Analysis of Volatile Organic Compounds

- Clinical Policy Bulletins
- Medical Clinical Policy Bulletins

Number: 0717

Table Of Contents

Policy

Scope of Policy

This Clinical Policy Bulletin addresses the analysis of volatile organic compounds.

Experimental, Investigational, or Unproven

Aetna considers the analysis of volatile organic compounds experimental, investigational, or unproven for the following indications (not an all-inclusive list) because the clinical effectiveness of this technique has not been established:

- Detection of bacteriuria
- Detection of bronchiolitis obliterans syndrome in lung transplant recipients
- Detection of cancer (e.g., bladder cancer, breast cancer, colorectal cancer, esophagogastric cancer, gallbladder cancer, gastric cancer, hepatobiliary cancer, leukemia/lymphoma, lung cancer and cancer of the pleura, pancreatic cancer, and renal cancer; not an all-inclusive list)
- Diagnosis and monitoring of pleural mesothelioma
- Diagnosis and monitoring of sarcoidosis
- Diagnosis of alcoholic hepatitis
- Diagnosis of autism spectrum disorders
- Diagnosis of celiac disease
- Diagnosis of idiopathic membranous nephropathy
- Diagnosis of infection
- Diagnosis of inflammatory bowel disease
- Diagnosis of juvenile idiopathic arthritis
- Diagnosis of lung disease (e.g., asthma)
- Diagnosis of neuromuscular disease (e.g., amyotrophic lateral sclerosis)
- Diagnosis of non-alcoholic fatty liver disease
- Diagnosis of non-healing surgical wounds
- Diagnosis of obstructive sleep apnea
- Diagnosis of oral candidiasis
- Diagnosis of Parkinson's disease
- Diagnosis of pneumonia
- Diagnosis of tuberculosis
- Differential diagnosis of breast diseases (e.g., breast cancer, cyclomastopathy, and mammary gland fibroma)
- Prediction of asthma exacerbations
- Prediction of broncho-pulmonary dysplasia in infants born pre-term
- Prediction of development of childhood obesity
- Prediction of development of necrotizing enterocolitis
- Screening for COVID-19
- Use as biomarkers of chronic obstructive pulmonary disease
- Use as markers for monitoring hemodialysis efficiency.

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes not covered for indications listed in the CPB:

Code	Code Description
There is no specific code for analysis of volatile organic compounds **:**	

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

A15.0 - A19.9	Tuberculosis
B37.0	Candidal stomatitis
C00.0 - C96.9	Malignant neoplasms
D00.1	Carcinoma in situ of esophagus
D00.2	Carcinoma in situ of stomach
D05.00 - D05.92	Carcinoma in situ of breast
D24.1 - D24.9	Benign neoplasm of breast
D48.60 - D48.62	Neoplasm of uncertain behavior of breast
D49.3	Neoplasm of unspecified behavior of breast
D86.0 - D86.89	Sarcoidosis
E66.01 - E67.8	Overweight, obesity and other hyperalimentation [prediction of development of childhood obesity]
F84.0 - F84.9	Pervasive developmental disorders [autism spectrum disorders]
G12.21	Amyotrophic lateral sclerosis
G20.A1 – G20.C	Parkinson's disease
G47.33	Obstructive sleep apnea (adult) (pediatric)
G70.00 - G70.9	Myasthenia gravis and other myoneural disorders
J18.9	Pneumonia, unspecified organism
J41.0 - J42	Simple and mucopurulent chronic bronchitis
J43.0 - J43.9	Emphysema
J44.0 - J44.9	Chronic obstructive pulmonary disease, unspecified
J45.20 - J45.998	Asthma
J84.89	Other specified interstitial pulmonary diseases. [for bronchiolitis obliterans syndrome in lung transplant recipients]
K50.00 - K50.919	Crohn's disease [regional enteritis]
K51.00 - K51.919	Ulcerative colitis
K58.0 - K58.9	Irritable bowel syndrome
K70.10 - K70.11	Alcoholic hepatitis with or without ascites
K76.0	Fatty (change of) liver, not elsewhere classified [non-alcoholic]
K90.0	Celiac disease
M08.00 - M08.99	Juvenile arthritis
N03.0 - N05.9	Chronic nephritic syndrome
N18.6	End stage renal disease [use as markers for monitoring hemodialysis efficiency]
N39.0	Urinary tract infection, site not specified [bacteriuria]
N60.01 - N65.1	Disorders of breast
P27.1	Bronchopulmonary dysplasia originating in the perinatal period
P77.1 - P77.9	Necrotizing enterocolitis of newborn [prediction of development of necrotizing enterocolitis]
T81.89XA - T81.89XS	Other complications of procedures, not elsewhere classified [non-healing surgical wounds]
T86.810 - T86.819	Complications of lung transplant [for bronchiolitis obliterans syndrome in lung transplant recipients]
Z11.52	Encounter for screening for COVID-19
Z12.0 -Z12.9	Encounter for screening for malignant neoplasms
Z99.2	Dependence on renal dialysis [use as markers for monitoring hemodialysis efficiency]

Background

Urinary tract infections (UTIs) are a leading cause of morbidity and health care expenditures in persons of all ages. Individuals at increased risk include sexually active young women, the elderly and those undergoing genitourinary instrumentation or catheterization (Orenstein and Wong, 1999). The diagnosis of UTI may be made on the basis of clinical signs and symptoms in combination with urinalysis results. A urinalysis that reveals both bacteriuria and pyuria is considered clinically diagnostic of UTI. Traditionally, confirmatory cultures have been obtained to verify the infection and identify the specific organism(s) involved; however, this standard is evolving. If a culture is obtained, the presence of at least 100,000 colony-forming units (CFU) of bacteria on a voided specimen has classically been used as the culture-based definition of UTI. Lower colony counts (100 CFU or less) may be used to establish a clinical diagnosis in catheterized or aspirated specimens from symptomatic patients (Griebling, 2004).

Research directed towards rapid and early detection of UTI to exclude probable negatives have facilitated the development of sensor technology and the production of devices known as “electronic noses” that can detect and discriminate the production of volatile compounds from microbial infections in situ. Such qualitative and semi-quantitative approaches could play a significant role in the early diagnosis of microbial diseases. Using artificial intelligence and web-based knowledge systems, electronic noses might also have a valuable role in monitoring disease epidemiology (Turner and Magan, 2004).

Aathithan et al (2001) reported on the use of the Osmetech Microbial Analyzer (OMA) (Osmetech plc, Crewe, UK) for the analysis of bacteria in urine. The OMA is an automated headspace (the volume above the liquid sample) analyzer fitted with four polymer sensors that respond to different volatile organic compounds released from microorganisms in urine. The OMA technique is based on the principle that volatile compounds from bacteria are released and can then be detected by gas sensors. The detection of volatile organic compounds in urine by gas-liquid chromatography (GLC) was demonstrated by earlier investigators (Coloe, 1978; Manja and Rao, 1983; Hayward, 1983); however, these methods were only moderately successful in detecting infected and non-infected urine and did not develop into practical diagnostic tools. The OMA consists of a carousel where sample vials are kept at a constant temperature. A co-axial needle is automatically inserted through a sample vial septum and nitrogen gas at 50 % relative humidity is introduced above the surface of the urine via the inner lumen of the needle. The outer needle lumen allows the sample headspace to be delivered across a sensor array for 3 minutes at a flow rate of 60 ml/min. The sensor is then allowed to recover before humid nitrogen gas is passed over the sensor for a 4-min wash. The resistance of each of the polymer sensors is measured during the sampling period, and the change from the initial resistance is calculated. The needle is then removed; the carousel moves the next sample into position, and the process is repeated. The system is computer-controlled, and data are captured on to a computer hard disk. The authors compared the effectiveness of the OMA with standard culture results on 534 urine samples. When bacteriuria was defined as 100,000 CFU/ml, the sensitivity and specificity of the OMA device were reported as 84 % and 88 %, respectively. When bacteriuria was defined as 10,000 CFU/ml, the sensitivity fell and the specificity rose, 72 % and 89 %, respectively.

Aathithan and colleagues (2001) concluded that the OMA shows promise as an automated system for the rapid routine screening of urine specimens; however, the following limitations were reported:

1. it was unclear which of the volatile compounds in the headspace the instrument was responding to; therefore, the present sensors may not be optimized for urine analysis;
2. the detection of volatile compounds is limited by the present array of sensors; therefore, other significant volatile compounds could be missed;
3. bacterial volatile products could be lost, either by adsorption onto urinary cells or protein or by dissipation during delays between specimen collection and analysis;
4. some bacterial species may not produce volatile compounds; and
5. processing speed is limited by the need for the sensors to recover after each sample.

The authors reported that clinical trials with more-refined versions of the instrument are in progress.

The Osmetch Microbial Analyserä - Urinary Tract Infection Detector (OMAä-UTI) (Osmetech plc, Crewe, UK) received 510(k) pre-marketing clearance from the U.S. Food and Drug Administration (FDA) in 2001. The OMA is intended for use by clinical laboratories as an aid to diagnosis UTI. According to the 510(k) summary, the OMA-UTI was compared to an existing device, the Uriscreenä (Diatech Diagnostics, Inc.), to establish substantial equivalence. Urine results with the OMA-UTI were compared to standard culture (a positive culture was defined as 100,000 CFU/ml) in 1,038 urine samples. The sensitivity and specificity of the OMA-UTI were reported as 81.0 % and 83.1 %, respectively. The FDA determined the performance of the OMA-UTI compared favorably with the Uriscreen, which reported a sensitivity of 95 % and specificity of 73 % when compared to standard culture. However, the manufacturer was not required to submit to the FDA the evidence of efficacy that is necessary to support a premarket approval application (PMA).

The analysis of volatile organic compounds in urine to detect bacteria is promising (Aathithan et al, 2001; Pavlou et al, 2002); however, there is inadequate evidence of the clinical effectiveness of this technique. Clinical outcome studies published in the peer-reviewed medical literature are necessary to determine the clinical value of the analysis of volatile organic compounds in urine.

The Work Loss Data Institute's guideline on "Lung cancer and cancer of the pleura: Pulmonary (acute & chronic)" (2013) stated that "Other surveillance techniques include sputum analyses for biomarkers, the presence of volatile organic compounds in the exhaled air, and screens for deoxyribonucleic acid (DNA) alterations. The value of these tests is undergoing research at the current time and their use cannot be recommended".

Yuan et al (2014) stated that exposures to polycyclic aromatic hydrocarbons (PAHs) from various environmental and occupational sources are considered a primary risk factor for lung cancer among lifelong never smokers, based largely on results from epidemiologic studies utilizing self-reported exposure information. Prospective, biomarker-based human studies on the role of PAH and other airborne carcinogens in the development of lung cancer among lifelong non-smokers have been lacking. These researchers prospectively investigated levels of urinary metabolites of a PAH and volatile organic compounds (VOCs) in relation to lung cancer risk in a nested case-control study of 82 cases and 83 controls among lifelong never smokers of the Shanghai Cohort Study, a prospective cohort of 18,244 Chinese men aged 45 to 64 years at enrollment. These investigators quantified 3 PAH metabolites: r-1,t-2,3,c-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT), 3-hydroxyphenanthrene (3-OH-Phe) and total hydroxyphenanthrenes (total OH-Phe, the sum of 1-, 2-, 3- and 4-OH-Phe), as well as metabolites of the VOCs acrolein (3-hydroxypropyl mercapturic acid), benzene (S-phenyl mercapturic acid), crotonaldehyde (3-hydroxy-1-methylpropylmercapturic acid) and ethylene oxide (2-hydroxyethyl mercapturic acid). Urinary cotinine was also quantified to confirm non-smoking status. Compared with the lowest quartile, odds ratios (95 % confidence intervals [CI]) for lung cancer risk for the highest quartile levels of PheT, 3-OH-Phe and total OH-Phe were 2.98 (1.13 to 7.87), 3.10 (1.12 to 7.75) and 2.59 (1.01 to 6.65) (all p trend < 0.05), respectively. The authors concluded that none of the metabolites of the VOCs were associated with overall lung cancer risk.

Jiang et al (2015) stated that amyotrophic lateral sclerosis (ALS) is a rapid progressive motor neuron disease. Currently, there are no specific or reliable biomarkers for the diagnosis of this disease, and there are no effective medical treatments. The early diagnosis and treatment of this disease has the potential to prolong the survival of ALS patients, but typically, approximately 1 year passes between the onset of symptoms and the diagnosis of this disease. Thus, there is an urgent need to find specific biomarkers to enable early diagnosis and therapeutic intervention in this disease. Analyzing the VOCs present in the blood and exhaled breath is a useful and convenient approach for investigating potential biomarkers. These investigators examined the VOCs present in blood samples from copper zinc superoxide dismutase 1 (SOD1) glycine to alanine mutation at position 93 (G93A) mice to determine whether a specific biomarker pattern exists in these transgenic mice. Blood samples from ALS mice and their age-matched littermates were analyzed using gas chromatography-mass spectrometry. A total of 12 independent compounds associated with oxidative stress were identified at the early stage of disease. The data showed that there is a specific pattern of blood VOCs in ALS mice that could potentially be used as biomarkers that could improve the diagnosis of this disease. Furthermore, these compounds could also potentially be used to monitor the response to neuro-protective agents and to better understand the underlying mechanisms of ALS.

Cozzolino and colleagues (2014) stated that autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders which have a severe life-long effect on behavior and social functioning, and which are associated with metabolic abnormalities. Their diagnosis is on the basis of behavioral and developmental signs usually detected before 3 years of age, and there is no reliable biological marker. The objective of this study was to establish the volatile urinary metabolomic profiles of 24 autistic children and 21 healthy children (control group) to investigate VOCs as potential biomarkers for ASDs. Solid-phase micro-extraction (SPME) using DVB/CAR/PDMS sorbent coupled with gas chromatography-mass spectrometry was used to obtain the metabolomic information patterns. Urine samples were analyzed under both acid and alkaline pH, to profile a range of urinary components with different physicochemical properties. Multi-variate statistics techniques were applied to bio-analytical data to visualize clusters of cases and to detect the VOCs able to differentiate autistic patients from healthy children. In particular, orthogonal projections to latent structures discriminant analysis (OPLS-DA) achieved very good separation between autistic and control groups under both acidic and alkaline pH, identifying discriminating metabolites. Among these, 3-methyl-cyclopentanone, 3-methyl-butanal, 2-methyl-butanal, and hexane under acid conditions, and 2-methyl-pyrazine, 2,3-dimethyl-pyrazine, and isoxazolo under alkaline pH had statistically higher levels in urine samples from autistic children than from the control group. The authors concluded that further investigation with a higher number of patients should be performed to outline the metabolic origins of these variables, define a possible association with ASDs, and verify the usefulness of these variables for early-stage diagnosis.

Wang et al (2014a) stated that the association between cancer and volatile organic metabolites in exhaled breaths has attracted increasing attention from researchers. These researchers reported on a systematic study of gas profiles of metabolites in human exhaled breath by pattern recognition methods. Exhaled breath was collected from 85 patients with histologically confirmed breast disease (including 39 individuals with infiltrating ductal carcinoma, 25 individuals with cyclo-mastopathy and from 21 individuals with mammary gland fibroma) and 45 healthy volunteers. Principal component analysis and partial least squares discriminant analysis were used to process the final data. The volatile organic metabolites exhibited significant differences between breast cancer and normal controls, breast cancer and cyclo-mastopathy, and breast cancer and mammary gland fibroma; 21, 6, and 8 characteristic metabolites played decisive roles in sample classification, respectively ($p < 0.05$). Three volatile organic metabolites in the exhaled air, 2,5,6-trimethyloctane, 1,4-dimethoxy-2,3-butanediol, and cyclohexanone, distinguished breast cancer patients from healthy individuals, mammary gland fibroma patients, and patients with cyclo-mastopathy ($p < 0.05$). The authors concluded that the identified 3 volatile organic metabolites associated with breast cancer may serve as novel diagnostic biomarkers.

Wang et al (2014b) noted that many recent studies have focused on the connection between the composition of specific VOCs in exhaled breath and various forms of cancer. However, the composition of exhaled breath is affected by many factors, such as lung disease, smoking, and diet. Volatile organic compounds are released into the bloodstream before they are exhaled; therefore, the analysis of VOCs in blood will provide more accurate results than the analysis of VOCs in exhaled breath. Blood were collected from 16 colorectal cancer (CRC) patients and 20 healthy controls, then solid phase micro-extraction-chromatography-mass spectrometry (SPME-GC-MS) was used to analysis the exhaled VOCs. The statistical methods principal component analysis (PCA) and partial least-squares discriminant analysis (PLSDA) were performed to deal with the final dates. Three metabolic biomarkers were found at significantly lower levels in the group of CRC patients than in the normal control group ($P<0.01$): phenyl methylcarbamate, ethylhexanol, and 6-t-butyl-2,2,9,9-tetramethyl-3,5-decadien-7-yne. In addition, significantly higher levels of 1,1,4,4-tetramethyl-2,5-dimethylene-cyclohexane were found in the group of CRC patients than in the normal control group ($p < 0.05$). Compared with healthy individuals, patients with CRC exhibited a distinct blood metabolic profile with respect to VOCs. The authors concluded that the analysis of blood VOCs appears to have potential clinical applications for CRC screening.

Alkhouri and colleagues (2014) examined the association of breath VOCs with the diagnosis of non-alcoholic fatty liver disease (NAFLD) in children. Patients were screened with an ultrasound of the abdomen to evaluate for NAFLD. Exhaled breath was collected and analyzed per protocol using selective ion flow tube mass spectrometry (SIFT-MS). A total of 60 patients were included in the study (37 with NAFLD and 23 with normal liver). All children were over-weight or obese. The mean age was 14.1±2.8 years and 50 % were female. A comparison of the SIFT-MS results of patients with NAFLD with those with normal liver on ultrasound revealed differences in concentration of more than 15 compounds. A panel of 4 volatile organic compounds can identify the presence of NAFLD with good accuracy (area under the receiver operating characteristic curve [AUC] of 0.913 in the training set and 0.763 in the validation set). Breath isoprene, acetone, trimethylamine, acetaldehyde, and pentane were significantly higher in the NAFLD group compared with normal liver group (14.7 ppb versus 8.9 for isoprene; 71.7 versus 36.9 for acetone; 5.0 versus 3.2 for trimethylamine; 35.1 versus 26.0 for acetaldehyde; and 13.3 versus 8.8 for pentane, $p < 0.05$ for all). The authors concluded that exhaled breath analysis is a promising non-invasive method to detect fatty liver in children. Isoprene, acetone, trimethylamine, acetaldehyde, and pentane are novel biomarkers that may help to gain insight into pathophysiological processes leading to the development of NAFLD.

Alkhouri and associates (2015) investigated changes in VOCs in exhaled breath in over-weight/obese children compared with their lean counterparts. Single exhaled breath was collected and analyzed per protocol using SIFT-MS. A total of 60 over-weight/obese children and 55 lean controls were included. Compared with the lean group, the obese group was significantly older (14.1 ± 2.8 versus 12.1 ± 3.0 years), taller (164.8 ± 10.9 versus 153.3 ± 17.1 cm) and more likely to be Caucasian (60 % versus 35.2 %); $p < 0.05$ for all. A comparison of the SIFT-MS results of the obese group with the lean group revealed differences in concentration of more than 50 compounds. A panel of 4 VOCs can identify the presence of over-weight/obesity with excellent accuracy. Further analysis revealed that breath isoprene, 1-decene, 1-octene, ammonia and hydrogen sulfide were significantly higher in the obese group compared with the lean group ($p < 0.01$ for all). The authors concluded that obese children have a unique pattern of exhaled VOCs. They stated that changes in VOCs observed in this study may help to gain insight into pathophysiological processes and pathways leading to the development of childhood obesity.

In a prospective cross-sectional, single-center study, Zeft et al (2014) analyzed exhaled VOCs to evaluate for the presence of a unique breath pattern to differentiate pediatric patients with juvenile idiopathic arthritis (JIA) from healthy controls. This study included pediatric JIA patients and healthy controls (age range of 5 to 21 years). The diagnosis of JIA was determined using standard clinical criteria. Exhaled breath was collected and analyzed using SIFT-MS to identify new markers of JIA. A total of 76 patients were included in the study (21 with JIA and 55 healthy controls). Juvenile idiopathic arthritis phenotype was as follows: 12 polyarticular RF-negative, 2 persistent oligoarticular, 4 extended oligoarticular, 2 psoriatic, and 1 enthesitis-related arthritis. Routinely analyzed VOCs for SIFT-MS quantification showed significant differences in 13 VOCs peaked between JIA patients and healthy controls. Discriminant analysis via step-wise variable selection of mass scanning ion peak data demonstrated that 4 VOCs can classify patients with JIA or as healthy controls with only 3 mis-classifications; $p < 0.001$. Further analysis revealed that breath 1-decene, 1-octene, and 3-methyhexane (all markers of oxidative stress) were significantly higher in the JIA group compared to controls (11.5 ± 6.7 ppb versus 2.1 ± 0.2 for 1-decene; 10.5 ± 2.2 versus 4.5 ± 0.7 for 1-octene; and 17.5 ± 3.7 versus 10.4 ± 1.4 for 3-methyhexane, p value < 0.001 for all). The authors concluded that exhaled breath analysis is a promising non-invasive method to distinguish children with JIA from healthy children. These researchers provided pilot data to support the hypothesis that a unique breath-print can be demonstrated for JIA in the exhaled metabolome.

Dawiskiba et al (2014) evaluated the utility of serum and urine metabolomic analysis in diagnosing and monitoring of inflammatory bowel diseases (IBD). Serum and urine samples were collected from 24 patients with ulcerative colitis (UC), 19 patients with the Crohn's disease (CD) and 17 healthy controls. The activity of UC was assessed with the Simple Clinical Colitis Activity Index, while the activity of CD was determined using the Harvey-Bradshaw Index. The analysis of serum and urine samples was performed using proton nuclear magnetic resonance (NMR) spectroscopy. All spectra were exported to Matlab for preprocessing which resulted in 2 data matrixes for serum and urine. Prior to the chemometric analysis, both data sets were unit variance scaled. The differences in metabolite finger-prints were assessed using partial least-squares-discriminant analysis (PLS-DA). Receiver operating characteristic curves and area under curves were used to evaluate the quality and prediction performance of the obtained PLS-DA models. Metabolites responsible for separation in models were tested using STATISTICA 10 with the Mann-Whitney-Wilcoxon test and the Student's t test ($\alpha = 0.05$). The comparison between the group of patients with active IBD and the group with IBD in remission provided good PLS-DA models (p value 0.002 for serum and 0.003 for urine).

The metabolites that allowed distinction of these groups were: N-acetylated compounds and phenylalanine (up-regulated in serum), low-density lipoproteins and very low-density lipoproteins (decreased in serum) as well as glycine (increased in urine) and acetoacetate (decreased in urine). The significant differences in metabolomic profiles were also found between the group of patients with active IBD and healthy control subjects providing the PLS-DA models with a very good separation (p value < 0.001 for serum and 0.003 for urine). The metabolites that were found to be the strongest biomarkers included in this case: leucine, isoleucine, 3-hydroxybutyric acid, N-acetylated compounds, acetoacetate, glycine, phenylalanine and lactate (increased in serum), creatine, dimethyl sulfone, histidine, choline and its derivatives (decreased in serum), as well as citrate, hippurate, trigonelline, taurine, succinate and 2-hydroxyisobutyrate (decreased in urine). No clear separation in PLS-DA models was found between CD and UC patients based on the analysis of serum and urine samples, although 1 metabolite (formate) in uni-variate statistical analysis was significantly lower in serum of patients with active CD, and 2 metabolites (alanine and N-acetylated compounds) were significantly higher in serum of patients with CD when comparing jointly patients in the remission and active phase of the diseases. Contrary to the results obtained from the serum samples, the analysis of urine samples allowed to distinguish patients with IBD in remission from healthy control subjects. The metabolites of importance included in this case up-regulated acetoacetate and down-regulated citrate, hippurate, taurine, succinate, glycine, alanine and formate. The authors concluded that NMR-based metabolomic finger-printing of serum and urine has the potential to be a useful tool in distinguishing patients with active IBD from those in remission.

Patel et al (2014) stated that breath testing is becoming an important diagnostic method to evaluate many disease states. In the light of rising healthcare costs, it is important to develop a simple non-invasive tool to potentially identify pediatric patients who need endoscopy for IBD. In a pilot study, these researchers analyzed exhaled VOCs and investigated the presence of a unique breath patterns to differentiate pediatric patients with IBD from healthy controls. This single-center study included pediatric IBD patients and healthy controls (age range of 5 to 21 years). The diagnosis of IBD was confirmed by endoscopic, histological and radiographic data. Exhaled breath was collected and analyzed using SIFT-MS to identify new markers or patterns of IBD. A total of 117 patients (62 with IBD and 55 healthy controls) were included in the study. Linear discriminant analysis and principle component analysis of mass scanning ion peak data demonstrated 21 pre-selected VOCs correctly classify patients with IBD or as healthy controls; p < 0.0001. Multi-variable logistic regression analysis further showed 3 specific VOCs (1-octene, 1-decene, (E)-2-nonene) had excellent accuracy for predicting the presence of IBD with an AUC of 0.96 (95 % confidence interval [CI]: 0.93 to 0.99). No significant difference in VOCs was found between patients with CD or UC, and no significant correlation was seen with disease activity. The authors concluded that these pilot data supported the hypothesis that a unique breath-print potentially exists for pediatric IBD in the exhaled metabolome.

In a prospective, cross-sectional study, Navaneethan et al (2014) identified potential VOCs in the headspaces (gas above the sample) of bile in patients with malignant biliary strictures from pancreatic cancer. Bile was aspirated in 96 patients undergoing ERCP for benign and malignant conditions. Selected ion flow tube mass spectrometry (VOICE200R SIFT-MS instrument; Syft Technologies Ltd, Christchurch, New Zealand) was used to analyze the headspace and to build a predictive model for pancreatic cancer. The headspaces from 96 bile samples were analyzed, including 24 from patients with pancreatic cancer and 72 from patients with benign biliary conditions. The concentrations of 6 compounds (acetaldehyde, acetone, benzene, carbon disulfide, pentane, and trimethylamine [TMA]) were increased in patients with pancreatic cancer compared with controls (p < 0.05). By using receiver-operating characteristic curve analysis, these researchers developed a model for the diagnosis of pancreatic cancer based on the levels of TMA, acetone, isoprene, dimethyl sulfide, and acetaldehyde. The model [10.94 + 1.8229* log (acetaldehyde) + 0.7600* log (acetone) - 1.1746* log (dimethyl sulfide) + 1.0901* log (isoprene) - 2.1401 * log (trimethylamine) greater than or equal to 10] identified the patients with pancreatic cancer (AUC = 0.85), with 83.3 % sensitivity and 81.9 % specificity. The authors concluded that measurement of biliary fluid VOCs may help to distinguish malignant from benign biliary strictures. Moreover, they stated that further studies are needed to validate these observations.

Queralto et al (2014) noted that cancer diagnosis is typically delayed to the late stages of disease due to the asymptomatic nature of cancer in its early stages. Cancer screening offers the promise of early cancer detection, but most conventional diagnostic methods are invasive and remain ineffective at early detection. Breath analysis is, however, non-invasive and has the potential to detect cancer at an earlier stage by analyzing volatile biomarkers in exhaled breath. These researchers summarized breath sampling techniques and recent developments of various array-based sensor technologies for breath analysis. Significant advancements were made by a number of different research groups in the development of nanomaterial-based sensor arrays, and the ability to accurately distinguish cancer patients from healthy controls based on VOCs in exhaled breath has been demonstrated. Optical sensors based on colorimetric sensor array technology were also discussed, where preliminary clinical studies suggested that metabolic VOC profiles could be used to accurately diagnose various forms of lung cancer. The authors concluded that recent studies have demonstrated the potential of using metabolic VOCs for cancer detection, but further standardization and validation is needed before breath analysis can be widely adopted as a clinically useful tool.

Mochalski et al (2014) noted that monitoring VOCs in exhaled breath shows great potential as a non-invasive method for assessing hemodialysis efficiency. These researchers identified and quantified of a wide range of VOCs characterizing uremic breath and blood, with a particular focus on species responding to the dialysis treatment. Gas chromatography with mass spectrometric detection coupled with SPME as pre-concentration method. A total of 60 VOCs were reliably identified and quantified in blood and breath of patients with chronic kidney disease. Excluding contaminants, 6 compounds (isoprene, dimethyl sulfide, methyl propyl sulfide, allyl methyl sulfide, thiophene and benzene) changed their blood and breath levels during the hemodialysis treatment. The authors concluded that uremic breath and blood patterns were found to be notably affected by the contaminants from the extracorporeal circuits and hospital room air. Consequently, patient exposure to a wide spectrum of

volatile species (hydrocarbons, aldehydes, ketones, aromatics, heterocyclic compounds) is expected during hemodialysis. Whereas highly volatile pollutants were relatively quickly removed from blood by exhalation, more soluble ones were retained and contributed to the uremic syndrome. At least 2 of the species observed (cyclohexanone and 2-propenal) are uremic toxins. Perhaps other volatile substances reported within this study may be toxic and have negative impact on human body functions. They stated that further studies are needed to investigate if VOCs responding to HD treatment could be used as markers for monitoring hemodialysis efficiency.

Kurada and colleagues (2015) reviewed medical literature on VOCs in exhaled human breath in gastro-intestinal (GI) disorders, focusing on diagnosis and differentiation of IBD. These investigators performed a systematic search in PubMed, Ovid Medline and Scopus using appropriate keywords. In addition, a bibliography search of each article was performed. Mean breath pentane, ethane, propane, 1-octene, 3-methylhexane, 1-decene and nitric oxide (NO) levels were elevated ($p < 0.05$ to $p < 10(-7)$) and mean breath 1-nonene, (E)-2-nonene, hydrogen sulphide and methane were decreased in IBD compared to healthy controls ($p = 0.003$ to $p < 0.001$). A combined panel of 3 VOCs (octene, (E)-2-nonene and decene) showed the best discrimination between pediatric IBD and controls (AUC 0.96). Breath condensate cytokines were higher in IBD compared to healthy individuals ($p < 0.008$). Breath pentane, ethane, propane, isoprene and NO levels correlated with disease activity in IBD patients. Breath condensate interleukin-1β showed an inverse relation with clinical disease activity. The authors concluded that breath analysis in IBD is a promising approach that is not yet ready for routine clinical use, but data from other GI diseases suggested the feasibility for use of this technology in clinical practice. They stated that well-designed future trials, incorporating the latest breath detection techniques, are needed to determine the exact breath metabolome pattern linked to diagnosis and phenotype of IBD.

Diagnosis of Alcoholic Hepatitis

Hanouneh et al (2014) examined if concentrations of volatile compounds in breath samples correlated with the diagnosis of alcoholic hepatitis (AH) and the severity of liver disease in patients with AH. These investigators recruited patients with liver disease from a single tertiary care center. The study population was divided between those with AH with cirrhosis (n = 40) and those with cirrhosis with acute decompensation from etiologies other than alcohol (n = 40); individuals without liver disease served as control subjects (n = 43). These researchers used selected-ion flow-tube mass spectrometry to identify and measure 14 volatile compounds in breath samples from fasted subjects. They used various statistical analyses to compare clinical characteristics and breath levels of compounds among groups and to test the correlation between levels of compounds and severity of liver disease. Logistic regression analysis was performed to build a predictive model for AH. The authors identified 6 compounds (2-propanol, acetaldehyde, acetone, ethanol, pentane, and trimethylamine [TMA]) whose levels were increased in patients with liver disease compared with control subjects. Mean concentrations of TMA and pentane (TAP) were particularly high in breath samples from patients with AH, compared with those with acute decompensation or control subjects (for both, $p < 0.001$). Using receiver operating characteristic curve analysis, these researchers developed a model for the diagnosis of AH based on breath levels of TAP -- TAP scores of 36 or higher identified the patients with AH (area under the receiver operating characteristic curves = 0.92) with 90 % sensitivity and 80 % specificity. The levels of exhaled TMA had a low level of correlation with the severity of AH based on model for end-stage liver disease score ($r = 0.38$; 95 % CI: 0.07 to 0.69; $p = 0.018$). The authors concluded that based on levels of volatile compounds in breath samples, they can identify patients with AH versus patients with acute decompensation or individuals without liver disease. They noted that levels of exhaled TMA moderately correlate with the severity of AH; these findings might be used in diagnosis of AH or in determining patient prognosis. These findings need to be validated by well-designed studies.

Prediction of Development of Necrotizing Enterocolitis

de Meij et al (2015) tested the hypothesis that fecal VOCs analysis by electronic nose (eNose) allows for early detection of necrotizing enterocolitis (NEC). In 3 neonatal intensive care units, fecal samples of infants born at gestational age less than or equal to 30 weeks were collected daily, up to the 28th day of life. Included infants were allocated in 3 subgroups:

1. NEC,
2. sepsis, and
3. matched controls.

Three time windows were defined:

1. T-5, T-4 (5 and 4 days before diagnosis);
2. T-3, T-2 (3 and 2 days before diagnosis); and
3. T-1, T-0 (day before and day of diagnosis).

Three subgroups were analyzed by eNose. Fecal VOC profiles of infants with NEC (n = 13) could significantly be discriminated from matched controls (n = 14) at T-3, T-2 (area under the curve ± 95 % CI, p value, sensitivity, specificity: 0.77 ± 0.21, p = 0.02, 83 %, 75 %); the accuracy increased at T-1, T-0 (0.99 ± 0.04, $p \leq 0.001$, 89 %, 89 %). Volatile organic compounds profiles of infants with NEC were also significantly different from those with sepsis (n = 31) at T-3, T-2 (0.80 ± 0.17, p = 0.004, 83 %, 75 %), but not at T-1, T-0 (0.64 ± 0.18, p = 0.216, 89 %, 57 %). The authors concluded that in this proof of principle study, they observed that fecal VOC profiles of infants with NEC could be discriminated from controls, from 2 to 3 days predating onset of

clinical symptoms. These researchers stated that their observations suggested that VOC-profiling by eNose has potential as a non-invasive tool for the early prediction of NEC.

Diagnosis of Asthma

van Mastrigt and associates (2015) noted that current monitoring strategies for respiratory diseases are mainly based on clinical features, lung function and imaging. As airway inflammation is the hallmark of many respiratory diseases in childhood, non-invasive methods to assess the presence and severity of airway inflammation might be helpful in both diagnosing and monitoring pediatric respiratory diseases. At present, the measurement of fractional exhaled nitric oxide is the only non-invasive method available to assess eosinophilic airway inflammation in clinical practice. These researchers examined if the analysis of VOCs in exhaled breath (EB) and biomarkers in exhaled breath condensate (EBC) is helpful in diagnosing and monitoring respiratory diseases in children. An extensive literature search was conducted in Medline, Embase and PubMed on the analysis and applications of VOCs in EB and EBC in children. These investigators retrieved 1,165 papers, of which 9 contained original data on VOCs in EB and 84 on biomarkers in EBC. These were included in this review. The authors gave an overview of the clinical applications in childhood and summarized the methodological issues. Several VOCs in EB and biomarkers in EBC have the potential to distinguish patients from healthy controls and to monitor treatment responses. Lack of standardization of collection methods and analysis techniques hampered the introduction in clinical practice. The measurement of metabolomic profiles may have important advantages over detecting single markers. There is a lack of longitudinal studies and external validation to reveal whether EB and EBC analysis have added value in the diagnostic process and follow-up of children with respiratory diseases. The authors concluded that the use of VOCs in EB and biomarkers in EBC as markers of inflammatory airway diseases in children is still a research tool and not validated for clinical use.

In a systematic review and meta-analysis, Rufo and colleagues (2016) evaluated the value and classification rate of exhaled VOCs in asthma diagnosis. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-oriented systematic search for published studies regarding exhaled VOCs in asthma diagnosis was conducted based on pre-defined criteria. Studies presenting sensitivity and specificity values for the test were included in the meta-analysis. Pooled diagnosis odds ratios (DOR), AUC and positive and negative likelihood ratios (LR) for exhaled VOC profiles were calculated; and publication bias, threshold effect and heterogeneity were estimated. A total of 18 studies were selected for the qualitative analysis and 6 met the criteria for inclusion in the quantitative analysis. Mean (95 % CI) pooled DOR, positive and negative LR were 49.3 (15.9 to 153.3), 5.86 (3.07 to 11.21) and 0.16 (0.10 to 0.26), respectively. The AUC value was 0.94. Only 3 of the 18 reviewed studies performed an external validation of the model using a different data set. The authors concluded that the findings from the revised studies suggested that exhaled VOCs are promising biomarkers for asthma diagnosis and that several compounds, mainly alkanes, may be significantly associated with asthma inflammation. Moreover, they stated that there are still various constraints associated with standardization; and externally validated studies are needed to introduce exhaled VOC profiling in a clinical scenario.

Peel et al (2023) stated that inhaled mannitol provokes broncho-constriction via mediators released during osmotic degranulation of inflammatory cells; thus, representing a useful diagnostic test for asthma and model for acute attacks. These researchers hypothesized that the mannitol challenge would trigger changes in exhaled VOCs, generating both candidate biomarkers and novel insights into their origin. Subjects with a clinical diagnosis of asthma, or undergoing examination for suspected asthma, were recruited. Inhaled mannitol challenges were carried out, followed by a sham challenge after 2 weeks in subjects with bronchial hyper-responsiveness (BHR). VOCs were collected before and after challenges and analyzed using gas chromatography-mass spectrometry (GC-MS). A total of 46 patients (mean (SD) age of 52 (16) years) completed a mannitol challenge, of which 16 (35 %) were positive, and 15 of these completed a sham challenge. Quantities of 16 of 51 identified VOCs changed following mannitol challenge ($p < 0.05$), of which 11 contributed to a multi-variate sparse partial least square discriminative analysis model, with a classification error rate of 13.8 %; 5 of these 16 VOCs also changed ($p < 0.05$) in quantity following the sham challenge, along with 4 further VOCs. In patients with BHR to mannitol distinct post-challenge VOC signatures were observed compared with post-sham challenge. The authors concluded that inhalation of mannitol was associated with changes in breath VOCs, and in individuals with BHR resulting in a distinct exhaled breath profile when compared with a sham challenge. These differentially expressed VOCs were likely associated with acute airway inflammation and/or broncho-constriction and merit further investigation as potential biomarkers in asthma.

Diagnosis of Gallbladder Cancer

Zhang et al (2022) noted that as no reliable diagnostic methods are available, gallbladder cancer (GBC) is often diagnosed until advanced stages, resulting in a poor prognosis. These researchers examined if VOCs could be used as a diagnostic tool for GBC. The VOCs in bile samples collected from 32 GBC patients were detected by GC-ion mobility spectrometry (GC-IMS), and 54 patients with benign gallbladder diseases (BGD) were used as controls. Both principal component analysis and unsupervised hierarchical clustering analysis gave a clear separation of GBC and BGD based on the bile VOC data collected from GC-IMS. A total of 12 differentially expressed VOCs were identified, including 4 up-regulated (cyclohexanone, 2-ethyl-1-hexanol, acetophenone, and methyl benzoate) and 8 down-regulated [methyl acetate, (E)-hept-2-enal, hexanal, (E)-2-hexenal, (E)-2-pentenal, pentan-1-ol, 1-octen-3-one, and (E)-2-octenal] in GBC compared with BGD. ROC analysis demonstrated a 12-VOC panel constructed by 4 machine learning algorithms, which was superior to the traditional tumor marker, CA19-9. Among them, support vector machines and linear discriminant analysis provided the highest area under the curve (AUC) of 0.972, with a

sensitivity of 100 % and a specificity of 94.4 % in the diagnosis of GBC. The authors concluded that the sample size of this trial was small; thus, it was difficult to avoid bias. These researchers stated that a large, multi-center study is needed to validate these findings. Meanwhile, it is necessary to further examine the relevant mechanism between the production of endogenous VOCs and the occurrence and development of GBC or BGD. These investigators stated that the findings of this study provided an experimental basis for the use of VOC analysis in GBC and made it possible to be employed in the early diagnosis of GBC.

Diagnosis of Gastro-Intestinal Diseases

Markar et al (2015) stated that investigation of gastro-intestinal (GI) diseases is often invasive to the patient and costly. Exhaled breath analysis of VOCs may provide a non-invasive diagnostic tool to allow the assessment and stratification of risk. These investigators evaluated the current role of VOC breath analysis in the diagnosis and assessment of endoluminal GI disease. Medline, Embase, Cochrane, trial registries, conference proceedings, and reference lists were searched for relevant diagnostic studies. Gastro-intestinal diseases studied included (IBD, celiac disease, and CRC and gastro-esophageal cancer. A total of 11 studies comprising 934 patients were included. Inflammatory bowel disease was associated with an increase in breath alkanes compared with controls, and the degree of increase was correlated with disease activity in some studies. Colorectal cancer could be distinguished from controls on the basis of VOC profiling; however, the metabolites analyzed varied between studies preventing the generation of a reproducible diagnostic model. In isolated cohort studies, significant differences in the VOC profiles from EB of patients with gastro-esophageal cancer were observed, suggesting that this may have a future role as a non-invasive diagnostic test. Assessment of the cumulative level of surrogate validity for disease-specific breath analysis suggested that the best evidence is for esophagogastric cancer followed by CRC and IBD. The authors concluded that EB analysis of VOCs provides a potential non-invasive tool to determine risk of GI disease. Moreover, they stated that future areas for research include: standardizing breath tests and improving mechanistic understanding of the VOCs associated with specific GI states in large, multi-center population studies.

In a systematic review, Bannaga and colleagues (2019) examined the next-generation diagnosis of IBD in adults and children using VOCs. An in-depth literature-based search of current clinical studies of VOCs in the diagnosis of IBD was conducted. Accuracy of IBD detection varied according to the technologies applied. Breath VOCs studies were pooled giving an overall sensitivity of 85 % (95 % CI: 79 to 89 %) and specificity of 79 % (95 % CI: 73 to 84 %) while pooled fecal VOCs studies revealed a sensitivity of 87 % (95 % CI: 77 to 93 %) and specificity of 91 % (95 % CI: 82 to 96 %). Studies were limited by the variance of techniques applied in VOCs detection and the absence of well-designed longitudinal studies. The authors concluded that VOCs can be consistently and effectively detected in urine, breath, and stool in IBD patients. The sensitivity of breath VOCs in detecting IBD was comparable to feces. However, optimal VOCs detection methodology and biological sampling still need to be standardized.

Diagnosis of Hepatobiliary Cancer

Pelling et al (2023) stated that hepatobiliary cancers are notoriously difficult to detect, often leading to diagnosis in later stages of disease when curative treatment is not an option. The currently used biomarkers such as AFP (alpha-fetoprotein) and CA19.9 lack sensitivity and specificity; thus, there is an unmet need for an alternative biomarker. In a systematic review and meta-analysis, these investigators examined the diagnostic accuracy of VOCs for the detection of hepatobiliary and pancreatic cancers. They carried out a systematic review of VOCs' use in the detection of hepatobiliary and pancreatic cancers. A meta-analysis was conducted using the software R. Heterogeneity was examined via meta-regression analysis. A total of 18 studies with 2,296 patients were evaluated. Pooled sensitivity and specificity of VOCs for the detection of hepatobiliary and pancreatic cancer were 0.79 (95 % CI: 0.72 to 0.85) and 0.81 (97.5 % CI: 0.76 to 0.85), respectively. The AUC was 0.86; meta-regression analysis showed that the sample media used contributed to heterogeneity. Bile-based VOCs showed the highest precision values, although urine and breath were preferred for their feasibility. The authors concluded that VOCs have the potential to be used as an adjunct tool to aid in the early diagnosis of hepatobiliary cancers. These researchers stated that the findings of this systematic review/meta-analysis were highly promising and may provide a solution for early cancer detection and treatment. Furthermore, the lack of variability in their performance for the detection of different types of hepatobiliary and pancreatic cancers may cast some new insights into their complex mechanistic origin. These investigators stated that in the future, studies that examine the prognostic or predictive value of certain VOCs may aid in the understanding of disease progression and have a role in preventative medicine.

The authors stated that this study had several drawbacks. First, most of the studies were observational in nature and had a limited sample size; and pilot studies were also included in this review. Second, the recruitment process of subjects was not well-described. These could have introduced a “selection” bias. Third, the stage of the cancer was not well-described in the included studies. Fourth, the heterogeneity was largely due to the sample media used. Although this was further examined via subgroup analysis, the number of studies under each subgroup was small; therefore, the results should be interpreted with caution.

Diagnosis of Neuromuscular Diseases

Dragonieri et al (2016) noted that ALS is a neurodegenerative disease characterized by a progressive degeneration of the cortical and spinal motor neuron. Exhaled molecular profiles that have potential in the diagnosis of several respiratory and

systemic diseases can be obtained by analyzing human breath with an electronic nose. These researchers hypothesized that exhaled molecular profiling may discriminate well-characterized patients with ALS from controls. A total of 20 ALS patients (mean age of 63.5 ± 12.3 years), and 20 healthy controls (mean age of 58.1 ± 4.4) years participated in a cross-sectional study. A Tedlar bag was used to collect EB by using a validated method. Bags were then sampled by an electronic nose (Cyranose 320). Statistical analysis on sensor responses was performed off-line by principal component analysis, linear discriminant analysis and receiver operating characteristic (ROC) curves. Breath-prints from patients with ALS were discriminated from healthy controls (CVA: 75.0 %; p = 0.003; AUC 0.795). The authors concluded that based on these findings, patients with ALS can be discriminated from healthy controls; suggesting that EB analysis has potential for screening and/or diagnosis of this neuromuscular disease.

Diagnosis of Non-Healing Surgical Wounds

Reeves et al (2022) stated that the normal healing of surgical wounds can be disrupted by infection and/or dehiscence, resulting in development of chronic, non-healing wounds (NHW). Diagnosis of NHWs is via clinical acumen and analysis of microbiology wound swabs. VOCs are emitted generally by human subjects and specifically as products of bacterial metabolism and are detected in the wound area. In a systematic review, these investigators examined the potential use of VOCs released by surgical wounds as a non-invasive method for identifying bacterial species and the progression to NHW. They carried out a systematic search of studies, via PRISMA guidelines. Of 220 papers screened, 7 studies were included. Outcome data were extracted on methods for VOC analysis and wound/bacterial VOC profiles. The studies have shown that VOC profiles were identified by 2 methods: GC-MS and electronic nose. There were VOC profiles associated with causative bacterial species, with early indications that they could be anatomically specific or could monitor treatment effects. The authors concluded that VOC profiling of bacterial species within wounds was possible and could become a point of care test. However, these researchers stated that further investigation is needed on specific VOC profiles to wound location and whether these profiles may predict progression to NHW.

Diagnosis of Renal Cancer

Wang et al (2016) noted that currently, there is no adequate, sensitive, reproducible, specific and non-invasive biomarker that can reliably be used to detect renal cell carcinoma (RCC). Previous studies have elucidated the urinary non-volatile metabolic profile of RCC. However, whether urinary VOC profiles are able to identify RCC remains to be elucidated. In the present study, urine was collected from 22 patients with RCC and 25 healthy subjects. Principal component analysis and orthogonal partial least square discriminant analysis were used to compare the data of patients and healthy subjects, and pre-operative and post-operative patients undergoing radical nephrectomy. In total, 11 VOC biomarkers were elevated in the RCC patients compared to the healthy subjects, which were phenol; decanal; 1,6-dioxacyclododecane-7,12-dione; 1-bromo-1-(3-methyl-1-pentenylidene)-2,2,3,3-tetramethyl-cyclopropane; non-anal; 3-ethyl-3-methylheptane; isolongifolene-5-ol; 2,5-cyclohexadiene-1,4-dione, 2,6-bis(1,1-dimethylethyl); tetradecane; aniline; and 2,6,10,14-tetramethyl-pentadecane. Three biomarkers were decreased in RCC patients: styrene, 4-heptanone and dimethylsilanediol. In pre-operative patients, 2-ethyl-1-hexanol and cyclohexanone were elevated, while 6-t-butyl-2,2,9,9-tetramethyl-3,5-decadien-7-yne were decreased when compared to post-operative patients. The authors concluded that compared with the healthy subjects, RCC has a unique VOC profile, suggesting that VOC profiles may be a useful diagnostic assay for RCC.

Monteiro and colleagues (2017) stated that the analysis of VOCs emanating from biological samples appears as one of the most promising approaches in metabolomics for the study of diseases, namely cancer. In fact, it offers advantages, such as non-invasiveness and robustness for high-throughput applications. These researchers examined the urinary volatile metabolic profile of patients with renal cell carcinoma (RCC; n = 30) and controls (n = 37) with the aim of identifying a potential specific urinary volatile pattern as a non-invasive strategy to detect RCC. Moreover, the effect of some confounding factors such as age, gender, smoking habits and BMI was evaluated as well as the ability of urinary VOCs to discriminate RCC subtypes and stages. A headspace solid-phase micro-extraction/GC-MS-based method was performed, followed by multi-variate data analysis. A variable selection method was applied to reduce the impact of potential redundant and noisy chromatographic variables, and all models were validated by Monte Carlo cross-validation and permutation tests. Regarding the effect of RCC on the urine VOCs composition, a panel of 21 VOCs descriptive of RCC was defined, capable of discriminating RCC patients from controls in principal component analysis. Discriminant VOCs were further individually validated in two independent samples sets (nine RCC patients and 12 controls, seven RCC patients with diabetes mellitus type 2) by univariate statistical analysis. Two VOCs were found consistently and significantly altered between RCC and controls (2-oxopropanal and, according to identification using NIST14, 2,5,8-trimethyl-1,2,3,4-tetrahydronaphthalene-1-ol), strongly suggesting enhanced potential as RCC biomarkers. Gender, smoking habits and BMI showed negligible and age-only minimal effects on the urinary VOCs, compared to the deviations resultant from the disease. Moreover, in this cohort, the urinary volatilome did not show ability to discriminate RCC stages and histological subtypes. The authors concluded that the findings of this study validated the value of urinary volatilome for the detection of RCC and advanced with the identification of potential RCC urinary biomarkers.

Diagnosis of Idiopathic Membranous Nephropathy

Wang and colleagues (2017) examined the use of urinary VOCs as potential biomarkers in idiopathic membranous nephropathy (IMN) independent of renal biopsy. These researchers detected urinary VOCs in patients with IMN and normal controls. Gas

chromatography/mass spectrometry (GC/MS) was used to assess the urine collected from 63 IMN patients and 15 normal controls. The statistical methods of principal component analysis (PCA) and partial least squares discriminant analysis (PLSDA) were performed to process the final data in CDF format which were converted from GC/MS data. A total of 6 VOCs in the urine of IMN patients exhibited significant differences from those of normal controls: carbamic acid, mono-ammonium salt, 2-pentanone, 2,4-dimethyl-pentanal, hydrogen azide, thiourea and 4-heptanone were significantly higher than in controls ($p < 0.05$). The authors concluded that 6 urinary VOCs were isolated from patients with IMN using GC/MS. They stated that the analysis of the urinary VOCs using GC/MS could be developed into a non-invasive detection of IMN.

Diagnosis of Oral Candidiasis

Hertel and colleagues (2018) examined if specific VOCs can be detected in oral candidiasis patients using breath analysis in order to develop a point-of-care diagnostic tool. Breath samples of 10 diseased patients and 10 subjects carrying no Candida spp. were analyzed using GC and MS. In infected patients, breath tests were performed before and after anti-fungal therapy. Breath testing was positive for 143 volatiles in both healthy subjects and diseased patients. Among those, specific signature volatiles known to be emitted by Candida spp. In-vitro were not detected. Even though no specific signature was retrieved from the diseased patients, a pattern containing 9 compounds (2-methyl-2-butanol, hexanal, longifolene, methyl acetate, 1-heptene, acetophenone, decane, 3-methyl-1-butanol, chlorbenzene) was identified, which showed characteristic changes after anti-fungal therapy. The authors concluded that focusing on the identified pattern, breath analysis may be applied to confirm the absence of Candida spp. after therapy in terms of a confirmatory test supplementing clinical examination, thereby replacing microbial testing. However, microbial testing will still be needed to initially confirm clinical diagnoses, as no specific signature was found.

Diagnosis of Pneumonia

Douglas (2016) stated that pneumonia leading to severe sepsis and critical illness including respiratory failure remains a common and therapeutically challenging diagnosis. Current clinical approaches to surveillance, early detection, and conventional culture-based microbiology are inadequate for optimal targeted antibiotic treatment and stewardship. Efforts to enhance diagnosis of community-acquired and health care-acquired pneumonia, including ventilator-associated pneumonia (VAP), are the focus of recent studies. Newer surveillance definitions are sensitive for pneumonia in the intensive care unit (ICU) including VAP, but consistently under-detect patients whom have clinically shown to have bacterial VAP based on clinical diagnostic criteria and response to antibiotic treatment. Routinely measured plasma biomarkers, including procalcitonin and C-reactive protein (CRP), lack sufficient precision and predictive accuracy to confer diagnosis. The authors concluded that novel rapid microbiological diagnostics, including nucleic-acid amplification, MS, and fluorescence microscopy-based technologies are promising approaches for the future. In addition, exhaled breath biomarkers, including measurement of VOCs, represent a future approach.

Biomarkers of Chronic Obstructive Pulmonary Disease

Besa and associates (2015) noted that chronic obstructive pulmonary disease (COPD) is a chronic airway inflammatory disease characterized by incompletely reversible airway obstruction. This clinically heterogeneous group of patients is characterized by different phenotypes. Spirometry and clinical parameters, such as severity of dyspnea and exacerbation frequency, are used to diagnose and assess the severity of COPD. These researchers examined if VOCs could be detected in the exhaled breath of patients with COPD and whether these VOCs could distinguish COPD patients from healthy subjects. They also examined if VOCs could be used as biomarkers for classifying patients into different subgroups of the disease. Ion mobility spectrometry (IMS) was used to detect VOCs in the exhaled breath of COPD patients. A total of 137 peaks were found to have a statistically significant difference between the COPD group and the combined healthy smokers and non-smoker group; 6 of these VOCs were found to correctly discriminate COPD patients from healthy controls with an accuracy of 70 %. Only 15 peaks were found to be statistically different between healthy smokers and healthy non-smokers. Furthermore, by determining the cut-off levels for each VOC peak, it was possible to classify the COPD patients into breath-print subgroups. Forced expiratory volume in 1 second (FEV1), body mass index (BMI), and CRP appeared to play a role in the discrepancies observed in the different breath-print subgroups. Moreover, they stated that further studies with larger sample size are needed to completely characterize these subgroups, as well as to identify the underlying substances of the VOCs.

The authors noted that this study had 2 main drawbacks:

1. Repeated IMS measurements were performed in healthy subjects on the same day, showing good reproducibility. However, reproducibility was not tested in COPD patients. It was suggested that sample variability and short-term effects of practice or exertion should be considered in breath analysis tests. Incalzi et al suggested that VOC patterns are reproducible in healthy subjects and patients with very severe COPD, whereas these are less reproducible in COPD patients with less severe disease. This finding may reflect hypoxemia, which characterized these patients. As the majority of the patients measured in this study suffered from severe COPD, variability of IMS measurement might not be a confounding factor in this study,
2. no information was collected regarding medication of the patients.

Further studies are needed to test the possible effects of medication on exhaled breath and to test repeatability and reproducibility in COPD patients.

Gaida and co-workers (2016) noted that there is increasing evidence that breath VOCs have the potential to support the diagnosis and management of inflammatory diseases such as COPD. In this study, these researchers used a novel breath sampling device to search for COPD-related VOCs. They included a large number of healthy controls and patients with mild-to-moderate COPD, recruited subjects at 2 different sites and carefully controlled for smoking. A total of 222 subjects were recruited in Hannover and Marburg, and inhaled cleaned room air before exhaling into a stainless steel reservoir under exhalation flow control. Breath samples (2.5 L) were continuously drawn onto 2 Tenax TA adsorption tubes and analyzed in Hannover using thermal desorption-GC-MS (TD-GC-MS). Data of 134 identified VOCs from 190 subjects (52 healthy non-smokers, 52 COPD ex-smokers, 49 healthy smokers, 37 smokers with COPD) were included into the analysis. Active smokers could be clearly discriminated by higher values for combustion products and smoking related VOCs correlated with exhaled carbon monoxide (CO), indicating the validity of these data. Subjects from the study sites could be discriminated even after exclusion of cleaning related VOCs. Linear discriminant analysis correctly classified 89.4 % of COPD patients in the non/ex-smoking group (cross validation (CV): 85.6 %), and 82.6 % of COPD patients in the actively smoking group (CV: 77.9 %). These investigators extensively characterized 134 breath VOCs and provided evidence for 14 COPD-related VOCs of which 10 have not been reported before. The authors concluded that these findings showed that, for the utilization of breath VOCs for diagnosis and disease management of COPD, not only the known effects of smoking but also site-specific differences need to be considered. They detected novel COPD-related breath VOCs that now need to be tested in longitudinal studies for reproducibility, response to treatment and changes in disease severity.

Allers and associates (2016) stated that due to its high sensitivity, compact size and low cost, IMS has the potential to become a point-of-care breath analyzer. These researchers developed a prototype of a compact, closed gas loop IMS with GC pre-separation and high resolving power of R = 90. In this study, these investigators evaluated the performance of this GC-IMS under clinical conditions in a COPD study to find correlations between VOCs (10 ppbv to 1 ppmv) and COPD. Furthermore, in order to examine possible correlations between ultra-low concentrated breath VOCs (0.1 pptv to 1 ppbv) and COPD, a modified MS with atmospheric pressure chemical ionization (APCI) and GC pre-separation (GC-APCI-MS) was used. The GC-IMS has been used in 58 subjects (21 smokers with moderate COPD, 12 ex-smokers with COPD, 16 healthy smokers and 9 non-smokers). GC-APCI-MS data were available for 94 subjects (21 smokers with moderate COPD, 25 ex-smokers with COPD, 25 healthy smokers and 23 non-smokers). For 44 subjects, a comparison between GC-IMS and GC-APCI-MS data could be performed. Due to service intervals, subject availability and corrupt data, patient numbers were different for GC-APCI-MS and GC-IMS measurements. Using GC-IMS, 3 VOCs have been found showing a significant difference between healthy controls and patients with COPD. In the GC-APCI-MS data, these investigators only observed 1 distinctive VOC, which has been identified as 2-pentanone. The authors concluded that this proof-of-principle study showed the potential of the high-resolution GC-IMS in the clinical environment. However, due to different linear dynamic response ranges, the data of GC-IMS and GC-APCI-MS were only comparable to a limited extent.

Christiansen and colleagues (2016) stated that COPD is, according to the World Health Organization (WHO), the 5th leading cause of death worldwide, and is expected to increase to rank 3rd in 2030. Few robust biomarkers for COPD exist, and several attempts have been made to find suitable molecular marker candidates. One rising research area is breath analysis, with several published attempts to find exhaled compounds as diagnostic markers. The field is broad and no review of published COPD breath analysis studies exists yet. These investigators conducted a systematic review examining the state of art and identified 12 suitable papers, which they examined in detail to extract a list of potential COPD breath marker molecules. First, these researchers observed that no candidate markers were detected in all 12 studies. Only 3 were reported in more than 1 paper, thus reliable exhaled markers are still missing. A major challenge is the heterogeneity in breath sampling technologies, the selection of appropriate control groups, and a lack of sophisticated (and standardized) statistical data analysis methods. No cross-hospital/study comparisons have been published yet. The authors concluded that future efforts should concentrate on making breath data analysis more comparable through standardization of sampling, data processing, and reporting.

Detection of Bronchiolitis Obliterans Syndrome in Lung Transplant Recipients

Kuppers and colleagues (2018) stated that chronic lung allograft dysfunction with its clinical correlative of bronchiolitis obliterans syndrome (BOS) remains the major limiting factor for long-term graft survival. Currently there are no established methods for the early diagnosis or prediction of BOS. To evaluate the feasibility of breath collection as a non-invasive tool and the potential of breath VOC for the early detection of BOS, these researchers compared the breath VOC composition between transplant patients without and different stages of BOS. A total of 75 out-patients (25 BOS stage 0, 25 BOS stage 1 + 2, 25 BOS stage 3) after bilateral lung transplantation were included. Exclusion criteria were active smoking, oxygen therapy and acute infection. Patients inhaled room air through a VOC and sterile filter and exhaled into an aluminum reservoir tube. Breath was loaded directly onto Tenax TA adsorption tubes and was subsequently analyzed by GC/MS. The 3 groups were age- and gender-matched, but differed with respect to time since transplantation, the spectrum of underlying disease, and treatment regimes. Relative to patients without BOS, BOS stage 3 patients showed a larger number of different VOCs, and more pronounced differences in the level of VOCs as compared to BOS stage 1 + 2 patients. Logistic regression analysis found no differences between controls and BOS 1 + 2, but 4 VOCs (heptane, isopropyl-myristate, ethyl-acetate, ionone) with a significant contribution to the discrimination between controls and BOS stage 3. A combination of these 4 VOCs separated these groups with an AUC of 0.87. The authors concluded that breath sample collection using the reservoir sampler in the clinical environment was

feasible. They stated that these findings suggested that breath VOCs can discriminate severe BOS. However, convincing evidence for VOCs with a potential to detect early onset BOS is lacking.

Diagnosis of Cancers

Oakley-Girvan and Davis (2017) noted that detecting VOCs could provide a rapid, non-invasive, and inexpensive screening tool for detecting cancer. In this systematic review, these researchers identified specific exhaled breath VOCs correlated with breast colorectal, and lung cancer. They identified relevant studies published in 2015 and 2016 by searching PubMed and Web of Science. The protocol for this systematic review was registered in PROSPERO and the PRISMA guidelines were used in reporting; VOCs and performance data were extracted. A total of 333 records were identified and 43 papers were included in the review, of which 20 were review articles themselves. These investigators identified 17 studies that listed the VOCs with at least a subset of statistics on detection cut-off levels, sensitivity, specificity, AUC, and gradient. The authors concluded that breath analysis for cancer screening and early detection showed promise, because samples can be collected easily, safely, and frequently. While gas chromatography-mass spectrometry was considered the gold standard for identifying specific VOCs, breath analysis has moved into analyzing patterns of VOCs using a variety of different multiple sensor techniques, such as eNoses and nanomaterials. Moreover, they stated that further development of VOCs for early cancer detection requires clinical trials with standardized breath sampling methods.

Mochalski and colleagues (2018) noted that the presence of certain VOCs in the breath of patients with gastric cancer has been reported by a number of research groups; however, the source of these compounds remains controversial. Comparison of VOCs emitted from gastric cancer tissue to those emitted from non-cancerous tissue would help in understanding which of the VOCs are associated with gastric cancer and provide a deeper knowledge on their generation. Gas chromatography with mass spectrometric detection (GC-MS) coupled with head-space needle trap extraction (HS-NTE) as the pre-concentration technique, was used to identify and quantify VOCs released by gastric cancer and non-cancerous tissue samples collected from 41 patients during surgery. Excluding contaminants, a total of 32 compounds were liberated by the tissue samples. The emission of 4 of them (carbon disulfide, pyridine, 3-methyl-2-butanone and 2-pentanone) was significantly higher from cancerous tissue, whereas 3 compounds (isoprene, butyrolactone and dimethyl sulfide) were in greater concentration from the non-cancerous tissues (Wilcoxon signed-rank test, $p < 0.05$). Furthermore, the levels of 3 VOCs (2-methyl-1-propene, 2-propenenitrile and pyrrole) were correlated with the occurrence of H. pylori; and 4 compounds (acetonitrile, pyridine, toluene and 3-methylpyridine) were associated with tobacco smoking. Ex-vivo analysis of VOCs emitted by human tissue samples provided a unique opportunity to identify chemical patterns associated with a cancerous state and could be considered as a complementary source of information on volatile biomarkers found in breath, blood or urine. The authors concluded that the findings of this study implied that VOCs emitted by gastric cancer tissue form a cancer-specific chemical fingerprint. The components of this fingerprint secreted from the human organism, via f breath or urine, could assist in the non-invasive diagnosis of gastric cancer.

Janssens and associates (2020) noted that VOCs have shown potential as non-invasive breath biomarkers for lung cancer; however, their unclear biological origin currently limits clinical applications. In a systematic review, these investigators examined headspace analysis of VOCs in patient-derived body fluids and lung cancer cell lines to pinpoint lung cancer-specific VOCs and uncover their biological origin. They carried out a search in the databases Medline and Web of Science. A total of 22 articles were included in this systematic review. Since there is no standardized approach to analyze VOCs, a plethora of techniques and matrices/cell lines were examined, which was reflected in the various VOCs identified. However, comparing VOCs in the headspace of urine, blood and pleural effusions from patients and lung cancer cell lines showed some overlapping VOCs, indicating their potential use in lung cancer diagnosis. The authors concluded that the findings of this review demonstrated that VOCs are promising biomarkers for lung cancer; however, due to lack of inter-matrix consensus, standardized prospective trials are needed to validate clinically relevant biomarkers.

Wen and colleagues (2020) stated that the analysis of urinary VOCs is a promising field of research with the potential to discover new biomarkers for cancer early detection. In a systematic review, these researchers examined the published literature regarding cancer-associated urinary VOCs. They carried out a systematic online literature search to identify studies reporting urinary VOC biomarkers of cancers in accordance with the recommendations of the Cochrane Library and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. A total of 13 studies comprising 1,266 participants in total were included in the review. Studies reported urinary VOC profiles of 5 cancer subtypes: prostate cancer, gastro-intestinal (GI) cancer, leukemia/lymphoma, lung cancer, and bladder cancer. A total of 48 urinary VOCs belonging to 11 chemical classes were identified with high diagnostic performance; VOC profiles were distinctive for each cancer type with limited cross-over. The metabolic analysis suggested distinctive phenotypes for prostate and GI cancers. The authors concluded that the heterogenicity of study design, methodological and reporting quality may have contributed to inconsistencies between studies. Urinary VOC analysis has shown promising performance for non-invasive diagnosis of cancer; however, drawbacks in study design have resulted in inconsistencies between studies. These drawbacks were summarized and discussed in order to support future studies.

The authors stated that this systematic review suffered from several drawbacks that primarily concerned the relatively small number of published studies within this field. A wide variation in the methodologies used by individual studies was observed, making it difficult to draw strong conclusions. Studies rarely employed robust quality control strategies, and few studies validated findings within an independent patient cohort. Inadequate reporting of clinical parameters, including cancer stage, made it difficult to examine the performance of urinary VOC analysis on diagnosing early-stage cancer. For those studies that

did report cancer stage, it was evident that the majority of enrolled patients had locally advanced disease; thus, observed metabolic differences could not been seen to truly represent “early” disease that is the ultimate target of the test. Furthermore, it should be noted that the majority of the articles in this review originated from Europe; thus, may not be representative of other populations.

Leja and co-workers (2021) noted that detection of disease by means of VOCs from breath samples using sensors is an attractive approach to fast, non-invasive and inexpensive diagnostics; however, these techniques are still limited to applications within the laboratory settings. These researchers reported on the development and use of a fast, portable, and IoT-connected point-of-care (POC) device (so-called, SniffPhone) to detect and classify gastric cancer to potentially provide new qualitative solutions for cancer screening. This was a validation study of patients with gastric cancer, patients with high-risk pre-cancerous gastric lesions, and controls that was carried out with 2 SniffPhone devices. Linear discriminant analysis (LDA) was used as a classifying model of the sensing signals obtained from the examined groups. For the testing step, an additional device was added. The study group included 274 patients: 94 with gastric cancer, 67 who were in the high-risk group, and 113 controls. The results of the test set showed a clear discrimination between patients with gastric cancer and controls using the 2-device LDA model (area under the curve, 93.8 %; sensitivity, 100 %; specificity, 87.5 %; overall accuracy, 91.1 %), and acceptable results were also achieved for patients with high-risk lesions (the corresponding values for dysplasia were 84.9 %, 45.2 %, 87.5 %, and 65.9 %, respectively). The test-phase analysis showed lower accuracies, though still clinically useful. The authors concluded that the findings of this study demonstrated that a portable breath sensor device could be useful in POC settings; it showed a promise for detection of gastric cancer as well as for other types of disease.

Diagnosis of Lung Disease

The European Respiratory Society’s technical standard on “Exhaled biomarkers in lung disease” (Horvath et al, 2017) stated that breath tests cover the fraction of NO in expired gas (FeNO), VOCs, variables in EBC and other measurements. For EBC and for FeNO, official recommendations for standardized procedures are more than 10 years old and there is none for exhaled VOCs and particles. The aim of this document was to provide technical standards and recommendations for sample collection and analytic approaches and to high-light future research priorities in the field. For EBC and FeNO, new developments and advances in technology have been evaluated in the current document. This report was not intended to provide clinical guidance on disease diagnosis and management. Clinicians and researchers with expertise in exhaled biomarkers were invited to participate. Published studies regarding methodology of breath tests were selected, discussed and evaluated in a consensus-based manner by the Task Force members. Recommendations for standardization of sampling, analyzing and reporting of data and suggestions for research to cover gaps in the evidence have been created and summarized. The authors concluded that application of breath biomarker measurement in a standardized manner will provide comparable results, thereby facilitating the potential use of these biomarkers in clinical practice.

Diagnosis of Infection

Ahmed and colleagues (2017) stated that with heightened global concern of microbial drug resistance, advanced methods for early and accurate diagnosis of infection are urgently needed. Analysis of exhaled breath VOCs toward detecting microbial infection potentially allows a highly informative and non-invasive alternative to current genomics and culture-based methods. These researchers performed a systematic review of research literature reporting human and animal exhaled breath VOCs related to microbial infections. They found that a wide range of breath sampling and analysis methods are used by researchers, which significantly affects inter-study method comparability. Studies either performed targeted analysis of known VOCs relating to an infection, or non-targeted analysis to obtain a global profile of volatile metabolites. In general, the field of breath analysis is still relatively immature, and there is much to be understood about the metabolic production of breath VOCs, particularly in a host where both commensal microflora as well as pathogenic microorganisms may be manifested in the airways. The authors concluded that they anticipated that measures to standardize high throughput sampling and analysis, together with an increase in large scale collaborative international trials, will bring routine breath VOC analysis to improve diagnosis of infection closer to reality.

Prediction of Asthma Exacerbations

van Vliet and colleagues (2017) stated that asthma control does not yet meet the goals of asthma management guidelines. Non-invasive monitoring of airway inflammation may help to improve the level of asthma control in children. These researchers identified a set of exhaled VOCs that is most predictive for an asthma exacerbation in children, and elucidated the chemical identity of predictive biomarkers. In a 1-year prospective, observational study, a total of 96 asthmatic children participated . During clinical visits at 2 month intervals, asthma control, FeNO, lung function (FEV1, FEV1/vital capacity [VC]) and VOCs in exhaled breath were determined by means of GC time-of-flight MS. Random Forrest classification modeling was used to select predictive VOCs, followed by plotting of ROC-curves. An inverse relationship was found between the predictive power of a set of VOCs and the time between sampling of exhaled breath and the onset of exacerbation. The sensitivity and specificity of the model predicting exacerbations 14 days after sampling were 88 % and 75 %, respectively. The area under the ROC-curve was 90 %. The sensitivity for prediction of asthma exacerbations within 21 days after sampling was 63 %. In total, 7 VOCs were selected for the classification model: 3 aldehydes, 1 hydrocarbon, 1 ketone, 1 aromatic compound, and 1 unidentified VOC. The authors concluded that VOCs in exhaled breath showed potential for predicting asthma exacerbations in children within 14 days

after sampling. Moreover, they stated that before using this in clinical practice, the validity of predicting asthma exacerbations should be studied in a larger cohort.

Diagnosis and Monitoring of Pleural Mesothelioma

Brusselmans and associates (2018) noted that malignant pleural mesothelioma (MPM) is a tumor related to a historical exposure to asbestos fibers. Currently, the definite diagnosis is made only by the histological examination of a biopsy obtained through an invasive thoracoscopy. However, diagnosis is made too late for curative treatment because of non-specific symptoms mainly appearing at advanced stage disease. Hence, due to its biologic aggressiveness and the late diagnosis, survival rate is low and the patients' outcome poor. In addition, radiological imaging, like computed tomographic (CT) scans, and blood biomarkers are found not to be sensitive enough to be used as an early diagnostic tool. Detection in an early stage is assumed to improve the patients' outcome but is hampered due to non-specific and late symptomology. Thus, there is a need for a new screening and diagnostic test which could improve the patients' outcome. Despite extensive research has focused on blood biomarkers, not a single has been shown clinically useful, and therefore research recently shifted to "breathomics" techniques to recognize specific VOCs in the breath of the patient as potential non-invasive biomarkers for disease. In a systematic review, these investigators summarized the acquired knowledge regarding the use of breath analysis for diagnosing and monitoring MPM and asbestos-related disorders (ARD). Gas chromatography-mass spectrometry (GC-MS), the gold standard of breath analysis, appeared to be the method with the highest accuracy (97 %) to differentiate MPM patients from at risk asbestos-exposed subjects. There have already been found some interesting biomarkers that are significantly elevated in asbestosis (NO, 8-isoprostane, leukotriene B4, α-Pinene) and MPM (cyclohexane) patients. Regrettably, the different techniques and the plethora of studies suffered some limitations. Most studies were pilot studies with the inclusion of a limited number of patients. Nevertheless, given the promising results and easy sampling methods, the authors concluded that breath analysis may become a useful tool in the future to screen for MPM, but further research is needed.

Catino and colleagues (2019) stated that MPM is a rare neoplasm related to asbestos exposure and with high mortality rate. The management of patients with MPM is complex and controversial, particularly with regard to early diagnosis. In the last few years, breath analysis has been greatly implemented with this aim. In this review the strengths of breath analysis and preliminary results in searching breath biomarkers of MPM were discussed. Through a systematic electronic literature search, collecting papers published from 2000 until December 2018, a total of 15 relevant scientific papers were selected. All papers considered were prospective, comparative, observational case-control studies although every single one pilot and based on a relatively small number of samples. The identification of diagnostic VOCs pattern, through breath sample characterization and the statistical data treatment, allowed to obtain a strategic information for clinical diagnostics. To-date the collected data provided just preliminary information and, despite the promising results and diagnostic accuracy, conclusions could not be generalized due to the limited number of individuals included in each cohort study. Furthermore none of studies was externally validated, although validation process is a necessary step towards clinical implementation. The authors concluded that breathomics-based biomarker approach should be further examined to confirm and validate preliminary findings and to evaluate its potential role in monitoring the therapeutic response.

Toreyin and colleagues (2020) stated that MPM is mainly related to previous asbestos exposure. There is still a scarcity of information on non-invasive biomarkers to detect MPM at early stages. Human studies on exhaled breath biomarkers of cancer and asbestos-related diseases show encouraging results. In a systematic review, these investigators examined the evidence regarding exhaled breath analysis in MPM diagnosis. They carried out a search on Medline (PubMed), Embase and Web of Science databases to identify relevant studies. Quality assessment was performed by the Newcastle-Ottawa Scale. A total of 6 studies were identified, all of which showed fair quality and examine VOC-based breath profile using GC-MS, ion mobility spectrometry coupled to multi-capillary columns (IMS-MCC) or pattern-recognition technologies. Sample sizes varied between 39 and 330. Some compounds (i.e., cyclohexane, P3, P5, P50, P71, diethyl ether, limonene, nonanal, VOC IK 1287) that can be indicative of MPM development in asbestos exposed population were identified with high diagnostic accuracy rates. E-nose studies reported breath-prints being able to distinguish MPM from asbestos exposed individuals with high sensitivity and a negative predictive value (NPV). The authors concluded that although the results on human studies were encouraging, small sample sizes and methodological diversities among studies limited the translation of results into clinical practice. Furthermore, a great majority of the studies lacked external validation. These researchers stated that more prospective studies with standardized methodologies in line with the most recent guidelines should be conducted and external validation of the results should be tested on larger populations.

Diagnosis and Monitoring of Sarcoidosis

Terrington and colleagues (2019) noted that sarcoidosis is a chronic granulomatous disease of unknown etiology with a variable clinical course and prognosis. There is a growing need to identify non-invasive biomarkers to differentiate between clinical phenotypes, identify those at risk of disease progression and monitor response to treatment. In a systematic review and meta-analysis, these investigators evaluated the utility of breath-based biomarkers in discriminating sarcoidosis from healthy controls, alongside correlation with existing non-breath based biomarkers used in clinical practice, radiological stage, markers of disease activity and response to treatment. Electronic searches were undertaken during November 2017 using PubMed, Ebsco, Embase and Web of Science to capture relevant studies evaluating breath-based biomarkers in adult patients with sarcoidosis. A total of 353 papers were screened; 21 met the inclusion criteria and assessed 25 different biomarkers alongside VOCs in exhaled breath gas or condensate. Considerable heterogeneity existed among the studies in terms of participant characteristics,

sampling and analytical methods. Elevated biomarkers in sarcoidosis included 8-isoprostane, carbon monoxide, neopterin, TGF-β1, TNFα, CysLT and several metallic elements including chromium, silicon and nickel; 3 studies exploring VOCs were able to distinguish sarcoidosis from controls. Meta-analysis of 4 studies assessing alveolar nitric oxide showed no significant difference between sarcoidosis and healthy controls (2.22ppb; 95 % CI: -0.83 to 5.27); however, a high degree of heterogeneity was observed with an I2 of 93.4 % ($p < 0.001$). Inconsistent or statistically insignificant results were observed for correlations between several biomarkers and radiological stage, markers of disease activity or treatment. The authors concluded that the evidence for using breath biomarkers to diagnose and monitor sarcoidosis remains inconclusive with many studies limited by small sample sizes and lack of standardization. These researchers stated that VOCs have shown promising potential but further research is needed to evaluate their prognostic role.

van der Sar et al (2022) noted that diagnosing sarcoidosis can be challenging, and a non-invasive diagnostic method is lacking. The electronic nose (eNose) technology profiles VOCs in exhaled breath and has potential as a POC diagnostic tool. In a cross-sectional study, these researchers examined if eNose technology could be used to distinguish accurately between sarcoidosis, interstitial lung disease (ILD), and healthy control subjects, and between sarcoidosis subgroups. Exhaled breath of patients with sarcoidosis and ILD and healthy control subjects was analyzed by using an eNose (SpiroNose). Clinical characteristics were collected from medical files. Partial least squares discriminant and ROC analyses were employed to a training and independent validation cohort. The study included 252 patients with sarcoidosis, 317 with ILD, and 48 healthy control subjects. In the validation cohorts, eNose distinguished sarcoidosis from control subjects with an AUC of 1.00 and pulmonary sarcoidosis from other ILD (AUC, 0.87; 95 % CI: 0.82 to 0.93) and hypersensitivity pneumonitis (AUC, 0.88; 95 % CI: 0.75 to 1.00). Exhaled breath of sarcoidosis patients with and without pulmonary involvement, pulmonary fibrosis, multiple organ involvement, pathology-supported diagnosis, and immunosuppressive treatment revealed no distinctive differences. Breath profiles differed between patients with a slightly and highly elevated soluble IL-2 receptor level (median cut-off of 772.0 U/ml; AUC, 0.78; 95 % CI: 0.64 to 0.92). The authors concluded that patients with sarcoidosis can be distinguished from ILD and healthy control subjects by using eNose technology, indicating that this method may facilitate accurate diagnosis in the future. Moreover, these investigators stated that further investigation is needed to ascertain the value of eNose in monitoring sarcoidosis activity. They noted that longitudinal studies are needed to examine the ability of this tool to monitor disease activity.

The authors stated that a drawback of this trial was the absence of patients with granulomatous diseases such as TB and sarcoid-like reactions, due to the low prevalence of these diseases. Previous studies showed that TB can be accurately differentiated from healthy control subjects and from patients with suspected TB using an eNose. eNose technology therefore holds the potential to guide multi-disciplinary team discussions in patients with a granulomatous disease. Future studies should examine the value of eNose technology in differentiating between a broader range of granulomatous entities. Especially in areas with limited access to diagnostic procedures and/or a high prevalence of TB, eNose might be of added value as an easily accessible and accurate POC tool in clinical practice. Another drawback of this study was that the current dataset contained some missing data. Soluble IL-2 receptor (sIL-2R) values were not available for all patients, which might influence the outcome and strength of the analysis. Therefore, further studies to extend and confirm these results are needed. Moreover, the compared groups were not matched regarding certain baseline variables such as sex, smoking status, and age. However, additional subgroup analyses did not show an effect of these variables on results. Lastly, the results of this single-center study still need to be confirmed and validated by external patient cohorts in a multi-center multi-national study. External validation, design of a diagnostic algorithm, and test cohorts are needed steps before implementation of the SpiroNose as a diagnostic tool can be realized.

Diagnosis of Obstructive Sleep Apnea

Finamore and colleagues (2019) noted that obstructive sleep apnea syndrome (OSAS) represents an independent risk factor for cardiovascular, metabolic and neurological events. Polysomnography (PSG) is the gold-standard for the diagnosis; however, PSG is expensive and time-consuming and not suitable for widespread use. Breath analysis is an innovative, non-invasive technique, able to provide clinically relevant information regarding OSAS. In a systematic review, these investigators examined the evidence on the role of exhaled breath analysis in OSAS, taking into account the techniques' level of adherence to the recently proposed technical standards. Studies reporting original data on exhaled breath analysis in OSAS were identified through a computerized and manual literature search and screened. Duplicate publications, case-reports, case-series, conference papers, expert opinions, comments, reviews and meta-analysis were excluded. Fractional exhaled nitric oxide (FeNO) is higher in OSAS patients than controls, however, its absolute value is within reported normal ranges. FeNO association with apnea-hypopnea index (AHI) is controversial, as well as its change after continuous positive airway pressure (C-PAP) therapy. Exhaled breath condensate (EBC) is acid in OSAS, cytokines and oxidative stress markers are elevated, they positively correlate with AHI and normalize after treatment. The analysis of VOCs by spectrometry or electronic nose is able to discriminate OSAS from healthy controls. Breath-print analysis of VOCs might have practical applications and could act as an instrument in OSAS management in the future. Breath-print analysis might complement, or even replace questionnaires in the screening process and, consequently, improve the cost/effectiveness ratio of PSG. However, the main technical issues concerns the dilution of EBC and the lack of external validation in VOCs studies. The authors concluded that exhaled breath analysis has a promising role in the understanding of mechanisms underpinning OSAS and has demonstrated a clinical relevance in identifying individuals affected by the disease, in assessing the response to treatment and, potentially, to monitor patient's adherence to mechanical ventilation. Moreover, these researchers stated that although the majority of the technical standards proposed by the ERS committee have been followed by existing papers, further work is needed to uniform the methodology.

Screening for Colorectal Cancer

In a meta-analysis, Zhou and colleagues (2020) examined the usefulness of VOC as a potential novel biomarker for CRC. These investigators searched PubMed, Embase, Web of Science, and Cochrane Library data-bases for observational studies (published before November 25, 2019; no language restrictions) comparing the VOC analysis between patients with CRC and healthy controls. They assessed the pooled sensitivity, specificity, DOR, positive and negative likelihood ratio (PLR and NLR), as well as summary ROC curve and AUC. These researchers identified a total of 10 observational studies that included 381 patients with CRC and 436 healthy controls. Bi-variate analysis yielded a pooled sensitivity of 0.82 (95 % CI: 0.77 to 0.86), specificity of 0.79 (95 % CI: 0.71 to 0.85), PLR of 3.8 (95 % CI: 2.8 to 5.3), and NLR of 0.23 (95 % CI: 0.17 to 0.30). The AUC was 0.87 (95 % CI: 0.84 to 0.90). The pooled DOR was 17 (95 % CI: 10 to 28). Sensitivity analysis indicated that the pooled results were stabilized. The Deeks' funnel plot asymmetry test (p = 0.41) suggested no potential publication bias. The authors concluded that the pooled data confirmed the associations between VOC analysis and CRC, highlighting the usefulness of VOC analysis as a potential novel screening tool for CRC. However, standardization of VOC collection and analysis methods for CRC screening is needed in future research.

The authors stated that a drawback of this analysis was that most available studies to-date were case-control and cross-sectional studies. Cancer-specific biomarkers (e.g., VOC) need to be used in prospective, longitudinal studies that recruit patients with CRC to understand what extent the VOC are associated with disease severity. Second, limited available studies and subjects were included in this meta-analysis, which may have lowered the statistical power. More clinical studies with larger sample sizes need to be performed in the future. Third, different VOC sources and analytical platforms were included in this meta-analysis, which might be the major sources of heterogeneity. Finally, this systematic review was not registered, and therefore there may be minor biases, but it was still strictly performed in accordance with the MOOSE guidelines. Previous meta-analysis highlighted the non-invasive nature of breath testing that enhanced patient acceptability. However, the composition of exhaled breath is affected by many factors, such as smoking, diet, and lung disease. Indeed, in addition to breath, lots of VOC in various bodily fluids and metabolic wastes are generated from a pure exogenous origin, which are neither human nor bacterial metabolites. These compounds might be related to medicines ingested, occupational exposure, household chemicals, environmental pollutants, and fuel combustion. Thus, it is critical to confirm which source of VOC is able to provide more accurate diagnosis results. This study was the 1st one to examine the problem and perform a subgroup analysis based on the different sources. Unfortunately, the number of available studies to-date was relatively limited and these investigators failed to get the pooled area under the SROC curve of exhaled breath VOC. Furthermore, current studies lack the standardization of VOC collection and analysis, which might be related to the potential heterogeneity of this study. The results of VOC testing depend on the method of sample collection and test environment. Although no evidence of a threshold effect was observed in this analysis, it was necessary to establish test thresholds for separating patients with CRC at different stage before embarking on masked validation studies in future research. In addition, although it is essential to examine potential novel technologies in VOC analysis, the reproducibility of results and reliability of instruments are also the future directions.

van Liere et al (2023) noted that the fecal immunochemical test (FIT) suffers from suboptimal performance and participation in CRC screening. Urinary VOCs may be a useful alternative. In a systematic review and meta-analysis, these investigators examined the diagnostic potential of urinary VOCs for CRC/adenomas. By relating VOCs to known pathways, these researchers aimed to gain insight into the pathophysiology of colorectal neoplasia. They carried out a systematic search in PubMed, Embase and Web of Science. Original studies on urinary VOCs for CRC/adenoma detection with a control group were included. QUADAS-2 tool was used for quality assessment. Meta-analysis was carried out by adopting a bi-variate model for sensitivity/specificity. Fagan's nomogram estimated the performance of combined FIT-VOC. Neoplasm-associated VOCs were linked to pathways using the KEGG database. A total of 16 studies entailing 837 CRC patients and 1,618 controls were included; 11 conducted chemical identification and 7 chemical fingerprinting. In all studies, urinary VOCs discriminated CRC from controls. Pooled sensitivity and specificity for CRC based on chemical fingerprinting were 84 % (95 % CI: 73 % to 91 %) and 70 % (95 % CI: 63 % to 77 %), respectively. The most distinctive individual VOC was butanal (AUC 0.98). The estimated probability of having CRC following negative FIT was 0.38 %, whereas 0.09 % following negative FIT-VOC. Combined FIT-VOC would detect 33 % more CRCs. In total 100 CRC-associated urinary VOCs were identified; especially hydrocarbons, carboxylic acids, aldehydes/ketones and amino acids, and predominantly involved in TCA-cycle or alanine/aspartate/glutamine/glutamate/phenylalanine/tyrosine/tryptophan metabolism, which was supported by previous research on (colorectal) cancer biology. The potential of urinary VOCs to detect pre-cancerous adenomas or gain insight into their pathophysiology appeared under-studied. The authors concluded that urinary VOCs hold potential for non-invasive CRC screening. Moreover, these researchers stated that multi-center validation studies are needed, as well as studies evaluating performance for adenomas, the optimal analytical strategy, confounding factors and cost-effectiveness.

The authors stated that this review was limited by the modest quality of included studies: most studies did not resemble a true screening setting, various sampling methodologies and statistical models were employed (or these were not reported in sufficient detail) and several studies were deemed at moderate or unclear risk of bias. The studies included in the meta-analysis (which all used chemical fingerprinting) were at lower risk of bias, nonetheless, the meta-analysis showed heterogeneity among included studies. Regarding the studies using chemical identification, on the other hand, the variation in methodology limited the matching of CRC-associated VOCs between studies. Moreover, these researchers stated that to move urinary VOCs forward towards clinical practice, standardized practices for sample preparation, sample analysis and data analysis are crucial, to ensure accuracy, head-to-head comparison and reproducibility of studies. While the optimal analytical strategy for urinary VOC analysis remains to be established, protocols and important considerations have been published. Regarding sample collection, samples

should be collected in sealed containers, immediately frozen after collection and analyzed within 9 to 12 months. Next to studies on the optimal analytical strategy, further studies should examine cost-effectiveness as well as external confounding variables that limit the detection of colorectal neoplasia (and thus should be corrected for). Lastly, multi-center validation studies on diagnostic performance for both CRC and its precursor lesions (being adenomas) are needed. To establish the patient number needed to produce solid evidence, the pooled data can be used for a formal power calculation. These validation studies should resemble a real-life screening setting, meaning that consecutive pre-diagnosed patients with a normal pre-test probability of CRC should be included. Ideally, all participants undergo colonoscopy as reference standard.

Electronic Nose as a Rule-Out Test for Tuberculosis

Teixeira and colleagues (2021) stated that to end the tuberculosis (TB) epidemic, efficient diagnostic tools are needed. In a previous calibration study, a portable POC electronic nose device (AeonoseTM) proved to be a promising tool in a hospital setting. These researchers examined this technology to detect TB in an indigenous population in Paraguay. A total of 131 subjects were enrolled. ENose results were compared with anamnesis, physical examinations, chest radiography and mycobacterial cultures in individual with sings and symptoms compatible with TB. The eNose analysis was carried out in 2 stages. First, the training with a combination of a previous study population plus 47 subjects from the new cohort (total n = 153). Second, the "blind prediction" of 84 subjects. A total of 21 % of all subjects (n = 131) showed symptoms and/or chest radiography abnormalities suspicious of TB. No sputum samples resulted culture positive for Mycobacterium tuberculosis complex. Only 1 patient had a positive smell print analysis. In the training model, the specificity was 92 % (95 % CI: 85 % to 96 %) and the NPV was 95 %. In the blind prediction model, the specificity and the NPV were 99 % (95 % CI: 93 % to 99 %) and 100%, respectively. Although the sensitivity and positive predictive value (PPV) of the eNose could not be examined in this cohort due to the small sample size, no active TB cases were found during a 1 year of follow-up period. The authors concluded that the eNose showed promising specificity and NPV and might therefore be developed as a rule-out test for TB in vulnerable populations.

The authors stated that this study has several drawbacks. First, there were no active TB cases detected in this small and isolated indigenous community; thus, the sensitivity and the PPV of the eNose could not be established. Given the TB incidence of 245/100,000 inhabitants for indigenous communities (data of PNCT), these researchers should have sampled at least a few thousand people to detect enough positive TB cases to evaluate its' accuracy. Amplifying the sample size with indigenous people from other communities would have introduced a potential bias as these investigators were not informed whether for example differences in genetics or food habits may influence a persons' breath signal. Second, these researchers did not procure sputum specimens of all subjects to exclude active TB disease. As the sensitivity of mycobacterial sputum culture is very low in asymptomatic people, and also the fact that during the follow-up period of 1 year no new TB diagnoses were established, the authors assumed that the NPV of the eNose in this cohort was adequate.

Screening for COVID-19

Chen et al (2021) stated that rapid screening of COVID-19 is key to controlling the pandemic; however, current nucleic acid amplification entails lengthy procedures in addition to the discomfort of taking throat/nasal swabs. These researchers described potential breath-borne VOC biomarkers together with machine learning that can be used for POC screening of COVID-19. Using a commercial GC-IMS, higher levels of propanol were detected in the exhaled breath of COVID-19 patients (n = 74) and non-COVID-19 respiratory infections (RI) (n = 30) than those of non-COVID-19 controls (NC)/health care workers (HCW) (n = 87), and backgrounds (n = 87). In contrast, breath-borne acetone was found to be significantly lower for COVID-19 patients than other subjects. A total of 12 key endogenous VOC species using supervised machine learning models (support vector machines, gradient boosting machines (GBMs), and Random Forests) were shown to exhibit strong capabilities in discriminating COVID-19 from (HCW + NC) and RI with a precision ranging from 91 % to 100 %. GBM and Random Forests models could also discriminate RI patients from healthy subjects with a precision of 100 %. Furthermore, the developed models using breath-borne VOCs could also detect a confirmed COVID-19 patient but with a false negative throat swab polymerase chain reaction (PCR) test. It took 10 mins to allow an entire breath test to finish, including analysis of the 12 key VOC species. The authors concluded that the developed technology provided a novel concept for non-invasive rapid POC-test screening for COVID-19 in various scenarios.

Subali et al (2022) noted that COVID-19 is a major problem with an increasing incidence and mortality. These researchers examined VOC-based breath analysis diagnostic performance for SARS-COV-2 infection compared to RT-PCR. They carried out a systematic review in 8 scientific databases based on the PRISMA guideline. Original English studies examining human breaths for COVID-19 screening and mentioning sensitivity and specificity value compared to RT-PCR were included. A total of 6 studies were included with 4,093 samples from various settings. VOCs-based breath analysis had the cumulative sensitivity of 98.2 % (97.5 % CI: 93.1 % to 99.6 %) and specificity of 74.3 % (97.5 % CI: 66.4 % to 80.9 %). Subgroup analysis on chemical analysis (GC-MS) and pattern recognition (eNose) revealed higher sensitivity in the eNose group. The authors concluded that COVID-19 patients showed a distinct pattern of VOCs. Through many studies, VOC-based breath analysis exhibited high sensitivity and NPV, supported with the rapid and more feasible procedure, yielding a high potential for COVID-19 screening in public settings. These investigators stated that in the future, VOC-based breath analysis can be integrated with cloud databases, and artificial intelligence (AI) as a promising POC COVID-19 mass-scaled screening.

The authors stated that due to the novelty of the topic discussed, there are limited resources of studies, and evidence regarding the evaluation of VOC-based breath analysis for COVID-19 screening. The currently available studies were considered to be preliminary research to examine breath analysis for COVID-19 screening. As a result, the included studies showed a wide heterogeneity in some aspects, such as varied population, and patients characteristics. Patients recruited in studies were diverse, from asymptomatic individuals, patients with suggestive symptoms of COVID-19, individuals having close contact history with COVID-19 confirmed patients, to critically ill acute respiratory distress syndrome (ARDS) patients needing ventilators. An extreme variation could also be observed in sample age, ranging from pediatric patients to elderly subjects, which may correlate with different clinical manifestations. Furthermore, the use of analytical methods and various electronic nose products may give different performances of breath analysis, which may introduce bias. The breath sampling technique was varied between each study and a study instructed the subjects with specific preparation before obtaining the sample. Variations between the use of real-time and stored breath samples may cause bias. In addition, the use of different AI methods for pattern recognition features in electronic noses may lead to different performances between the eNose. Subsequently, the threshold, and specific biomarkers of SARS-CoV-2 infection had not been established; thus, each study may report its own cut-off value and propose some VOCs that potentially be used as markers to detect COVID-19 patients.

Shlomo et al (2022) compared the Breath of Health, Ltd. (BOH) breath analysis system to PCR's ability to screen asymptomatic individuals for SARS-CoV-2 infection. The BOH system is mobile and combines Fourier-transform infrared (FTIR) spectroscopy with AI to generate results within 2 mins and 15 s. In contrast to prior SARS-CoV-2 breath analysis research, this study focused on diagnosing SARS-CoV-2 via disease specific spectrometric profiles rather than through identifying the disease specific molecules. Asymptomatic emergency room patients with suspected SARS-CoV-2 exposure in 2 leading Israeli hospitals were selected between February through April 2021. All were tested via nasal/throat-swab PCR and BOH breath analysis. A total of 297 patients were sampled (mean age of 57.08 ± SD 18.86 years, 156 men, 139 women, 2 unknowns). Of these, 96 were PCR-positive (44 men, 50 women, 2 unknowns), 201 were PCR-negative (112 men, 89 women). A total of 100 samples were used for AI identification of SARS-CoV-2 distinguishing spectroscopic wave-number patterns and diagnostic algorithm creation. Algorithm validation was tested in 100 proof-of-concept samples (34 PCR-positive, 66 PCR-negative) by comparing PCR with AI algorithm-based breath-test results determined by a blinded medical expert; 100 additional samples (12 true PCR-positive, 85 true PCR-negative, 3 confounder false PCR-positive [not included in the 297 total samples]) were evaluated by 2 blinded medical experts for further algorithm validation and inter-expert correlation. The BOH system identified 3 distinguishing wave numbers for SARS-CoV-2 infection. In the 1st phase, the single expert identified the first 100 samples correctly, yielding a 1:1 FTIR/AI:PCR correlation. The 2-expert 2nd-phase also yielded 1:1 FTIR/AI:PCR correlation for 97 non-confounders and null correlation for the 3 confounders. Inter-expert correlation was 1:1 for all results. In total, the FTIR/AI algorithm demonstrated 100 % sensitivity and specificity for SARS-CoV-2 detection when compared with PCR. The authors concluded that SARS-CoV-2 method of breath analysis via FTIR with AI-based algorithm demonstrated high PCR correlation in screening for asymptomatic individuals. These researchers stated that this was the 1st practical, rapid, POC breath analysis solution with such high PCR correlation in asymptomatic individuals. They stated that further validation is needed with a larger sample size.

The authors stated that this study had several drawbacks regarding sampling and subject-related conditions. First, although this method did not attempt to identify the distinguishing compound, it was likely that the distinguishing wave numbers represented products of innate immune system activation. Thus, it was conceivable that FTIR breath analysis could miss sub-populations of immunosuppressed SARS-CoV-2 positive patients in whom these production processes were subdued. Similarly, the study's design as a proof-of-concept with limited sample size and lack of subject co-morbidity data led to additional questions regarding sampling. The subject sample had a male predominance overall, with more males testing negative in all groups. Prior studies repeatedly demonstrated male gender as a risk factor for COVID-19 morbidity and mortality. This included gender differences in immune response. Recently, Liangou et al (2021) demonstrated age differences in the concentrations of various VOCs of individuals with COVID-19. It was possible that similar age and gender differences exist in organic product production in the asymptomatic phase. Furthermore, sampling occurred in the winter and early spring, yet subjects were not tested for possible infection, or co-infection, with other respiratory pathogens. Furthermore, it was conceivable that the subject group recruited in the emergency department was more homogenous and less representative of the general population screened in a non-medical public venue. Lastly, subject SARS-CoV-2 vaccination status was unknown and SARS-CoV-2 variant type was not determined in SARS-CoV-2 positive patients. The latter requires further clarification since the public health risk of the SARS-CoV-2 evolving genome demands that any potential SARS-CoV-2 diagnostic test undergo mutation and vaccine-specific validation. This was highlighted by the rapid global spread of the Omicron (B.1.1.529) variant at the time of this study's publication. Overall, any of the afore-mentioned factors could skew results, either by altering subject immune response, or by limiting generalizability.

Wilson and Forse (2023) stated that the established effectiveness of electronic VOC detection technologies as diagnostic tools for non-invasive early detection of COVID-19 and related coronaviruses has been demonstrated from multiple studies using a variety of experimental and commercial electronic devices capable of detecting precise mixtures of VOC emissions in human breath. The activities of numerous global research teams, developing novel electronic-nose (e-nose) devices and diagnostic methods, have generated empirical laboratory and clinical trial test results based on the detection of different types of host VOC-biomarker metabolites from specific chemical classes. COVID-19-specific volatile biomarkers are derived from disease-induced changes in host metabolic pathways by SARS-CoV-2 viral pathogenesis. The unique mechanisms proposed from recent researchers to explain how COVID-19 causes damage to multiple organ systems throughout the body are associated with unique symptom combinations, cytokine storms and physiological cascades that disrupt normal biochemical processes through gene dysregulation to generate disease-specific VOC metabolites targeted for e-nose detection. The authors reviewed recent methods and applications of e-nose and related VOC-detection devices for early, non-invasive diagnosis of SARS-CoV-2

infections. Furthermore, metabolomic (quantitative) COVID-19 disease-specific chemical biomarkers, consisting of host-derived VOCs identified from exhaled breath of patients, were summarized as possible sources of volatile metabolic biomarkers useful for confirming and supporting e-nose diagnoses.

The authors stated that researchers involved in COVID-19 diagnostics continue to examine and search for VOC target metabolites in exhaled air which are characteristic of the disease to improve the development of more effective electronic sensors and chemical detectors. Metabolomics is an evolving area of science that continues to change and improve as new technologies, analytical instruments, and associated methods are developed. Application of metabolomics in investigations of infectious disease diagnostics has been promoted by the urgency of the COVID-19 pandemic. Metabolomics approaches that rely on analysis of exhaled breath VOCs from COVID-19 patients hold promise for use in large-scale screening of human populations in POC settings. These researchers stated that additional future metabolomic research will hopefully provide more mechanistic details to explain why COVID-19-induced dysregulation of certain metabolites occurs within specific metabolic pathways. Determining which VOCs are most reliable as consistent chemical biomarkers of COVID-19 infections for patients with variable personal histories, health conditions, immune systems, and nutritional states would be most useful for improving COVID-19 diagnoses using e-nose devices.

Diagnosis of Cancers

Fan et al (2024) noted that lung cancer (LC), characterized by high incidence and mortality rates, presents a significant challenge in oncology. Despite advancements in treatments, early detection remains crucial for improving patient outcomes. The accuracy of screening for LC by detecting VOCs in exhaled breath remains to be determined. In a systematic review and meta-analysis, following PRISMA guidelines and analyzing data from 25 studies up to October 1, 2023, these investigators examined the effectiveness of different techniques in detecting VOCs. They carried out a systematic search in PubMed, Embase and Web of Science. Reviewers screened the studies' titles/abstracts and full texts, and used QUADAS-2 tool for quality assessment; then performed meta-analysis by adopting a bi-variate model for sensitivity and specificity. This study examined the potential of VOCs in exhaled breath as biomarkers for LC screening, offering a non-invasive alternative to traditional methods. In all studies, exhaled VOCs discriminated LC from controls. The meta-analysis revealed an integrated sensitivity and specificity of 85 % and 86 %, respectively, with an AUC of 0.93 for VOC detection. These researchers also carried out a systematic analysis of the source of the substance with the highest frequency of occurrence in the tested compounds. They noted that despite the promising results, variability in study quality and methodological challenges highlighted the need for further research. The authors concluded that this review emphasized the potential of VOC analysis as a cost-effective, non-invasive screening tool for early LC detection, which could significantly improve patient management and survival rates.

Zhou et al (2024) noted that the gradual evolution of the detection and quantification of VOCs has been instrumental in cancer diagnosis. In a systematic review and meta-analysis, these investigators examined the diagnostic potential of exhaled breath and urinary VOCs in cancer detection. As VOCs are indicative of tumor and human metabolism, this study also examined the metabolic pathways linked to the development of cancerous tumors. They carried out an electronic search in the PubMed database. Original studies on VOCs within exhaled breath and urine for cancer detection with a control group were included. A meta-analysis was performed using a bi-variate model to evaluate the sensitivity and specificity of the VOCs for cancer detection. Fagan's nomogram was designed to leverage the findings from the diagnostic analysis for the purpose of estimating the likelihood of cancer in patients. MetOrigin was used to carry out an analysis of the metabolic pathways associated with VOCs in relation to both human and/or microbiota. The pooled sensitivity, specificity and the AUC for cancer screening by means of exhaled breath and urinary VOCs were determined to be 0.89, 0.88, and 0.95, respectively. A pre-test probability of 51 % can be considered as the threshold for diagnosing cancers with VOCs. As the estimated pre-test probability of cancer exceeded 51 %, it became more appropriate to emphasize the “ruling in” approach. On the contrary, when the estimated pre-test probability of cancer fell below 51 %, it was more suitable to emphasize the “ruling out” approach. A total of 14, 14, 6, and 7 microbiota-related VOCs were identified in relation to lung, colorectal, breast, and liver cancers, respectively. The enrichment analysis of volatile metabolites revealed a significant enrichment of butanoate metabolism in the afore-mentioned tumor types. The authors concluded that the analysis of exhaled breath and urinary VOCs showed promise for cancer screening. Furthermore, the enrichment analysis of volatile metabolites showed a significant enrichment of butanoate metabolism in 4 tumor types, namely, lung, colorectum, breast, and liver. These findings hold significant implications for the prospective clinical application of multiomics correlation in disease management and the exploration of potential therapeutic targets.

Diagnosis of Inflammatory Bowel Disease

Krishnamoorthy et al (2024) stated that VOCs show promise as potential biomarkers of for UC and CD, 2 chronic, idiopathic, GI disorders with diagnostic and management challenges. Non-invasive biomarkers aid early diagnosis and management. In a systematic review and meta-analysis, these investigators examined studies of diagnostic accuracy of VOCs in IBD. They carried out a systematic search on the PubMed and Scopus databases; with 16 studies reviewed and meta-analysis performed on 10. Meta-analysis of 696 IBD cases against 605 controls revealed a pooled sensitivity and specificity of 87 % (95 % CI: 0.79 to 0.92) and 83 % (95 % CI: 0.73 to 0.90), respectively; AUC was 0.92. The authors concluded that VOCs performed very well as non-invasive biomarkers of IBD, with much scope for future improvement and research. Moreover, these researchers stated that prospective, larger, multi-center studies are needed to formulate the best methods of sampling, analyzing, and interpreting VOCs as biomarkers of IBD.

The authors stated that this study had several drawbacks. First, these were all case-control studies and there were no prospective, randomized studies with clear blinding procedures followed. This was reflected in the analysis of the studies by the QUADAS-2 tool where many studies were at risk of bias in the patient selection and index test domains. Second, there was heterogeneity among studies. There did not appear to be any consensus on which is the best VOC medium to analyze -- urine, feces, or breath -- although it is interesting that most studies looked at breath or feces except for 1 study that looked at urine. Breath is easier to sample than urine or feces from a patient point of view, and urine would be easier than feces to sample. There is also no consensus on the best analytical method -- whether it be through the use of more complex metabolomic techniques or electronic noses. However, it was interesting to note that researchers are yet to discover 1 or 2 compounds that are present in disease states compared with the healthy physiological state, for cancer or inflammation. This suggested that the overall picture/variable composition of VOCs is more pertinent, and thus metal oxide-based technology may be more appropriate going forward in this disease group. It also carries the advantage of being operable with minimal training. In addition, the fact that VOCs of all media show correlation with disease states meant that there are more potential future diagnostic targets, rather than being limited to a particular sample type. Third, whereas the studies in this meta-analysis appeared to differentiate IBD from controls very well, it appeared that differentiating UC from CD is more difficult. Nevertheless, the VOC profile of CD patients appeared more distinct than UC or healthy controls. These researchers proposed that this may be because CD is a transmural disease with greater perturbation of metabolic pathways when compared with UC. Fourth, the influence of confounding factors, such as age, gender, BMI, diet, drugs, smoking, and metabolic co-morbidities, into VOC abundance is another facet of this research area that needs further clarification and potential adjustment when using VOCs as biomarkers. For example, smokers would introduce certain exogenous VOCs into breath samples looking for disease; once these are known they could be accounted for, by adjustments to probabilistic neural networks generated from e-nose outputs.

Diagnosis of Parkinson's Disease

Habibzadeh et al (2023) noted that researchers are examining the potential of VOCs obtained from exhaled breath and sebum as non-invasive tools for early diagnosis of Parkinson's disease (PD). In a systematic review and meta-analysis, these investigators examined the feasibility of using VOC analysis for PD diagnosis and determined the overall diagnostic accuracy of the proposed tests. They carried out systematic searches based on the PRISMA guidelines to identify relevant studies on VOCs in PD diagnosis using exhaled breath or sebum samples. The selected studies were described, and meta-analysis was performed on those that provided the sensitivity and specificity data. Out of 1,268 studies initially identified, 8 met the inclusion criteria and provided specific sensitivity and specificity data for PD, which were included in the current meta-analysis. The pooled analysis of these findings showed a mean area under the receiver operating characteristic curve (AUROC) of 0.85, a sensitivity of 0.81 (95 % CI: 0.72 to 0.88), and a specificity of 0.76 (95 % CI: 0.66 to 0.84). The authors concluded that the analysis of VOCs in exhaled breath and sebum has shown promise as a new avenue for non-invasive diagnosis of PD. VOCs' ability to distinguish PD from healthy controls suggested their potential clinical utility in screening for the disease. Consequently, VOCs hold significant potential as biomarkers for PD diagnosis and offer a promising novel approach to identifying and diagnosing the condition.

Furthermore, an UpToDate review on “Diagnosis and differential diagnosis of Parkinson disease” (Chou, 2024) does not mention the use of volatile organic compounds as a management tool.

Prediction of Broncho-Pulmonary Dysplasia in Infants Born Pre-Term

Wright et al (2021) noted that VOCs are hydrocarbons that originate within different healthy and diseased tissues. VOCs can be secreted into the circulation and then excreted in the urine and feces. In the lungs, VOCs are locally produced and can be detected in exhaled breath. VOCs can be identified using non-invasive techniques, which make their use in pre-term infants safe and desirable. These researchers carried out a systematic search of the literature in PubMed, Embase and Web of Science looking for VOCs techniques and diagnostic performance in pre-term infants. A total of 50 studies were identified with 7 included in the final analysis in accordance with the PRISMA guidelines. VOCs could diagnose necrotizing enterocolitis (NEC) up to 4 days before a clinical diagnosis; for late onset sepsis, up to 3 days before; and for broncho-pulmonary dysplasia (BPD), up to 2 weeks before. In addition to these diagnostic uses, VOCs analysis could also distinguish breast-fed from formula-fed pre-term neonates in the 1st month of life. The authors concluded that VOCs analysis is a non-invasive tool that made its use in pre-term infants of preference. Moreover, these investigator stated that VOCs analytic techniques require more research and consensus between researchers to overcome their limitations.

Course et al (2021) stated that VOCs detected in human breath, urine, stool, sweat, saliva, and blood result from metabolic processes in the body during health or disease. Using sophisticated measurement systems, small amounts of these compounds could be detected in the afore-mentioned bodily fluids. Many studies in adults and children have shown the potential of these compounds to differentiate between healthy individuals and patients by detecting profiles of compounds in non-invasively collected samples. However, the detection of biomarkers in VOCs from neonates is especially attractive due to the non-invasive nature of its approach, and its ability to track disease progress by longitudinal sampling. In a systematic review, these investigators examined the literature on the use of VOCs in neonates and identified areas for future research. They noted that there are only a few studies of VOCs in neonates, often with a small number of infants and sometimes from the same cohort. However, these studies should be considered as proof-of-principle showing promise for studying these methodologies in larger longitudinal cohorts of newborn infants with specific conditions such as NEC, sepsis, and BPD. In addition to the issues of prediction and validity, any potential test requires implementation at, or near, the neonatal unit; and a rapid enough result to aid

in guiding the clinician. For some measures this lag maybe acceptable in the region of hours or even days (e.g., the development of chronic lung disorders where results may guide long-term ventilation of respiratory support strategies), while other diseases processes progress much faster and require rapid turn-around to be of clinical use (e.g., developing infections). The authors concluded that stated that detailed studies on VOCs involving neonatal patients including sick pre-term infants and term infants with specific morbidities are needed. These studies should collect longitudinal samples using non-invasive methods for the detection of potential biomarkers.

Romijn et al (2023) examined the predictive performances of exhaled breath VOCs for development of BPD in infants born pre-term. Exhaled breath was collected from infants born less than 30 weeks' gestation at days 3 and 7 of life. Ion fragments detected by GC-MS analysis were employed to derive and internally validate a VOC prediction model for moderate or severe BPD at 36 weeks of post-menstrual age (PMA). These investigators tested the predictive performance of the National Institute of Child Health and Human Development (NICHD) clinical BPD prediction model with and without VOCs. Breath samples were collected from 117 infants (mean gestation of 26.8 ± 1.5 weeks); 33 % of the infants developed moderate or severe BPD. The VOC model showed a c-statistic of 0.89 (95 % CI: 0.80 to 0.97) and 0.92 (95 % CI: 0.84 to 0.99) for the prediction of BPD at days 3 and 7, respectively. Adding the VOCs to the clinical prediction model in non-invasively supported infants resulted in significant improvement in discriminative power on both days (day 3: c-statistic 0.83 versus 0.92, p value of 0.04; day 7: c-statistic 0.82 versus 0.94, p value of 0.03). The authors concluded that the findings of this study might have implications for future research and clinical practice. Early and accurate identification of pre-term infants at risk of developing BPD by a prediction model including clinical predictors and VOCs in exhaled breath will allow new interventions to reduce the risk of BPD in those infants that would benefit most. Identifying a high-risk group of infants with a predicted probability for developing BPD of 60 %, will likely improve the benefit-harm balance on neurologic damage of the already-established treatment with systemic corticosteroids. Lastly, the fact that VOCs in exhaled breath also can be measured in infants on non-invasive support, opened the possibility to significantly improving BPD prediction in a group of infants who were previously thought not to be at risk of developing BPD, an idea that is no longer considered true, given that many of these infants still have significant lung disease and often are managed on non-invasive support with high oxygen requirements. However, external validation of the model in a multi-center setting with the currently identified VOCs is needed before such a prediction model can be used in clinical practice.

The authors stated that this study had several drawbacks. First, this study had a modest sample size, which prevented subgroup analyses for specific patient groups (e.g., infants small for gestational age). In addition, no external validation was carried out. Second, the development of the VOC model was carried out with the exhaled breath samples collected during non-invasive respiratory support since analyses showed significant differences between the non-invasive and invasive samples. Further investigation is needed to examine if a separate VOC model is needed for both respiratory support modalities. Third, although several of the identified VOCs were reported before as potential biomarkers, these researchers could not rule out that their exhaled breath samples included compounds that were rather related to a patient’s exposome, than actual metabolites. Fourth, these investigators excluded the infants who died before the age of 36 weeks of PMA, because it was unclear if they would have developed BPD. Given the uncertainty whether these specific infants would have developed BPD, the sample size was too small to conduct a sensitivity analysis. These researchers stated that future larger studies with a greater number of infants not surviving until 36 weeks of PMA should examine what the discriminating accuracy of the VOC pattern would be including these infants.

Furthermore, an UpToDate review on “Bronchopulmonary dysplasia (BPD): Clinical features and diagnosis” (Eichenwald and Stark, 2024) does not mention the use of volatile organic compounds as a management tool.

References

The above policy is based on the following references:

1. Aathithan S, Plant JC, Chaudry AN, French GL. Diagnosis of bacteriuria by detection of volatile organic compounds in urine using an automated headspace analyzer with multiple conducting polymer sensors. J Clin Microbiol. 2001;39(7):2590-2593.
2. Ahmed WM, Lawal O, Nijsen TM, et al. Exhaled volatile organic compounds of infection: A systematic review. ACS Infect Dis. 2017;3(10):695-710.
3. Alkhouri N, Cikach F, Eng K, et al. Analysis of breath volatile organic compounds as a noninvasive tool to diagnose nonalcoholic fatty liver disease in children. Eur J Gastroenterol Hepatol. 2014;26(1):82-87.
4. Alkhouri N, Eng K, Cikach F, Patel N, et al. Breathprints of childhood obesity: Changes in volatile organic compounds in obese children compared with lean controls. Pediatr Obes. 2015;10(1):23-29.
5. Allers M, Langejuergen J, Gaida A, et al. Measurement of exhaled volatile organic compounds from patients with chronic obstructive pulmonary disease (COPD) using closed gas loop GC-IMS and GC-APCI-MS. J Breath Res. 2016;10(2):026004.
6. Bannaga AS, Farrugia A, Arasaradnam RP. Diagnosing Inflammatory bowel disease using noninvasive applications of volatile organic compounds: A systematic review. Expert Rev Gastroenterol Hepatol. 2019;13(11):1113-1122.
7. Besa V, Teschler H, Kurth I, et al. Exhaled volatile organic compounds discriminate patients with chronic obstructive pulmonary disease from healthy subjects. Int J Chron Obstruct Pulmon Dis. 2015;10:399-406.

8. Brusselmans L, Arnouts L, Millevert C, et al. Breath analysis as a diagnostic and screening tool for malignant pleural mesothelioma: A systematic review. Transl Lung Cancer Res. 2018;7(5):520-536.
9. Catino A, de Gennaro G, Di Gilio A, et al. Breath analysis: A systematic review of volatile organic compounds (VOCs) in diagnostic and therapeutic management of pleural mesothelioma. Cancers (Basel). 2019;11(6).
10. Chen H, Qi X, Zhang L, et al. COVID-19 screening using breath-borne volatile organic compounds. J Breath Res. 2021;15(4).
11. Chou KL. Diagnosis and differential diagnosis of Parkinson disease. UpToDate [online serial], Waltham, MA: UpToDate; reviewed July 2024.
12. Christiansen A, Davidsen JR, Titlestad I, et al. A systematic review of breath analysis and detection of volatile organic compounds in COPD. J Breath Res. 2016;10(3):034002.
13. Coloe PJ. Head-space gas liquid chromatography for rapid detection of Escherichia coli and Proteus mirabilis in urine. J Clin Pathol. 1978;31(4):365-369.
14. Course C, Watkins WJ, Müller CT, et al. Volatile organic compounds as disease predictors in newborn infants: A systematic review. J Breath Res. 2021;15(2).
15. Cozzolino R, De Magistris L, Saggese P, et al. Use of solid-phase microextraction coupled to gas chromatography-mass spectrometry for determination of urinary volatile organic compounds in autistic children compared with healthy controls. Anal Bioanal Chem. 2014;406(19):4649-4662.
16. Dawiskiba T, Deja S, Mulak A, et al. Serum and urine metabolomic fingerprinting in diagnostics of inflammatory bowel diseases. World J Gastroenterol. 2014;20(1):163-174.
17. de Meij TG, van der Schee MP, Berkhout DJ, et al. Early detection of necrotizing enterocolitis by fecal volatile organic compounds analysis. J Pediatr. 2015;167(3):562-567.
18. Douglas IS. New diagnostic methods for pneumonia in the ICU. Curr Opin Infect Dis. 2016;29(2):197-204.
19. Dragonieri S, Quaranta VN, Carratu P, et al. An electronic nose may sniff out amyotrophic lateral sclerosis. Respir Physiol Neurobiol. 2016;232:22-25.
20. Eichenwald EC, Stark AR. Bronchopulmonary dysplasia (BPD): Clinical features and diagnosis. UpToDate [online serial], Waltham, MA: UpToDate; reviewed July 2024.
21. Fan X, Zhong R, Liang H, et al. Exhaled VOC detection in lung cancer screening: A comprehensive meta-analysis. BMC Cancer. 2024;24(1):775.
22. Finamore P, Scarlata S, Cardaci V, Incalzi RA. Exhaled breath analysis in obstructive sleep apnea syndrome: A review of the literature. Medicina (Kaunas). 2019;55(9):538.
23. Gaida A, Holz O, Nell C, et al. A dual center study to compare breath volatile organic compounds from smokers and non-smokers with and without COPD. J Breath Res. 2016;10(2):026006.
24. Griebling TL. Urinary Tract Infection in Women. In: Urologic Diseases in America. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. MS Litwin, CS Saigal, eds. NIH Publication No. 04–5512. Washington, DC: US Government Publishing Office; 2004:169-183.
25. Guernion N, Ratcliffe NM, Spencer-Phillips PT, Howe RA. Identifying bacteria in human urine: Current practice and the potential for rapid, near-patient diagnosis by sensing volatile organic compounds. Clin Chem Lab Med. 2001;39(10):893-906.
26. Habibzadeh A, Ostovan VR, Keshavarzian O, et al. Volatile organic compounds analysis as promising biomarkers for Parkinson's disease diagnosis: A systematic review and meta-analysis. Clin Neurol Neurosurg. 2023;235:108022.
27. Hanna GB, Boshier PR, Markar SR, Romano A. Accuracy and methodologic challenges of volatile organic compound-based exhaled breath tests for cancer diagnosis: A systematic review and meta-analysis. JAMA Oncol. 2019;5(1): e182815.
28. Hanouneh IA, Zein NN, Cikach F, et al. The breathprints in patients with liver disease identify novel breath biomarkers in alcoholic hepatitis. Clin Gastroenterol Hepatol. 2014;12(3):516-523.
29. Hayward NJ. Head-space gas-liquid chromatography for the rapid laboratory diagnosis of urinary tract infections caused by enterobacteria. J Chromatogr. 1983;274:27-35.
30. Hertel M, Schuette E, Kastner I, et al. Volatile organic compounds in the breath of oral candidiasis patients: A pilot study. Clin Oral Investig. 2018;22(2):721-731.
31. Horvath I, Barnes PJ, Loukides S, et al. A European Respiratory Society technical standard: Exhaled biomarkers in lung disease. Eur Respir J. 2017;49(4).
32. Hua Q, Zhu Y, Liu H. Detection of volatile organic compounds in exhaled breath to screen lung cancer: A systematic review. Future Oncol. 2018;14(16):1647-1662.
33. Janssens E, van Meerbeeck JP, Lamote K, et al. Volatile organic compounds in human matrices as lung cancer biomarkers: A systematic review. Crit Rev Oncol Hematol. 2020;153:103037.
34. Jiang H, Wang C, Ren M, et al. Blood volatile organic compounds as potential biomarkers for amyotrophic lateral sclerosis: An animal study in the SOD1 G93A mouse. J Mol Neurosci. 2015;55(1):167-173.
35. Kodogiannis V, Wadge E. The use of gas-sensor arrays to diagnose urinary tract infections. Int J Neural Syst. 2005;15(5):363-376.
36. Kodogiannis VS, Lygouras JN, Tarczynski A, Chowdrey HS. Artificial odor discrimination system using electronic nose and neural networks for the identification of urinary tract infection. IEEE Trans Inf Technol Biomed. 2008;12(6):707-713.
37. Krishnamoorthy A, Chandrapalan S, Ahmed M, Arasaradnam RP. The diagnostic utility of volatile organic compounds in inflammatory bowel disease: A systematic review and meta-analysis. J Crohns Colitis. 2024;18(2):320-330.

38. Kuppers L, Holz O, Schuchardt S, et al. Breath volatile organic compounds of lung transplant recipients with and without chronic lung allograft dysfunction. J Breath Res. 2018;12(3):036023.
39. Kurada S, Alkhouri N, Fiocchi C, et al. Review article: Breath analysis in inflammatory bowel diseases. Aliment Pharmacol Ther. 2015;41(4):329-341.
40. Leja M, Kortelainen JM, Polaka I, et al. Sensing gastric cancer via point-of-care sensor breath analyzer. Cancer. 2021;127(8):1286-1292.
41. Liangou A, Tasoglou A, Huber HJ, et al. A method for the identification of COVID-19 biomarkers in human breath using proton transfer reaction time-of-flight mass spectrometry. EClinicalMedicine. 2021;42:101207.
42. Lumbiganon P, Laopaiboon M, Thinkhamrop J. Screening and treating asymptomatic bacteriuria in pregnancy. Curr Opin Obstet Gynecol. 2010;22(2):95-99.
43. Lung cancer and cancer of the pleura. In: Pulmonary (acute & chronic). Encinitas, CA: Work Loss Data Institute; October 29, 2013.
44. Manja KS, Rao KM. Gas-chromatographic detection of urinary tract infections caused by Escherichia coli and Klebsiella sp. J Clin Microbiol. 1983;17(2):264-266.
45. Markar SR, Wiggins T, Kumar S, Hanna GB. Exhaled breath analysis for the diagnosis and assessment of endoluminal gastrointestinal diseases. J Clin Gastroenterol. 2015;49(1):1-8.
46. Mochalski P, King J, Haas M, et al. Blood and breath profiles of volatile organic compounds in patients with end-stage renal disease. BMC Nephrol. 2014;15(1):43.
47. Mochalski P, Leja M, Gasenko E, et al. Ex vivo emission of volatile organic compounds from gastric cancer and non-cancerous tissue. J Breath Res. 2018;12(4):046005.
48. Monteiro M, Moreira N, Pinto J, et al. GC-MS metabolomics-based approach for the identification of a potential VOC-biomarker panel in the urine of renal cell carcinoma patients. J Cell Mol Med. 2017;21(9):2092-2105.
49. Navaneethan U, Parsi MA, Gutierrez NG, et al. Volatile organic compounds in bile can diagnose malignant biliary strictures in the setting of pancreatic cancer: A preliminary observation. Gastrointest Endosc. 2014;80(6):1038-1045.
50. Oakley-Girvan I, Davis SW. Breath based volatile organic compounds in the detection of breast, lung, and colorectal cancers: A systematic review. Cancer Biomark. 2017;21(1):29-39.
51. Orenstein R, Wong ES. Urinary tract infections in adults. Am Fam Physician. 1999;59(5):1225-1234.
52. Patel N, Alkhouri N, Eng K, et al. Metabolomic analysis of breath volatile organic compounds reveals unique breathprints in children with inflammatory bowel disease: A pilot study. Aliment Pharmacol Ther. 2014;40(5):498-507.
53. Pavlou A, Turner AP, Magan N. Recognition of anaerobic bacterial isolates in vitro using electronic nose technology. Lett Appl Microbiol. 2002;35(5):366-369.
54. Pavlou AK, Magan N, McNulty C, et al. Use of an electronic nose system for diagnoses of urinary tract infections. Biosens Bioelectron. 2002;17(10):893-899.
55. Pavlou AK, Turner AP. Sniffing out the truth: Clinical diagnosis using the electronic nose. Clin Chem Lab Med. 2000;38(2):99-112.
56. Peel A, Wang R, Ahmed W, et al. Changes in exhaled volatile organic compounds following indirect bronchial challenge in suspected asthma. Thorax. 2023;78(10):966-973.
57. Pelling M, Chandrapalan S, West E, Arasaradnam RP. A systematic review and meta-analysis: Volatile organic compound analysis in the detection of hepatobiliary and pancreatic cancers. Cancers (Basel). 2023;15(8):2308.
58. Queralto N, Berliner AN, Goldsmith B, et al. Detecting cancer by breath volatile organic compound analysis: A review of array-based sensors. J Breath Res. 2014;8(2):027112.
59. Reeves N, Phillips S, Hughes A, et al. Volatile organic compounds in the early diagnosis of non-healing surgical wounds: A systematic review. World J Surg. 2022;46(7):1669-1677.
60. Romijn M, van Kaam AH, Fenn D, et al. Exhaled volatile organic compounds for early prediction of bronchopulmonary dysplasia in infants born preterm J Pediatr. 2023;257:113368.
61. Rufo JC, Madureira J, Fernandes EO, Moreira A. Volatile organic compounds in asthma diagnosis: A systematic review and meta-analysis. Allergy. 2016;71(2):175-188.
62. Shlomo IB, Frankenthal H, Laor A, Greenhut AK. Detection of SARS-CoV-2 infection by exhaled breath spectral analysis: Introducing a ready-to-use point-of-care mass screening method. EClinicalMedicine. 2022 Mar;45:101308.
63. Subali AD, Wiyono L, Yusuf M, et al. The potential of volatile organic compounds-based breath analysis for COVID-19 screening: A systematic review & meta-analysis. Diagn Microbiol Infect Dis. 2022;102(2):115589.
64. Sun X, Shao K, Wang T. Detection of volatile organic compounds (VOCs) from exhaled breath as noninvasive methods for cancer diagnosis. Anal Bioanal Chem. 2016;408(11):2759-2780.
65. Terrington D, Hayton C, Peel AM, et al. The role of measuring exhaled breath biomarkers in sarcoidosis: A systematic review. J Breath Res. 2019;13(3):036015.
66. Teixeira RC, IJdema D, Gomez C, et al. The electronic nose as a rule-out test for tuberculosis in an indigenous population. J Intern Med. 2021;290(2):386-391.
67. Toreyin ZN, Ghosh M, Goksel O, et al. Exhaled breath analysis in diagnosis of malignant pleural mesothelioma: systematic review. Int J Environ Res Public Health. 2020;17(3):1110.
68. Turner AP, Magan N. Electronic noses and disease diagnostics. Nat Rev Microbiol. 2004;2(2):161-166.
69. U.S. Food and Drug Administration (FDA). The Osmetech Microbial Analyser ä Urinary Tract Infection Detector. 510(K) Premarket Notification Summary. 510k) No. K011043. Rockville, MD: FDA; November 30, 2001.
70. van der Sar IG, Moor CC, Oppenheimer JC, et al. Diagnostic performance of electronic nose technology in sarcoidosis. Chest. 2022;161(3):738-747.

71. van Liere ELSA, van Dijk LJ, Bosch S, et al. Urinary volatile organic compounds for colorectal cancer screening: A systematic review and meta-analysis. Eur J Cancer. 2023;186:69-82.
72. van Mastrigt E, de Jongste JC, Pijnenburg MW. The analysis of volatile organic compounds in exhaled breath and biomarkers in exhaled breath condensate in children - clinical tools or scientific toys? Clin Exp Allergy. 2015;45(7):1170-1188.
73. van Vliet D, Smolinska A, Jobsis Q, et al. Can exhaled volatile organic compounds predict asthma exacerbations in children? J Breath Res. 2017;11(1):016016.
74. Wang C, Li P, Lian A, et al. Blood volatile compounds as biomarkers for colorectal cancer. Cancer Biol Ther. 2014b;15(2):200-206.
75. Wang C, Sun B, Guo L, et al. Volatile organic metabolites identify patients with breast cancer, cyclomastopathy, and mammary gland fibroma. Sci Rep. 2014a;4:5383.
76. Wang D, Wang C, Pi X, et al. Urinary volatile organic compounds as potential biomarkers for renal cell carcinoma. Biomed Rep. 2016;5(1):68-72.
77. Wang M, Xie R, Jia X, Liu R. Urinary volatile organic compounds as potential biomarkers in idiopathic membranous nephropathy. Med Princ Pract. 2017;26(4):375-380.
78. Wen Q, Boshier P, Myridakis A, et al. Urinary volatile organic compound analysis for the diagnosis of cancer: A systematic literature review and quality assessment. Metabolites. 2020;11(1):17.
79. Wilson AD, Forse LB. Potential for early noninvasive COVID-19 detection using electronic-nose technologies and disease-specific VOC metabolic biomarkers. Sensors (Basel). 2023;23(6):2887.
80. Wright H, Bannaga AS, Iriarte R, et al. Utility of volatile organic compounds as a diagnostic tool in preterm infants. Pediatr Res. 2021;89(2):263-268.
81. Yuan JM, Butler LM, Gao YT, et al. Urinary metabolites of a polycyclic aromatic hydrocarbon and volatile organic compounds in relation to lung cancer development in lifelong never smokers in the Shanghai Cohort Study. Carcinogenesis. 2014;35(2):339-345.
82. Zeft A, Costanzo D, Alkhouri N, et al. A122: Metabolomic analysis of breath volatile organic compounds reveals unique breathprints in children with juvenile idiopathic arthritis. Arthritis Rheumatol. 2014;66 Suppl 11:S159.
83. Zhang X, Gui X, Zhang Y, et al. A panel of bile volatile organic compounds servers as a potential diagnostic biomarker for gallbladder cancer. Front Oncol. 2022;12:858639.
84. Zhou M, Wang Q, Lu X, et al. Exhaled breath and urinary volatile organic compounds (VOCs) for cancer diagnoses, and microbial-related VOC metabolic pathway analysis: A systematic review and meta-analysis. Int J Surg. 2024;110(3):1755-1769.
85. Zhou W, Tao J, Li J, Tao S. Volatile organic compounds analysis as a potential novel screening tool for colorectal cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2020;e20937.

Policy History

- Last Review 10/10/2024

  Effective: 10/04/2005

  Next Review: 08/14/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes