Prior Authorization Review Panel  
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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<th>Plan: Aetna Better Health</th>
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**Type of Submission – Check all that apply:**
- [x] New Policy
- [ ] Revised Policy*
- [ ] Annual Review – NoRevisions
- [ ] Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0717 Analysis of Volatile Organic Compounds**

This CPB has been revised to state that analysis of volatile organic compounds is considered experimental and investigational for diagnosis and monitoring of pleural mesothelioma and sarcoidosis.

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<th>Name of Authorized Individual (Please type or print):</th>
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<td>Dr. Bernard Lewin, M.D.</td>
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Proprietary  
Revised July 22, 2019
Analysis of Volatile Organic Compounds

Number: 0717

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers the analysis of volatile organic compounds experimental and investigational 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., breast cancer, colorectal cancer, esophagogastric cancer, gastric cancer, 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)

Policy History

Last Review
10/05/2019
Effective: 10/04/2005
Next Review: 07/24/2020

Definitions

Additional Information
Clinical Policy Bulletin
Notes
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: (i) 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; (ii) the detection of volatile compounds is limited by the present array of sensors; therefore, other significant volatile compounds could be missed; (iii) bacterial volatile products could be lost, either by adsorption onto urinary cells or protein or by dissipation during delays between specimen collection and analysis; (iv) some bacterial species may not produce volatile compounds; and (v) 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-methylbutanal, 2-methylbutanal, 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 cyclomastopathy 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 cyclomastopathy, 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 cyclomastopathy (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-decane, 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-decane; 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 (α = 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 \[10.94 + 1.8229 \times \log (\text{acetaldehyde}) + 0.7600 \times \log (\text{acetone}) - 1.1746 \times \log (\text{dimethyl sulfide}) + 1.0901 \times \log (\text{isoprene}) - \]
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.

Queraltó 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: (i) NEC, (ii) sepsis, and (iii) matched controls. Three time windows were defined: (i) T-5, T-4 (5 and 4 days before diagnosis); (ii) T-3, T-2 (3 and 2 days before diagnosis); and (iii) 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 ≤ 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 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.

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.

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 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-pentenyldene)-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.
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 (PLS-DA) 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: (i) 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, (ii) 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 Breast, Colon, Gastric, Lung, and Rectum 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.

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.
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.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

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<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
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<tr>
<td>B37.0</td>
<td>Candidal stomatitis</td>
</tr>
<tr>
<td>C00.0 - C96.9</td>
<td>Malignant neoplasms</td>
</tr>
<tr>
<td>D00.1</td>
<td>Carcinoma in situ of esophagus</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>D00.2</td>
<td>Carcinoma in situ of stomach</td>
</tr>
<tr>
<td>D05.00 - D05.92</td>
<td>Carcinoma in situ of breast</td>
</tr>
<tr>
<td>D24.1 - D24.9</td>
<td>Benign neoplasm of breast</td>
</tr>
<tr>
<td>D48.60 - D48.62</td>
<td>Neoplasm of uncertain behavior of breast</td>
</tr>
<tr>
<td>D49.3</td>
<td>Neoplasm of unspecified behavior of breast</td>
</tr>
<tr>
<td>D86.0 - D86.89</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>E66.01 - E67.8</td>
<td>Overweight, obesity and other hyperalimentation [prediction of development of childhood obesity]</td>
</tr>
<tr>
<td>F84.0 - F84.9</td>
<td>Pervasive developmental disorders [autism spectrum disorders]</td>
</tr>
<tr>
<td>G12.21</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>G70.00 - G70.9</td>
<td>Myasthenia gravis and other myoneural disorders</td>
</tr>
<tr>
<td>J18.9</td>
<td>Pneumonia, unspecified organism</td>
</tr>
<tr>
<td>J41.0 - J42</td>
<td>Simple and mucopurulent chronic bronchitis</td>
</tr>
<tr>
<td>J43.0 - J43.9</td>
<td>Emphysema</td>
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<tr>
<td>J44.0 - J44.9</td>
<td>Chronic obstructive pulmonary disease, unspecified</td>
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<tr>
<td>J45.20 - J45.998</td>
<td>Asthma</td>
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<tr>
<td>J84.89</td>
<td>Other specified interstitial pulmonary diseases. [for bronchiolitis obliterans syndrome in lung transplant recipients]</td>
</tr>
<tr>
<td>K50.00 - K50.919</td>
<td>Crohn's disease [regional enteritis]</td>
</tr>
<tr>
<td>K51.00 - K51.919</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>K58.0 - K58.9</td>
<td>Irritable bowel syndrome</td>
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<tr>
<td>K70.10 - K70.11</td>
<td>Alcoholic hepatitis with or without ascites</td>
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<tr>
<td>K76.0</td>
<td>Fatty (change of) liver, not elsewhere classified [non-alcoholic]</td>
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<tr>
<td>K90.0</td>
<td>Celiac disease</td>
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<tr>
<td>M08.00 - M08.99</td>
<td>Juvenile arthritis</td>
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<tr>
<td>N03.0 - N05.9</td>
<td>Chronic nephritic syndrome</td>
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<tr>
<td>N18.6</td>
<td>End stage renal disease [use as markers for monitoring hemodialysis efficiency]</td>
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<tr>
<td>N39.0</td>
<td>Urinary tract infection, site not specified [bacteriuria]</td>
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<tr>
<td>N60.01 - N65.1</td>
<td>Disorders of breast</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>P77.1 - P77.9</td>
<td>Necrotizing enterocolitis of newborn [prediction of development of necrotizing enterocolitis]</td>
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<tr>
<td>T86.810 - T86.819</td>
<td>Complications of lung transplant [for bronchiolitis obliterans syndrome in lung transplant recipients]</td>
</tr>
<tr>
<td>Z12.0 - Z12.9</td>
<td>Encounter for screening for malignant neoplasms</td>
</tr>
<tr>
<td>Z99.2</td>
<td>Dependence on renal dialysis [use as markers for monitoring hemodialysis efficiency]</td>
</tr>
</tbody>
</table>

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Amendment to
Aetna Clinical Policy Bulletin Number: 0717
Analysis of Volatile Organic Compounds

There are no amendments for Medicaid.