Analysis of Volatile Organic Compounds

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 cancer (e.g., breast cancer, colorectal cancer, esophagogastric cancer, lung cancer and cancer of the pleura, pancreatic cancer, and renal cancer; not an all-inclusive list)
- Diagnosis of alcoholic hepatitis
- Diagnosis of asthma
- Diagnosis of autism spectrum disorders
- Diagnosis of celiac disease
- Diagnosis of inflammatory bowel disease
- Diagnosis of juvenile idiopathic arthritis
- Diagnosis of neuromuscular disease (e.g., amyotrophic lateral sclerosis)

Policy History

Last Review 08/11/2016
Effective: 10/04/2005
Next Review: 08/10/2017

Definitions

Additional Information

Clinical Policy Bulletin Notes
- Diagnosis of non-alcoholic fatty liver disease
- Differential diagnosis of breast diseases (e.g., breast cancer, cyclomastopathy, and mammary gland fibroma)
- Prediction of development of childhood obesity
- Prediction of development of necrotizing enterocolitis
- 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: (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 (OMÄä-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 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-butane
diol, 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 overweight 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 overweight/obese children compared with their lean counterparts. Single exhaled breath was collected and analyzed per protocol using SIFT-MS. A total of 60 overweight/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 overweight/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 misclassifications; 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 fingerprinting 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 \[10.94 + 1.8229 \times \log(\text{acetaldehyde}) + 0.7600 \times \log(\text{acetone}) - 1.1746 \times \log(\text{dimethyl sulfide}) + 1.0901 \times \log(\text{isoprene}) - 2.1401 \times \log(\text{trimethylamine}) \geq 10\] 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 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 NO levels were elevated ($p < 1.5$ 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 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 Mastriigt 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 $63.5 \pm 12.3$ years), and 20 healthy controls (mean age of $58.1 \pm 4.4$) 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 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-pentenylidene)-2,2,3,3-tetramethylcyclopropane; 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-tetramethylpentadecane. 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.

<table>
<thead>
<tr>
<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</strong></td>
</tr>
<tr>
<td><strong>ICD-10 codes will become effective as of October 1, 2015:</strong></td>
</tr>
<tr>
<td><strong>There is no specific code for analysis of volatile organic compounds:</strong></td>
</tr>
<tr>
<td><strong>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</strong></td>
</tr>
<tr>
<td>C00.0 - C96.9</td>
</tr>
<tr>
<td>D05.00 - D05.92</td>
</tr>
<tr>
<td>D24.1 - D24.9</td>
</tr>
<tr>
<td>D48.60 - D48.62</td>
</tr>
<tr>
<td>D49.3</td>
</tr>
<tr>
<td>Code</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>E66.01 -</td>
</tr>
<tr>
<td>E67.8</td>
</tr>
<tr>
<td>F84.0 -</td>
</tr>
<tr>
<td>F84.9</td>
</tr>
<tr>
<td>G12.21</td>
</tr>
<tr>
<td>K50.00 -</td>
</tr>
<tr>
<td>K50.919</td>
</tr>
<tr>
<td>K51.00 -</td>
</tr>
<tr>
<td>K51.919</td>
</tr>
<tr>
<td>K58.0 -</td>
</tr>
<tr>
<td>K58.9</td>
</tr>
<tr>
<td>K70.10 -</td>
</tr>
<tr>
<td>K70.11</td>
</tr>
<tr>
<td>K76.0</td>
</tr>
<tr>
<td>M08.00 -</td>
</tr>
<tr>
<td>M08.99</td>
</tr>
<tr>
<td>N18.6</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>N39.0</td>
</tr>
<tr>
<td>N60.01 -</td>
</tr>
<tr>
<td>N65.1</td>
</tr>
<tr>
<td>P77.1 -</td>
</tr>
<tr>
<td>P77.9</td>
</tr>
<tr>
<td>Z12.0 -</td>
</tr>
<tr>
<td>Z12.9</td>
</tr>
<tr>
<td>Z99.2</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

2. Hayward NJ. Head-space gas-liquid chromatography for


AETNA BETTER HEALTH® OF PENNSYLVANIA

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

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania
Updated 03/01/2017