common UTI bacteria (*E coli*, *S saprophyticus*, *E faecalis*, *Klebsiella* spp) and sterile culture plates were analyzed using the ChemPro 100i device, consisting of IMS cell and six semiconductor sensors. Data analysis was conducted by linear discriminant analysis and LR. When comparing sterile and bacterial samples, a sensitivity of 95% and a specificity of 97% were achieved. Identification of bacterial species reached values of 95% for sensitivity and 96% for specificity compared with urine bacterial cultures. The obtained results demonstrate the potential of the used eNose to discriminate bacterial cultures.

A study conducted at a clinic included patients aged until 18 years with clinical suspicion of UTI and abnormal urinalysis.[39] Urine samples were characterized and divided into four groups according to no bacterial growth, contamination, colonization, and UTI. The Cyranose 320 was used to analyze the VOCs. The sensitivity, specificity, and AUC parameters for distinguishing between UTI and non-UTI samples were 67%, 70%, and 0.048, respectively. The diagnostic accuracy improved when comparing urine with no bacterial growth and urine with UTI (sensitivity 0.79, specificity 0.75, and AUC 0.80).[39]

The four urinary tract infections–related articles do not allow a concise analysis of the results because of the heterogeneity of the diagnostic measurements. More studies and standardization of analytical methods are needed to reduce heterogeneity in future studies.

Inflammatory bowel disease

A study conducted in the United Kingdom included 48 patients with IBD and 14 controls.[40] The VOCs emanated from the urine were analyzed using an eNose and a FAIMS. The data analysis was performed using PCA and discriminant function and showed the efficacy of the eNose in distinguishing diseased individuals from healthy controls with an accuracy higher than 75%.

Tuberculosis

In 2016, Lim et al introduced the use of a colorimetric sensor array for the detection of tuberculosis. The sensor composed of 73 different high-dimensional indicators. This study comprised the analysis of 63 urine samples, with 22 samples from patients with tuberculosis and 41 from symptomatic controls. The tests measured five distinct urine conditions (neat urine, acidic additive, basic additive, salt additive, and preoxidation). Measurements at the most adequate conditions yielded a sensitivity and specificity of 85.5% and 79.5%, respectively.[41]

In other study, the PEN3 (Airsense Analytics, Schwerin, Germany) eNose, consisting of ten different metal oxide sensors, was used to discriminate headspace volatiles between patients with pulmonary tuberculosis and healthy individuals.[42] The technique was successful in differentiating both groups with an accuracy, sensitivity, and specificity higher than 99%.[42]

The two articles of this section obtained promising diagnostic measurements, particularly those provided by the PEN3. However, external validation of the training sets is needed to properly confirm the potential of this electronic nose in diagnosing tuberculosis.

Kidney disease

In 1999, Corrado Di Natale et al[43] used an eNose to analyze the headspace of urine from patients with kidney disease (children aged 0–13 years) who aimed to distinguish samples containing blood. This study allowed the evaluation of the pH and the specific weight of urine. eNose was able to distinguish the urine with blood, and a feed forward neural network also demonstrated the capability of measuring pH and specific weight. However, it is important to note that the presence of blood in urine does not necessarily represent kidney disease, and therefore, the diagnosis method used in this study was more indirect than those applied in other studies.

Recently, Jokiniitty et al analyzed the urine of 95 patients; some samples were from patients with kidney disease, and others were from patients with normal kidney function. The samples were analyzed using an eNose with FAIMs technology. The patients were categorized according to the chronic kidney disease

classification (Glomerular filtration rate class) based on the epidemiology collaboration creatinine equation (CKD-EPI).[44] The eNose showed an accuracy of 81.4% in differentiating extremes of kidney function. This study showed that it might be possible to diagnose chronic kidney disease through urinary VOCs.[45]

Distinguishing between diseases

There were four studies that compared different diseases. The first, from 2000, aimed to study early illness detection. The presence of bacteria in urine may be related to UTI and the presence of mucus which may also indicate kidney stones. Nine samples were tested with the Cyranose 320 and then analyzed by using PCA. Two samples were from healthy individuals, one contained bacteria, and six mucus. The results were compared using the method of data gathering and differences by Cyranose using SPSS and PCA. In the nine samples, PC1 (principal components) results vary significantly when compared with PC2 results.[46]

Kodogiannis et al[47] examined different specimens in 45 urine samples from patients diagnosed with urinary, gastrointestinal, and respiratory infections, with an eNose composed of chemo-resistive sensors. This study combined already existing neural network techniques with advanced AI-based methodologies to create a classification tool. The results confirmed the legitimacy of the used methods and the potential of the new Genetic Algorithm Neural Networks technique.

A study aimed to distinguish urinary VOC profiles from patients with different diseases, such as Crohn disease, ulcerative colitis, and type II diabetes. The Cyranose 320 was capable of distinguishing between Crohn disease and IBD and diabetes with a rate of 97%.[48]

Finally, a study aimed to detect BAD using an Alpha MOS Fox 4000 eNose combined with an Owlstone Lonestar FAIMS.[49] This study compared BAD, ulcerative colitis, and healthy controls using linear discrimination analysis. The process was shown to be effective in the identification of 80% of the cases, suggesting a less expensive, faster, and easier tool to diagnose BAD.

Owing to the heterogeneity of the articles and diseases in this section, it is not possible to accurately evaluate the results as a whole. Nevertheless, the preliminary diagnostic measurements in these works suggest that there might be a promising application of eNose technology in clinical settings, and more studies are needed to properly evaluate the consistency of the aforementioned results.

Limitations

The present review has several limitations. First, it is important to acknowledge that the above-stated observations were subjected to the underlying bias associated with each reviewed study, and even considering that a quality analysis has been performed, it is difficult to weight the impact of such bias in the overall results. For instance, despite the apparent potential of the reviewed eNose instruments, they are known to have several drawbacks that were rarely mentioned in the reviewed studies, including sensor drift, limited sensor specificity, sensor poisoning, sensor life-time limitations, and high cost of manufacturing for replacement parts. In addition, many studies used a particularly low number of samples to estimate the DTA or simply refrained from mentioning DTA parameters at all. Most importantly, most of the studies failed to externally validate the results using a different testing set. This is specially concerning because conclusions were drawn without properly knowing the reproducibility of the results. Finally, some studies failed to report whether the presence of comorbidities was considered as confounding factors in the analysis and no information on possible contamination of samples by ambient air VOCs was reported.

The meta-analysis was able to illustrate the heterogeneity of the included studies (with the exception of studies on cancer), which might be explained by different populations, different urinary diseases, eNose instruments, study design, and analysis methods. The results must also be interpreted as a whole when considering the general use of eNose urinary analysis for diagnosing diseases.

Nevertheless, and independently of the aforementioned limitations, the confidence interval of the corrected DOR still suggests a promising potential for diagnosis of urinary diseases using an eNose instrument.

Conclusions

This systematic review compiled the results from 24 original studies. Overall, it was possible to conclude that commercially eNoses and those developed in academic institutions have several applications in the detection of VOC profiles characterizing different diseases. Most studies reported good results, with high values for sensitivity and specificity. Furthermore, most studies considered a large number of urine samples which support their reliability. This work suggests the promising use of the eNoses for a faster and enhanced diagnosis in clinical scenarios. The meta-analysis showed a positive and optimistic DOR suggesting a promising application of these devices. Additional studies should be performed to improve this detection method and to support the need for introducing these systems at the clinical practice.

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Conflicts of interest statement

The authors declare no conflicts of interest.

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