Volatolomics in healthcare and its advanced detection technology

Wenwen Hu[1,§], Weiwei Wu[2,§], Yingying Jian[2,§], Hossam Haick[3], Guangjian Zhang[4], Yun Qian[5] (✉), Miaomiao Yuan[6] (✉), and Mingshui Yao[7,8] (✉)

[1] *School of Aerospace Science and Technology, Xidian University, Xi'an 730107, China*
[2] *Interdisciplinary Research Center of Smart Sensors, School of Advanced Materials and Nanotechnology, Xidian University, Xi'an 730107, China*
[3] *Faculty of Chemical Engineering and Russell Berrie Nanotechnology Institute, Technion-Israel Institute of Technology, Haifa 3200002, Israel*
[4] *Department of Thoracic Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China*
[5] *Stomatology Hospital, School of Stomatology, Zhejiang University School of Medicine, Clinical Research Center for Oral Diseases of Zhejiang Province Key Laboratory of Oral Biomedical Research of Zhejiang Province, Cancer Center of Zhejiang University, Hangzhou 310006, China*
[6] *The Eighth Affiliated Hospital, Sun Yat-sen University, Shenzhen 518033, China*
[7] *State Key Laboratory of Multi-phase Complex Systems, Institute of Process Engineering, Chinese Academy of Sciences, Beijing 310006, China*
[8] *Institute for Integrated Cell-Material Sciences, Kyoto University Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan*
[§] *Wenwen Hu, Weiwei Wu, and Yingying Jian contributed equally to this work.*

ABSTRACT

Various diseases increasingly challenge the health status and life quality of human beings. Volatolome emitted from patients has been considered as a potential family of markers, volatolomics, for diagnosis/screening. There are two fundamental issues of volatolomics in healthcare. On one hand, the solid relationship between the volatolome and specific diseases needs to be clarified and verified. On the other hand, effective methods should be explored for the precise detection of volatolome. Several comprehensive review articles had been published in this field. However, a timely and systematical summary and elaboration is still desired. In this review article, the research methodology of volatolomics in healthcare is critically considered and given out, at first. Then, the sets of volatolome according to specific diseases through different body sources and the analytical instruments for their identifications are systematically summarized. Thirdly, the advanced electronic nose and photonic nose technologies for volatile organic compounds (VOCs) detection are well introduced. The existed obstacles and future perspectives are deeply thought and discussed. This article could give a good guidance to researchers in this interdisciplinary field, not only understanding the cutting-edge detection technologies for doctors (medicinal background), but also making reference to clarify the choice of aimed VOCs during the sensor research for chemists, materials scientists, electronics engineers, etc.

KEYWORDS

volatolomics, electronic nose, disease diagnosis, sensor, artificial olfaction, volatile organic compounds

1   Introduction

Healthcare is the permanent motif for human beings, which is now greatly challenged by cancers, cardiovascular diseases, infectious diseases, etc. [1]. For example, it has been estimated that there will be ca. 1.918 million diagnosed new cases and ca. 0.609 million deaths of cancer in USA, 2022 (Fig. 1) [2]. If those malignant tumors could be effectively diagnosed at an early stage [3], through screening of high-risk groups, timely treatment of malignant tumors can significantly stop the tumor fast-growing, lower the ratio of recurrence, and reduce the risk of patient mortality [4]. Besides cancers, other diseases, such as tuberculosis [5], COVID-19 [6], etc., also have a strong desire to achieve fast, early, and accurate diagnosis to not only suppress the spread of diseases but also to guide the early treatment after infections.

A precise and early diagnosis is the starting point of all clinical activities [7]. Clinical auxiliary diagnosis includes laboratory examination and special examination [8]. Laboratory examinations such as physical, chemical, and biological methods are used to detect the patient's blood, body fluids, secretions, excretions, or diseased tissue to determine etiological, pathological, or functional data [9]. Through special examinations such as X-ray, electrocardiogram, electroencephalogram, ultrasound, endoscopy and computed tomography, the location and shape of the lesions are determined [10]. Due to methodological constraints, auxiliary diagnosis has limitations [8], such as low sensitivity or specificity, invasive examination, long time, etc. Pathological diagnosis also relies on accurate sampling and high professionalism [11]. Therefore, it is necessary to develop convenient, efficient, and accurate diagnostic methods. In recent years, a lot of new diagnostic methods have emerged. Among them, volatolomics is one of the more valuable ones that may be used as a new development direction of future diagnostics [12–14], which is the non-invasive detection of volatile organic compounds (VOCs) emitted from patients.

VOCs are organic chemicals that have a high vapor pressure at

Estimated new cases

		Males	Females			
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	**983,160**	**100%**	**All sites**	**934,870**	**100%**

Estimated deaths

		Males	Females			
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	**322,090**	**100%**	**All sites**	**287,270**	**100%**

Figure 1 Ten leading cancer types for the estimated new cancer cases and deaths by sex, USA, 2022. Estimates are rounded to the nearest 10 and exclude basal cell and squamous cell skin cancers and *in-situ* carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data. Reproduced with permission from Ref. [2]. © Siegel, R. L. et al. 2022.

room temperature, i.e., low boiling points roughly in the range of 50 to 250 °C [15–17]. Most VOCs have unique odors [12, 18, 19]. There is a consensus between eastern and western traditional diagnosis of methodologies that smelling the breath from the upper respiration tract is an effective way for clarifying health conditions both in Hippocrates's Book of Prognostic written in 400 B.C. [20] and Bian Que's book of "The Yellow Emperor's Canon of 81 Difficult Issues" written in ca. 200 B.C. [21]. The nature of these diseases related special smells is caused by different VOCs, which is demonstrated by the nobel prize laureate that Linus Pauling's pioneer work on the breath analysis in 1971 using gas–liquid partition chromatography [22]. In the past 50 years, thousands of volatile biomarkers, i.e., VOCs, associated with various diseases or lesions, have been identified and classified from multi-body sources (Fig. 2) [23]. It boosts the development of this new era, volatolomics, such as human exhalation [18], skin emanations [24], urine headspace [25], blood [26], and feces [27], towards good-efficient, high-accuracy non-invasive, and painless disease diagnosis/screening.

Before the volatolomics diagnosis could be accepted as a new clinical golden standard, two major concerns should be well answered. One is what the solid relationship, between the specific set of volatolome and the aimed disease is, viz., what the volatolomics (bio-/chemical markers) of a special disease is. The other one is how the volatolome can be accurately and specifically detected and recognized in the real environment fulfilled with confounding factors. According to these two concerns, what is the philosophy of research methodology to answer these questions in
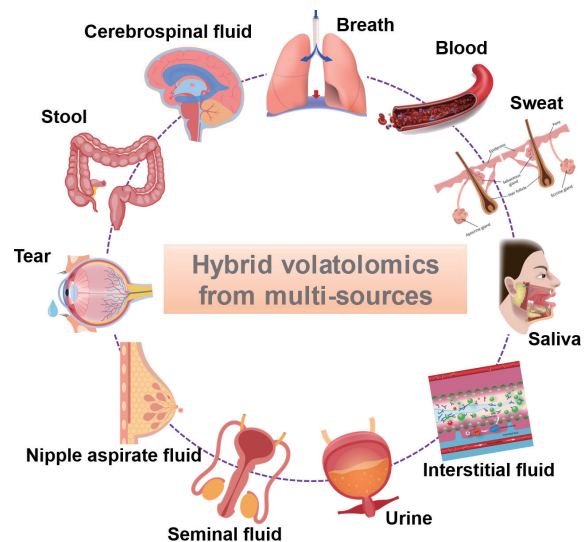
Figure 2 The scheme of hybrid volatolomics and the multiple VOCs sources.

such an interdisciplinary research field? Some critical review articles had been published [28–32], in which these concerns were partly considered. However, a systematical summary and elaboration is still necessary. In this review article, the research methodology of volatolomics in healthcare is critically thought and given out. Then, the sets of volatolome according to specific diseases through different body sources, and the analytical instruments for their identifications are systematically

summarized. Thirdly, the advanced electronic nose (E-nose) and photonic nose (P-nose) technologies for VOCs detection are well introduced. The existed obstacles and future perspectives are deeply thought and discussed. This article could give a good guidance to researchers in this interdisciplinary field, not only understanding the cutting-edge detection technologies for doctors (medicinal background), but also referring to clarify the choice of aimed VOCs during the sensor research for chemists, materials scientists, electronics engineers, etc.

2   The research methodology of volatolomics in healthcare

The emitted volatolome are complicated mixtures with confounding factors, e.g., food, smoking, alcohol drinking, environmental pollutions, etc., no matter which sources of the human body they come from. Therefore, to ensure the successful application in healthcare, a universal methodology is required to make all research results comparable. A brief introduction is depicted as a flow chart in Fig. 3.

First, volatolomics, the accurate bio-/chemical markers associated with the specific diseases, needs to be identified by analytical instrumental approaches, such as gas chromatography-mass spectrometry (GC-MS) [33–36], gas chromatography time-of-flight mass spectrometry (GC-ToF-MS) [37–39], etc., which is the building block of this new era. In addition, it is worth mentioning that the analytical instrumental approaches are still the most accurate way to analyze volatolome mixtures, although they are expensive, time-assuming, and high skill threshold. Nowadays, with the development of data mining technology, e.g., association analysis, clusters analysis, classification, and regression [40], accurate results can be obtained efficiently, facing big and complicated clinical data when all of them use the same sampling method.

Second, the sensing technology, E-nose [41] and P-nose [42], including sensitive materials, fabrications, recognition algorithm, etc., need to be developed according to the identified volatolome markers. In detail, the interaction between the volatolome and sensitive materials, needs to be well designed and verified according to different conditions. For example, in the disposable application such as P-nose, one-lock one-key strategy is widely used [28]. The sensor devices of fabrication process also need to be well considered. For example, the uniformity, scalability, and reproducibility of fabrication technology should be considered at the starting stage of research to narrow the big gap between laboratory and industry. The recognition algorithm is an effective tool to analyze data. The core includes feature's extraction and analysis (cluster, separation, etc.) [43]. Good research on recognition algorithms not only can enhance the performance of

E-nose and P-nose, but also can help the researchers to understand the sensing mechanism through the extracted features. In one word, the development of sensing technology is based on the volatolomics, and then, verified by the volatolomics.

Third, the developed sensors need to be validated by strict clinical trials with confounding factors. In this stage, the recognition algorithm is further trained by the real samples from the patients. The larger number of the tested patients, the more precise algorithm is, which is the precondition of the success in the blind test. After that, volatolomics might be considered as a candidate of golden standard of diagnostics. Till that, the volatolomics can start to apply the admission from food and drug administration (FDA), and might be authorized in the future.

3   The volatolomics of specific diseases from different body sources

3.1   The volatile organic compounds in breath and their associated diseases

Human breath is a gas exchange process mainly for inhaling O_2 and exhaling CO_2. Accompanying this process, large amounts of volatile metabolites are produced in some normal and abnormal metabolic biochemical pathways. Currently, various kinds of VOCs have been found in breath samples, thus, making it the most examined VOC source. The main pathways for adding VOCs to breath include but are not limited as:

• From the viewpoint of thermodynamics, there is a VOCs equilibrium distribution between "fat–blood–breath". The concentrations of VOCs in each part follow the fat–blood (λ_{fb}) and blood–air (λ_{bra}) equilibrium partition coefficients. Most cancer related VOCs are transported from different body sources to breathe in this way (Path ①) [44–58].

• The cell/tissue lesion in the mouth, on the inner surface of the alimentary canal and stomach, i.e., their headspace connects the respiratory tract, can directly emit VOCs to the breath (Path ②) [33, 45, 59–71].

• Infections caused odorous metabolites in the surrounded micro-environment, e.g., oral interstitial, helicobacter pylori, lung tuberculosis infections, etc., can directly emit VOCs to the breath (Path ③) [72–78].

Most diseases related VOCs, as shown in Fig. 4, and summarized in Table 1, are emitted along one or combined paths. The percentage's sum of alkane and alkene are higher in Alzheimer, lung cancer, breast cancer, colorectal cancer, Parkinson, head-and-neck cancer, and renal disease patients' breath, than those in others. This means such VOCs transport mainly, but not limited, along the Path ①, viz., "fat–blood–breath" routine. The percentage's sum of aldehyde, ketone, nitrile, amine, ester, alcohol, acid, i.e., polar VOCs, are higher in the gastrointestinal disease, gastric cancer, pulmonary arterial, and asthma patients' breath, than those in others. These diseases can directly emit their metabolites into the breath, i.e., they are mainly, but not limited, along the Path ②. The halitosis, chronic obstructive pulmonary disease (COPD), and tuberculosis are mainly along Path ③ and other combined paths.

3.2   Volatile organic compounds in blood and their associated diseases

Blood circulates in the whole body, exchange, and transport substance in most bio-chemical process, reflect the real-time nutritional, metabolic, and immune status. Theoretically, blood volatolomics could reveal full information of all diseases in the human body. The blood-related VOCs metabolic processes can be classified into two categories as follow:
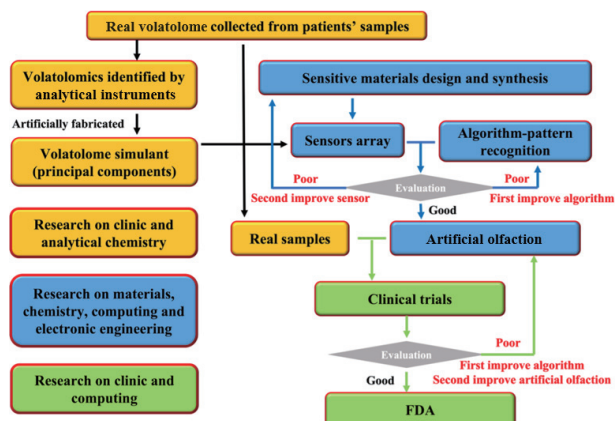

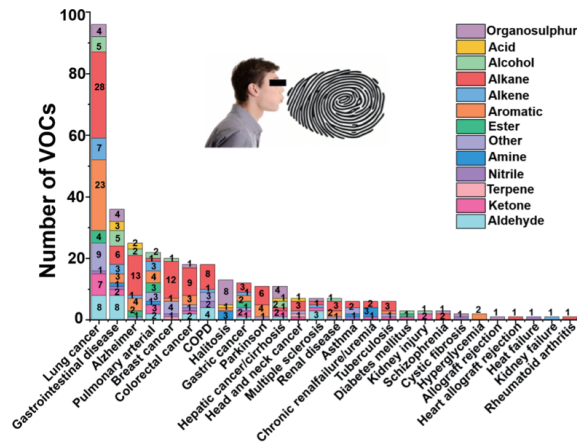**Figure 3**   The research methodology of volatolomics in healthcare.

Figure 4 The summary of the number of VOCs' kinds in the breath of different patients (data from Table 1).

• Exogenous VOCs, e.g., food, air pollution, and smoking, cause indirect oxidative stress. Those VOCs leak into the cytoplasm, then, attach to organs or organelles. The subsequent peroxidative damage to proteins, PUFAs and DNA produce VOCs that partially exchange into blood (Path ②) [30, 79].

Till now, many studies only examined the VOC profiles through *in-vitro* cell experiments that are greatly different from the real conditions surrounding tissue and blood vessels. The aforementioned thermodynamics model about VOCs equilibrium distribution between "fat–blood" decides the VOCs input by the fat–blood coefficient (λ_{fb}). The exchange processes of VOCs from blood to breath, urine, feces, and other things dominate the output. Therefore, the input and output of the blood VOCs decide the compositions and concentrations. However, in fact, the studies of volatolomics are not well concerned compared with the studies on biomarkers in blood. Very few researches show the VOCs in liver cancer, lung cancer, and hepatic cancer patients' blood as shown in Fig. 5 and summarized in Table 2. The less kinds of VOCs than that in breath and urine seem lost large amounts of information. The possible reasons might be:

• Damage to the cells by reactive oxygen species through direct oxidative stress processes generates a major source of VOCs that partially exchange into blood (Path ①) [32].

Table 1 The summary of disease-related VOCs in breath

Disease	Chemi-cals	VOCs	References
Allograft rejection	Organosulphur	Carbonyl sulfide	[96]
Alzheimer	Acid	2,2-Dimethyl-propanoic acid	[97]
		Oxalic acid	[97]
	Alcohol	2,6-Octadien-1-ol	[97]
		2-Butyl-1-octanol	[97]
	Alkane	1-Chloro-nonadecane	[97]
		1-Methylpropyl-cyclooctane	[97]
		2,3,5-Trimethylhexane	[97]
		2,3-Dimethyl-heptane	[97]
		2,5,6-Trimethyl-octane	[97]
		2,6,10-Trimethyl-dodecane	[97]
		2,6,10,14-Tetramethyl-hexadecane	[97]
		3,7-Dimethyl-decane	[97]
		3-Ethyl-2,2-dimethyl-pentane	[97]
		4-Methyl-octane	[97]
		5-Ethyl-2-methyl-octane	[97]
		Dodecane	[97]
		Heptane,2,2,4,6,6- pentamethyl-	[97]
	Alkene	2,4-Dimethyl-1-heptene	[97]
	Aromatic	1-Methylethyl-benzene	[97]
		Butylated hydroxytoluene	[97]
		Propyl benzene	[97]
		Styrene	[97]
	Ester	2-Ethylhexyl tetradecyl ester	[97]
		1,1'-Oxybis-octane (octyl ether)	[97]
	Other	3,7-Dimethyl-propanoate	[97]
Asthma	Alkane	Ethane	[98]
		Pentane	[99]
	Amine	Ammonia	[100]
	Nitrile	NO	[101–103]
	Other	8-Isoprostane	[104]
		Hydrogen peroxide	[105]

(Continued)

Disease	Chemi-cals	VOCs	References
Breast cancer	Alcohol	2-Hexyl-1-octanol	[53]
		2,3,4-Trimethyldecane	[49]
		3,3-Dimethyl pentane	[49]
		5-(2-Methylpropyl) nonane	[49]
		Dodecane, 4-methyl	[51]
		Nonadecane, 3-methyl	[51]
	Alkane	Nonane	[51]
		Octane, 2-methyl	[51]
		Pentadecane, 6-methyl	[51]
		Propane, 2-methyl	[51]
		Tridecane	[53]
		Tridecane, 5-methyl	[51]
		Undecane, 3-methyl	[51]
	Aromatic	Benzene, 1,2,4,5-tetramethyl-	[53]
	Nitrile	2-Amino-5-isopropyl-8-methyl-1-azulenecarbonitrile	[49]
		2,5-Cyclohexadiene-1,4-dione,2,6-bis(1,1-dimethylethyl)-	[53]
	Other	6-Ethyl-3-octyl ester 2- trifluoromethyl benzoic acid	[49]
		Cyclopropane, ethylidene	[53]
		(+)-Longifolene	[53]
	Terpene	D-limonene	[53]
Chronic renal failure/uremia	Alkane	2,2,6-Trimethyl-octane	[106]
		2,4-Dimethyl heptane	[106]
		Ammonia	[107]
	Amine	Dimethyl amine	[107]
		Trimethyl amine	[107]
	Ketone	2-Butanone	[106]
Colorectal cancer	Aldehyde	Decanal	[108]
		Nonanal	[108]
		2-Methylbutane	[108]
		2-Methyl-pentane	[108]
		3-Methylpentane	[108]
		4-Methyl-octane	[108]
	Alkane	Cyclohexane	[108]
		Methylcyclohexane	[108]
		1-Iodononane	[49]
		Methyl-cyclopentane	[108]
		1,2-Pentadiene	[108]
		1,1'-(1-Butenylidene) bis benzene	[49]
	Aromatic	1,3-Dimethylbenzene (m-xylene)	[108]
		P-xylene	[108]
	Ketone	4-Methyl-2-pentanone	[108]
	Nitrile	2-Amino-5-isopropyl-8-methyl-1-azulenecarbonitrile	[49]
	Organosulphur	(1,1-Dimethylethyl) thio acetic acid	[49]
	Other	4-(4-propylcyclohexyl)-,4'-cyano (7)-4-ylester benzoic acid	[49]
Chronic obstructive pulmonary disease	Aldehyde	Heptanal	[75]
		Hexanal	[75]
		Malondialdehyde	[75]
		Nonanal	[75]

(Continued)

Disease	Chemi-cals	VOCs	References
Chronic obstructive pulmonary disease	Alkane	2,6-Dimethyl-heptane	[76]
		4,7-Dimethyl-undecane	[76]
		4-Methyl-octane	[76]
		Ethane	[77]
		Hexadecane	[76]
		Octadecane	[76]
		Undecane	[76]
		2,4,6-Trimethyl-decane	[76]
	Alkene	Isoprene	[76]
	Nitrile	Benzonitrile	[76]
		NO	[109]
	Other	3,7-Dimethyl 1,3,6-octatriene	[76]
		Hydrogen peroxide	[110]
		Terpineol	[76]
Cystic fibrosis	Nitrile	NO	[111, 112]
	Organosulphur	Carbonyl sulfide	[113]
Diabetes mellitus	Alcohol	Ethanol	[114]
	Ester	Methyl nitrate	[115]
	Ketone	Acetone	[114]
Gastric Cancer	Aldehyde	Furfural	[45]
	Alkane	4,5-Dimethyl-nonane	[45]
		4-Methyl-octane	[63]
		Hexadecane	[63]
	Alkene	Isoprene	[45]
	Aromatic	1,2,3-Trimethyl-benzene	[45]
		A-methyl-styrene	[63]
	Ester	2-Pentyl acetate	[45]
		2-Butoxy-ethanol	[45]
	Ketone	2-Butanone	[63]
		6-Methyl-5-hepten-2-one	[45]
	Other	Acrylnitril	[63]
Gastrointestinal disease	Acid	Acetic acid	[64]
		Hexanoic acid	[64]
		Pentanoic acid	[64]
	Alcohol	1-Pentanol	[64]
		1-Propanol	[64]
		Butanol	[64]
		Ethanol	[65]
		Methanol	[64]
	Aldehyde	Butanal	[64]
		Decanal	[64]
		Heptanal	[64]
		Hexanal	[64]
		Nonanal	[64]
		Octanal	[64]
		Pentanal	[64]
		Propanal	[64]
Gastrointestinal disease	Alkane	3-Methyl-hexane	[65]
		5-Ethyl-2-methyl-octane	[65]
		Dodecane	[65]
		Ethane	[116]

(Continued)

Disease	Chemi-cals	VOCs	References
Gastrointestinal disease	Alkane	Pentane	[116, 117]
		Propane	[116]
	Alkene	2,4-Dimethyl-1-heptene	[65]
		Isoprene	[64]
		Tetrachloroethylene	[65]
	Amine	Ammonia	[64]
	Aromatic	Ethyl phenol	[64]
		Phenol	[64]
		Phenol, 4-methyl	[64]
	Ketone	2-Butanone	[65]
		Acetone	[64]
	Nitrile	Hydrogen cyanide	[64]
	Organosulphur	Carbon disulfide	[64]
		Dimethyl disulphide	[64]
		Dimethyl sulphide	[64]
		Hydrogen sulfide	[64]
Halitosis	Acid	Butyric acid	[73]
	Amine	Ammonia	[73]
		Dimethyl amine	[73]
		Trimethyl amine	[73]
	Aromatic	Skatole	[73]
	Organosulphur	Allyl mercaptan	[73]
		Allyl methyl sulfide	[73]
		Carbon disulfide	[73]
		Dimethyl sulphide	[73]
		Ethyl-propyl-sulfide	[73]
		Hydrogen sulfide	[74]
		Methyl mercaptan	[74]
		Propyl-mercaptan	[73]
Head and neck cancer	Acid	2,2-Dimethyl-propanoic acid	[48]
	Alkane	2,2-Dimethyl-decane	[48]
		2,4-Dimethyl heptane	[48]
		4,6-Dimethyl-dodecane	[48]
	Ketone	5-Methyl-3-hexanone	[48]
	Other	2,2,3-Erimethyl-, exobicyclo-2.2.1-heptane	[48]
	Terpene	Limonene	[48]
Heart allograft rejection	Alkane	Breath alkanes	[118]
Heat failure	Nitrile	NO	[66]
Hepatic cancer/cirrhosis	Acid	Propanoic acid	[67]
	Alcohol	1-Hexadecanol	[67]
		Isopropyl alcohol	[67]
	Aldehyde	Acetaldehyde	[68, 69]
	Alkane	Octane	[67]
	Ketone	2-Pentanone	[33]
		Acetone	[33]
	Organosulphur	Carbonyl sulfide	[68, 69]
		Dimethyl sulphide	[68, 69]
		Methyl mercaptan	[68, 69]
		Volatile ulphur containing compounds	[33, 119–121]

(Continued)

Disease	Chemi-cals	VOCs	References
Hyperglycemia	Aromatic	Ethylbenzene	[122]
		P-xylene	[122]
Kidney failure	Alkene	Isoprene	[123]
Kidney injury	Alcohol	Ethanol	[124]
	Ketone	2-Pentanone	[124]
		Acetone	[124]
		4-Penten-2-ol	[50]
	Alcohol	Ethanol	[125–127]
		Methanol	[125]
		A, α-4-trimethyl-3-cyclohexene-1-methanol	[50]
		P-menth-1-en-8-ol (alpha-terpineol)	[50]
	Aldehyde	Butanal	[128, 129]
		Formaldehyde	[55, 130]
		Heptanal	[57, 128, 131, 132]
		Hexanal	[57, 127, 128, 131, 132]
		Nonanal	[55, 128]
		Octanal	[55, 132]
		Pentanal	[128]
		Propanal	[128]
		1,1,2-Trichloro-1,2,2-trifluoro- ethane	[50]
		1-Methyl-2-pentyl-cyclopropane	[131]
		2,3,4-Trimethylhexane	[49]
		2,4-Dimethyl heptane	[131]
		2-Methylheptane	[131]
		2-Methylhexane	[125]
		2-Methyl-pentane	[54]
		3,3-Dimethyl pentane	[49]
		3-Methyl-hexane	[125]
		3-Methyl-nonane	[131]
Lung cancer		3-Methyl-octane	[54, 131]
		3-Methyltridecane	[125]
		4-Methyl-octane	[125]
		Hexane	[125]
		2-Methybutane	[129]
	Alkane	Butane	[38, 125, 133]
		Cyclohexane	[38, 127, 131, 134]
		Decane	[54, 131]
		Decane, 4-methyl	[135]
		Dodecane	[49]
		Heptane	[54, 57, 133]
		Heptane,2,2,4,6,6-pentamethyl-	[131]
		Methyl-cyclopentane	[131, 136]
		Methyl-cyclopropane	[61]
		Octane	[57, 126]
		Pentane	[54, 57, 133]
		Trichlorofluoro-methane	[131]
		Undecane	[131, 137, 138]
	Alkene	1,3-Butadiene,2-methyl- isoprene	[131]

(Continued)

Disease	Chemi-cals	VOCs	References
Lung cancer	Alkene	1,5,9-Trimethyl-1,5,9-cyclododecatriene	[135]
		1-Heptene	[54, 131, 133]
		1-Hexene	[61]
		2,3-Hexadiene	[50]
		5,5-Dimethyl-1,3-hexadiene	[50]
		Isoprene	[54, 57, 125, 127, 137]
	Aromatic	1,1-(1,2-Cyclobutanediyl) bis-, cis-benzene	[50]
		1,1'-(1-Butenylidene) bis benzene	[49]
		1,2,3,4-Tetrahydro-9-propyl- anthracene	[50]
		1,2,4,5-3,3,6,6-Tetraphenyl- tetroxane	[50]
		1,2,4-Trimethyl benzene	[54, 131]
		1,4-Dimethylbenzene (p-xylene)	[131]
		10,11-Dihydro-5H-dibenzo-(B,F)-azepin	[135]
		1-Methyl-4-(1-methylethyl)-benzene(p-cymee)	[49]
		1-Oxybis-benzene	[135]
		2,2-Diethyl-1,1-biphenyl	[135]
		2,3-Dihydro-1,1,3-trimethyl-3-phenyl-1-H-indene	[135]
		2,5-Dimethyl furan	[135]
		2-Ethyl-9,10-anthracenediol	[50]
		Aniline	[136]
		Benzene	[38, 54, 57, 125, 137, 138]
		Benzophenone	[50]
		Diethylbenzene-1,2-dicarboxylate	[135]
		Ethyl-4-ethoxybenzoate	[135]
		Ethylbenzene	[125]
		o-Toluidine	[130, 136]
		Propyl benzene	[57, 131, 138]
		Styrene	[38, 54, 131, 138]
		Toluene	[49, 54]
	Ester	2,2,4-Trimethyl-pentan-1,3-dioldiisobutyrate	[135]
		Propanoicacid,2,2,4-trimethyl-3-carboxyisopropyl,isobutylester	[50]
		2-Methyl-,1-(1,1-diamethylethyl)-2-methyl-1,3- propanediyl ester	[50, 135]
		2-Methoxy-2-methyl-propane	[50]
	Ketone	2,4-Dimethyl-3-pentanone	[135]
		2,5-Dimethyl-2,4-hexanedione	[135]
		2-Butanone	[137]
		2-Methyl-3-hexanone	[50]
		3-Hydroxy-2-butanone	[58, 137, 139]
		Acetone	[38, 57, 127, 137]
		A-isomethyl ionone	[50]
	Nitrile	Acetonitrile	[129]
	Organosulphur	1-(Methylthio)-(E)-1-propene	[50]
		1,1-[1-(Ethylthio)propylidene] bisbenzene	[50]
		Carbon disulfide	[125]
		Dimethyl sulphide	[125]
	Other	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	[50]
		2,2,7,7-Tramethyltricyclo-6.2.1.0(1,6)-undec-4-en-3-one	[50]

(Continued)

Disease	Chemi-cals	VOCs	References
Lung cancer	Other	2,5-2,6-Bis(1,1-dimethylethyl)-cyclohexadiene-1,4-dione	[135]
		2,6-Bis(1,1-dimethylethyl)-4-ethylidene-2,5-cyclohexadien- 1-one	[50]
		5-(Ethoxycarbonyl) bicycle [3.2.2] nonane-1-carboxylic acid	[50]
		5-Isopropenyl-2-methyl-7-oxabicyclo [4.1.0] heptan-2-ol	[50]
		7,7-Trimethyl-(1S)-bicyclo [2.2.1] eptan-2-one	[50]
		Camphor	[50]
Multiple sclerosis	Aldehyde	2,5-Dimethylfuran	[125]
		Decanal	[140]
		Hexanal	[141]
		Nonanal	[140]
	Alkane	5-Methyl-undecane	[141]
	Alkene	Heptadecane	[140]
	Ketone	Acetophenone	[140]
	Organosulphur	Sulfur dioxide	[140]
Parkinson	Alkane	Hexadecane	[142]
		2,3,5-Trimethylhexane	[142]
		2,3,6,7-Tetramethyl-octane	[142]
		2,3-Dimethyl-heptane	[142]
		3,7-Dimethyl-decane	[142]
		5-Ethyl-2-methyl-octane	[142]
	Aromatic	1-Methyl-3-(1-methylethyl)-benzene (m-cymene)	[142]
		Butylated hydroxytoluene	[142]
		Ethylbenzene	[142]
		Styrene	[142]
	Other	Decamethyl-cyclopentasiloxane	[142]
Prostate Cancer	Alkane	2,2-Dimethyl-decane	[49]
	Aromatic	p-Xylene	[49]
		Toluene	[49]
	Nitrile	2-Amino-5-isopropyl-8-methyl-1-azulenecarbonitrile	[49]
Pulmonary Arterial	Alcohol	Ethanol	[70]
		Isopropyl alcohol	[70]
	Aldehyde	Acetaldehyde	[70]
		Benzaldehyde	[70]
	Alkane	Pentane	[70]
	Alkene	1-Decene	[70]
		1-Octene	[70]
		2-Nonene	[70]
	Amine	Ammonia	[70]
	Aromatic	1-Methyl-4-(1-methylethyl)-benzene(p-Cymene)	[71]
		Aniline	[71]
		Benzenamine, n-ethyl-	[71]
		Benzothiazole	[71]
	Ester	Propanoic acid, 2-methyl-, 3- hydroxy-2,4,4-trimethylpentyl ester	[71]
		Propanoic acid, 2-methyl-, 3- hydroxyhexyl ester	[71]
		Tetrahydro-2, 2, 4, 4-tetramethyl furan	[71]
	Ketone	2,2-Dihydroxy-1-phenyl-ethanone	[71]
		4-Methyl-2-pentanone	[71]

(Continued)

Disease	Chemi-cals	VOCs	References
	Ketone	P-menthone	[71]
		1,6-Dioxacyclododecane-7,12-dione	[71]
Pulmonary Arterial	Other	7-Methyl-3-(1-methylethyl)-benzene(m-cymene)	[71]
		2-Menthene	[71]
	Alcohol	Isopropyl alcohol	[143]
		2,4-Dimethyl heptane	[143]
	Alkane	Isononane	[143]
Renal disease		Nonane	[143]
	Aromatic	Ethylbenzene	[143]
		Styrene	[143]
	Other	Methylene chloride	[143]
Rheumatoid arthritis	Alkane	Pentane	[144]
	Alkane	Ethane	[145]
Schizophrenia		Pentane	[145]
	Organosulphur	Carbon disulfide	[145]
		Methylcyclododecane	[72]
	Alkane	2,2,4,6,6-Pentamethyl-heptane	[72]
Tuberculosis		1,4-Dimethyl-cyclohexane	[72]
	Aromatic	1-Methyl-4-(1-methylethyl)-benzene	[72]
	Ketone	3-Heptanone	[72]
	Other	1-Methyl-naphthalene	[72]

• Fast solidification of blood makes hard sampling and examinations, although the study towards the blood VOCs is very important to understand the VOCs's generation and transport mechanism in the human body.

• The blood is not stable for storage due to the existence of erythrocyte, leucocyte, enzyme, bacterial, etc. These "dirties" can consume and/or emit VOCs in the blood, which makes the blood VOCs analysis complicated.

• Relatively low concentration of VOCs exists in the blood without any preconcentrating process compared with VOCs in urine, which makes concentrations of VOCs, sometimes, lower than the limit of detection of spectrometry instruments.

Therefore, the single volatolomics associated with blood in diagnostics still needs to be further studied.

3.3 The volatile organic compounds in excreta and their associated diseases

Human VOCs are present in a variety of excreta, especially urine and feces. There are two main advantages for VOCs in excreta. First, the VOCs can be directly released to the air along the intestine and urethra. Second, the excreta can be a good media for capturing and taking VOCs out of the body. The main pathways for emitting VOCs to excreta include but not limited as:

• The similar emission path as Path ① is mentioned in Section 3.1. The cancer-related VOCs are transported from different body sources to the intestine and urethra according to the "fat–blood–air" and "fat–blood–water" equilibrium distribution [80].

• The cell/tissue lesion on the inner surface of the intestine and urethra, i.e., their headspaces connect the environment, can directly emit VOCs to the air or water (Path ②) [81–85].

• Infections caused odorous metabolites in the surrounded micro-environment, e.g., urinary tract inflammation, enteritis, etc.,

can directly emit VOCs to the intestine and urethra, captured by the excreta (Path ③) [86, 87].

• The disease caused disorder of symbiotic bacteria (mainly in feces), e.g., *Escherichia coli*, can interfere with the bio-chemical reaction of food decomposition and absorption, which changes the compositions and concentrations of the VOCs (Path ④) [88–92].

• The VOCs emitted by tumor cells and/or lesions on the digestive tract or the organs nearby the digestive tract can be mixed with food and finally excreted in the feces along with the digestive process (Path ⑤) [93–95].

The VOCs in urine and feces contain abundant physiological information in volatolomics as shown in Fig. 6, and summarized in Tables 3 and 4. VOCs, mostly polar molecules such as acid, alcohol, ketone, and aldehyde, in urine, are directly linked to infectious diseases, cancers, and particular disorders. No alkane has been found in the urine, which is decided by the poor solubility of non-polar molecules in it. In the feces, ester, alcohol, ketone, and acid are mostly found. Interestingly, the volatolomes of the same disease in breath, urine, and feces are totally different, which means the distribution and emission path of VOCs are greatly different in different body sources.

Urine and feces volatolomics as the promising diagnostic option can be summarized as follow aspects:

• Urine samples are easier to be sampled and stored than invasively collected blood and non-invasively collected breath. Furthermore, when stored under the right conditions, urinary VOC samples are stable for long periods.

• Higher concentration of VOCs is obtained by the "pre-concentration" process in the kidney and semi-solid extraction process in the digestive tract. In other words, the key "VOCs signature" is "recognized and amplified" with increasing signal-to-noise ratios.

• Urine is much less affected by diet or the other commensal of bacteria in the gut than feces or breath.
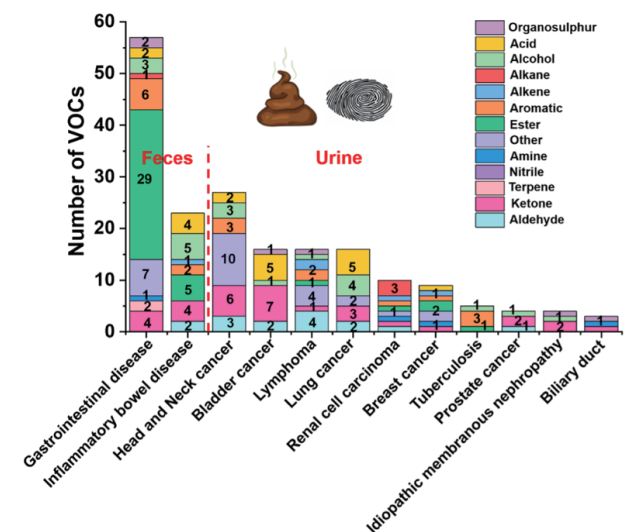
Table 2 The summary of disease-related VOCs in blood

Disease	Chemicals	VOC	References
		Hexanal	[47]
	Aldehyde	Heptanal	[47]
		Nonanal	[47]
	Ketone	6-Methyl-2-heptanone	[47]
		Methoxyphenyl oxime	[47]
		6,7-Dodecanedione	[47]
	Other	2-Pentylfuran	[47]
		2,4-Bis(1,1-dimethylethyl) phenol	[47]
		α-Pinene	[47]
Liver cancer		p-Xylene	[47]
	Aromatic	1-Ethyl-2-methylbenzene	[47]
		1,4-Dichlorobenzene	[47]
	Alkene	Limonene	[47]
		2,3-Dimethylcyclopentene	[47]
		Heptane	[47]
	Alkane	Octane	[47]
		Nonane	[47]
		Decane	[47]
	Alcohol	1-Octen-3-ol	[47]
	Amine	Ethylaniline	[146]
	Other	Caprolactam	[146]
Lung cancer		Tetramethylurea	[146]
	Alcohol	Dimethylphenylcarbinol	[146]
		Isolongifolene-5-ol	[146]
	Ester	Penyl methylcarbamate	[147]
Colorectal cancer	Alkane	1,1,4,4-Tetramethyl-2,5-dimetylene-cyclohexane	[147]
	Alcohol	Ethylhexanol	[147]
	Other	6-t-Butyl-2,2,9,9-tetramethyl-3,5-decadien-7-yne	[147]
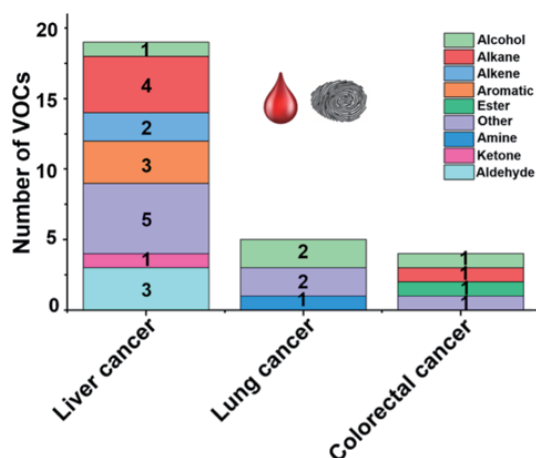
Figure 5 The summary of the number of VOCs' kinds in the blood of different patients (data from Table 2).

3.4 The volatile organic compounds on skin and their associated diseases

Skin is one of the largest organs for the human beings. The skin has a layered structure to perform as a barrier and achieve the matter exchange between body and air. Therefore, VOCs from the skin originate from four major sources:

Figure 6 The summary of the number of VOCs' kinds in the cereta of different patients (data from Tables 3 and 4).

• The gland secretion, which is related to the matter exchange process (Path ①) [184].

• The skin diseased related VOCs directly are emitted to air, and absorbed on the skin (Path ②) [185–189].

Table 3 The summary of the disease-related VOCs in feces

Disease	Chemicals	VOCs	References
Gastrointestinal disease	Acid	Acetic acid	[93]
		Pentanoic acid, 4-methyl	[93]
	Alcohol	1-Propanol, 2-methyl	[93]
		2-Butanol	[93]
		Methanol	[93]
	Aldehyde	Heptanal	[93]
		Pentanal	[93]
		Propanal	[93]
	Alkane	Undecane	[93]
	Amine	Ammonia	[148]
	Aromatic	1-Methyl-2-(1-methylethyl)-benzene (o-cymene)	[93]
		1-Methyl-3-(1-methylethyl)-benzene (m-cymene)	[93]
		Ethylbenzene	[93]
		Indole	[149]
		Phenol	[148]
		Phenol, 4-methyl	[93]
	Ester	Acetic acid, pentyl ester	[93]
		Benzoic acid, 2-hydroxy-, methyl ester	[93]
		Butanoic acid, 2-methyl-, propyl ester	[93]
		Butanoic acid, 2-methylbutyl ester	[93]
		Butanoic acid, 2-methylpropyl ester	[93]
		Butanoic acid, 3-methyl-, butyl ester	[93]
		Butanoic acid, 3-methyl-, methyl ester	[93]
		Butanoic acid, 3-methyl-, propyl ester	[93]
		Butanoic acid, 3-methyl-methyl ester	[93]
		Butanoic acid, butyl ester	[93]
		Butanoic acid, ethyl ester	[93]
		Butanoic acid, methyl ester	[93]
		Butanoic acid, propyl ester	[93]
		Cyclohexanecarboxylic acid, butyl ester	[93]
		Cyclohexanecarboxylic acid, ethyl ester	[93]
		Cyclohexanecarboxylic acid, methyl ester	[93]
		Cyclohexanecarboxylic acid, propyl ester	[93]
		Ethanoic acid, 3-methyl-1-butyl ester	[93]
		Ethanoic acid, ethyl ester	[93]
		Hexanoic acid, methyl ester	[93]
		Pentanoic acid, 4-methyl-, pentyl ester	[93]
		Pentanoic acid, butyl ester	[93]
		Pentanoic acid, methyl ester	[93]
		Propanoic acid, 2-methyl-, methyl ester	[93]
		Propanoic acid, 2-methylpropyl ester	[93]
		Propanoic acid, 3-methy1-butyl ester	[93]
		Propanoic acid, butyl ester	[93]
		Propanoic acid, methyl ester	[93]
		Propanoic acid, propyl ester	[93]
	Ketone	2-Heptanone, 6-methyl	[93]
		2-Piperidinone	[93]
		5-Methyl-2-(1-methylethyl)-cyclohexanone	[93]

(Continued)

Disease	Chemicals	VOCs	References
Gastrointestinal disease	Ketone	6-Methyl-5-hepten-2-one	[93]
	Organosulphur	S-methyl 3-methylbutanethioate	[93]
		Thiopivalic acid	[93]
		1-Butanol, 3-methyl-, propanoate	[93]
		4-Methyl-1-indole	[93]
	Other	5-Methyl-2-(1-methylethyl)- cyclohexanol	[93]
		A´-Phellandrene	[93]
		Copaene	[93]
		Methoxy-phenyl-oxime	[93]
	Terpene	A´-Pinene	[93]
		γ-Terpinene	[93]
	Aldehyde	Benzaldehyde	[94]
		Nonanal	[94]
		2-Piperidi-none	[94]
	Ketone	6-Methyl-2-heptanone Methanethiol	[94]
		6-Methyl-2-heptanone	[94]
		2-Piperidinone	[94]
		2-Methyl-propyl ester	[94]
		3-Methyl-1-butyl ester	[94]
	Ester	2-Methyl-propyl ester	[94]
		Propanoic acid propyl ester	[94]
Inflammatory bowel disease		Ethanoic acid ethyl ester	[94]
	Aromatic	3-Methyl-phenol	[94]
		1-nitro-heptane	[94]
	Alkene	Decane	[94]
		Heptanal	[94]
		1-Octen-3-ol	[94]
	Alcohol	Isopropyl alcohol	[94]
		2-Butanol	[94]
		3,7-Dimethyl-1,6-octadiene 3-ol	[94]
		Butanoic acid	[94]
	Acid	Ethanoic acid	[94]
		Heptanoic acid	[94]

• The metabolites of skin microbiota that is barred out of the body but stayed on the skin surface (Path ③) [190–193].

• The exogenous VOCs, e.g., food, air pollution, and smoking, which are absorbed on the skin surface (Path ④) [194].

Eccrine excretion (sweat), similar to urine, usually contains 98% water, with the rest being various organic and inorganic compounds (sodium chloride, lactate, and urea), which is mainly transferred by osmosis. Extracellular fluid is the origin of eccrine secretion, and thus reflects blood plasma chemistry. However, the skin VOCs caused by eccrine excretion are very different from the urinary VOCs as shown in Fig. 7 and summarized in Table 5. For example, the alkanes, rare to be found in urine, can be detected in melanoma skin samples. The profiles of tuberculosis volatolome are identified from clinical samples. There is also a difference between breath and skin volatolome. Very interesting, for aging people, the 2-nonenal is clearly confirmed as the chemical markers comparing the volatolome emitted by people elder and younger than 40 years old [183]. According to the bacteria infection, acids are very frequently found in the volatolome, which may be related to fat oxidation and other pathways.

More than 500 VOCs have been identified from human skin extracts, however, the identifications of volatile markers towards specific diseases in/on the skin are still challenged due to more confounding factors on body odor, such as food, environment, and body clean, which requires a more advanced algorithm to assist the analysis of spectrometry results. The latest efforts on diagnosis towards tuberculosis through detecting the skin VOCs by E-nose had been achieved in India and southern Africa [24], which might be an effective demonstration for developing new wearables and skin electronics, based on the skin volatolome, in the future.

4 The detection of volatile organic compounds by E-nose and P-nose

The individual sensor device is the basic functional element, and

Table 4 The summary of disease-related VOCs in urine

Diseases	Chemicals	VOCs	References
Head and Neck	Aldehyde	Heptanal	[81]
		Hexanal	[81]
		Nonanal	[81]
	Ketone	3,4-Dehydro-b-ionone	[81]
		3,4-Dimethyl-2, 5-furanedione	[81]
		3-Heptanone	[81]
		3-Methyl-2-heptanone	[81]
		4-Methyl-2-heptanone	[81]
		Acetone	[81]
	Other	2-Methyl-5-(methylthio) furan	[81]
		2-Methylthiophene	[81]
		Dimethyl disulfide	[81]
		Dimethyl trisulfide	[81]
		Ethylbenzene	[81]
		m-Cresol	[81]
		Phenol	[81]
		Tetrahydro-2,2-dimethyl-5-(1-methyl 1-propenyl) furan	[81]
		Tetrahydro-2,2,5,5-tetramethylfuran	[81]
		Thiophene	[81]
		4-Tert-butylphenolpheno	[81]
	Aromatic	Benzene	[81]
		Ethylbenzene	[81]
	Alkene	Styrene	[81]
	Alcohol	2-Methylbutanal	[81]
		Linalool	[81]
		α-Terpineol	[81]
	Acid	2-Methyl-butyric acid	[81]
		Ethanoic acid	[81]
Biliary Duct	Ketone	2-Propanol	[150]
	Amine	Trimethyl amine	[150]
	Organosulphur	Carbon disulfide	[150]
Bladder Cancer	Aldehyde	Hexanal	[82]
		Benzaldehyde	[82]
	Ketone	2-Pentanone	[82]
		2;3-Butanedione	[82]
		4-Heptanone	[82]
		Butyrophenone	[82]
		2-Butanone	[82]
		Piperitone	[82]
		Thujone	[82]
	Alcohol	2-Propanol	[82]
	Acid	Acetic acid	[82]
		cis-3-hexanoic acid	[82]
		Trans-3-hexanoic acid	[82]
		Benzoic acid	[82]
		3-Hydroxyanthranilic acid	[82]
	Organosulphur	Dimethyl disulphide	[82]
Lymphoma	Aldehyde	Hexanal	[151]

(Continued)

Diseases	Chemicals	VOCs	References
Lymphoma	Aldehyde	2-Methyl-3-phenyl-2-propenal	[151]
		Heptanal	[151]
		Anisole	[151]
	Ketone	3-Heptanone	[151]
		2-Methoxythiophene	[151]
	Other	1,2-Dihydro-1,1,6-trimethyl-naphthalene	[151]
		1,4,5-Trimethyl-naphthalene	[151]
		2,7-Dimethyl-quinoline	[151]
	Ester	4-Methyl-phenol	[151]
	Aromatic	1,2,4-Trimethylbenzene	[151]
		p-Cymene	[151]
	Alkene	γ-Terpinene	[151]
		Bornylene	[151]
	Alcohol	1-Octanol	[151]
	Organosulphur	Dimethyl disulphide	[151]
Lung cancer	Aldehyde	Hexanal	[83]
		Heptanal	[83]
	Ketone	2-Pentanone	[84]
		Cyclohexanone	[84]
		Isophorone	[84]
	Other	Tetrahydrofuran	[84]
		2-Methylpyrazine	[84]
	Alcohol	2-Chloroethanol	[84]
		2-Ethyl-1-hexanol	[84]
		2-Phenyl-2-propanol	[84]
		2,6-Diisopropylphenol	[84]
	Acid	Hippuric acid	[85]
		Pipecolic acid	[85]
		Phenylalanine	[85]
		3-Hexaprenyl-4-hydroxy-5-Methoxybenzoic acid	[85]
		Taurine	[85]
Renal cell carcinoma	Aldehyde	Decanal	[152]
	Ketone	1,6-Dioxacyclododecane-7,12-Dione	[152]
	Amine	Aniline	[152]
	Other	Phenol	[152]
	Ester	1-Bromo-1-(3-methyl-1-pentenylidene)-2,2,3,3-tetramethyl-cyclopro-pane	[152]
	Aromatic	2,5-Cyclohexadiene-1,4-dione,2,6-bis(1,1-dimethylethyl)	[152]
	Alkene	Isolongifolene-5-ol	[152]
	Alkane	3-ethyl-3-methylheptane	[152]
		Tetradecane	[152]
		2,6,10,14-Tetramethyl-pentadecane	[152]
Breast Cancer	Ketone	3-Heptanone	[153]
	Amine	Urea	[154]
	Other	Phenol	[153]
		2-Methoxythiophene	[153]
	Ester	Homovanillate	[154]
		4-Hydroxyphenylacetate	[154]
	Aromatic	1,2,4-Trimethylbenzene	[154]

(Continued)

Diseases	Chemicals	VOCs	References
Breast Cancer	Alkene	4-Carene	[154]
	Acid	5-Hydroxyindoleacetate	[153]
Tuberculosis	Ester	Isopropyl acetate	[86]
	Alcohol	3-Pentanol	[86]
		1-Methyl-4-(1-methylethyl)- benzene (p-cymene)	[86]
	Aromatic	2,6-Dimethylstyrene	[86]
		O-xylene	[86]
Prostate Cancer	Aldehyde	Pentanal	[155]
	Ketone	3-Octanone	[155]
		2-Octanone	[155]
	Alcohol	2,6-Dimethyl-7-octen-2-ol	[155]
Idiopathic membranous nephropathy	Ketone	2-Pentanone	[156]
		4-Heptanone	[156]
	Alcohol	2,4-Dimethyl-pentanal	[156]
	Organosulphur	Thiourea	[156]
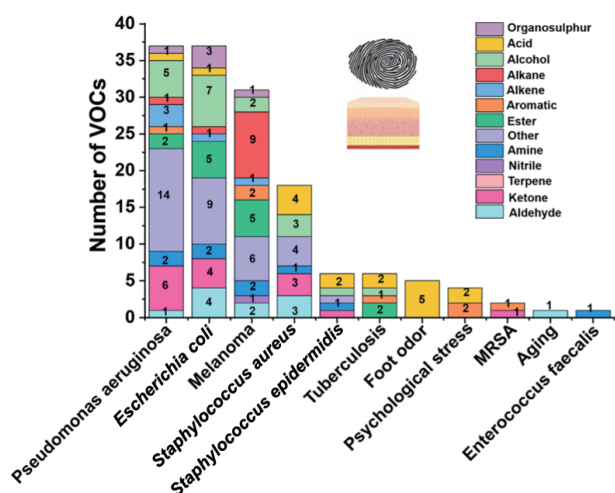
Figure 7 The summary of the number of VOCs' kinds from the skin of different patients (data from Table 5).

thus determines the overall performances of artificial olfaction as a whole (Fig. 8). The basic gas sensors for breath analysis are classified into three categories according to the transducer (i.e., mass, electrical and optical) and are discussed below with selected examples (Fig. 8). Most of the E-noses are constructed by the same type of gas sensors with distinct performances (homo gas sensor arrays or homo-transducer arrays). Recently, E-nose consists of different types of sensors that have been developed (hybrid gas sensor arrays or multi-transducer arrays) [195, 196], which can reduce correlations between the responses of different sensor types, and thus improve the power of data analysis [197–199].

The quartz crystal microbalance (QCM) [200, 201] and surface acoustic wave (SAW) [202, 203] sensors are two common types of mass transduced gas sensor arrays applied in breath analysis. As for optical transduced gas sensors, colorimeter [204, 205] and nondispersive infrared (NDIR, for CO_2 monitoring) [206] types are used. Different from optical or mass transduced sensors, electrically-transduced gas sensors normally required semiconductive/conductive ability or other sensitive electrical properties of the active materials (e.g., capacitance (C), inductance (L), resistance (R), and work function (ϕ)) [207, 208]. Various electrically-transduced gas sensors including chemiresistors [41],

field-effect transistors (FETs) [209], chemical diodes [207, 210], chemicapacitors [211], and electrochemical sensors [197, 212] are excellent candidates for the construction of E-nose [43, 213].

For mass-transduced E-nose for the detection of VOCs, a typical example is the use of SAW sensor arrays, in which a biomimetic olfactory receptor-based biosensor with better performances was reported by improving the immobilization efficiency of molecular detectors for breath analysis (Fig. 9) [202]. The specific olfactory receptors (ODR-10) were used to functionalize the sensitive area of the SAW chip with a self-assembled monolayers (SAMs) of 16-mercaptohexadecanoic acid (MHDA). The responses to the various VOCs were recorded by monitoring the mass loading affected the resonance frequency shifts of SAW. The functionalized SAW showed the ultrasensitive detection (LOD = 1.2×10^{-11} mM) with high selectivity compared to butanone and 2,3-pentanedione [202].

Chemiresistors are the extensively studied types of electrically-transduced gas sensors for E-nose. For example, gold nanoparticle (GNP) based E-noses was reported in the successful diagnosis of lung cancer using breath samples from real patients (Fig. 10(a)) [41]. Firstly, the sensors were selected and trained by simulated vapors of healthy and cancerous breath according to GC-MS results (Fig. 10(b)). Then the selected sensor arrays were exposed to the breath of normal healthy and cancerous patients. Principal component analysis (PCA), a commonly used statistical procedure to reduce a set of possibly correlated variables into a set of values of linearly uncorrelated variables via an orthogonal transformation [43, 213–215], was employed in the post-treatment of the sensing results. The complete separation of the output PCA results indicated that such sensor arrays could discriminate between the different smells of healthy people and patients with lung cancer (Fig. 10(c)). Representative works of E-nose based on other chemiresistive materials such as chemically modified carbon nanotubes (CNTs) [216, 217], metal oxides [43, 218], surface-modified Si nanowires [219], and polymer-carbon hybrids [220, 221] were also successfully applied to disease diagnosis with high accuracy. In addition, the newly emerging sensing materials such as crystalline porous materials (e.g., metal-organic framework/porous coordination polymers [222–226], black phosphorus [227–230], covalent-organic frameworks (COFs) [231, 232], and Mxenes [233–235]) and their hybrid materials/thin films [236, 237] based chemiresistors with low temperature

Table 5 The summary of disease-related VOCs in skin

Disease	Chemicals	VOC	References
Tuberculosis	Ester	Hexyl butyrate	[24]
	Aromatic	Toluene	[24]
	Alkane	Ethyl-cyclopropane	[24]
	Alcohol	2-Ethyl-1-hexanol	[24]
	Acid	Acetic acid	[24]
		Octanoic acid	[24]
Melanoma	Alcohol	1-Eicosanol	[157]
		1-Hexadecanol	[157, 158]
	Aldehyde	Decanal	[157]
		Nonanal	[157, 158]
	Alkane	1-Iodo nonane	[157]
		2,4-Dimethyl heptane	[157]
		4,7-Dimethyl-undecane	[157]
		Cyclohexane, ethyl	[157]
		Decane	[157, 158]
		Decane, 4-methyl	[157, 158]
		Dodecane	[157, 158]
		Pentane, 2,3,4-trimethyl	[157]
		Undecane	[157, 158]
	Alkene	1-Hexadecene	[157]
	Amine	Formamide	[157]
		Adenosine, 5'-amino-5'-deoxy	[157]
	Aromatic	1,3,5-Trimethyl-benzene	[157]
		Bis(2-ethylhexyl) phthalate	[157]
		1,2-Benzenedicarboxylic acid, diisooctyl ester	[157]
		Isopropyl palmitate	[157]
	Ester	Phthalic acid, isobutyl 4-octyl ester	[157]
		2-Butoxy-ethanol	[157]
		Ethylene oxide	[157]
	Nitrile	2-Isopropylamino-4-methylbenzonitrile	[157]
	Organosulphur	N-morpholinomethyl-isopropyl-sulfide	[157]
	Other	1,3-Cyclopentadiene, 5-(1-methylethylidene)-	[157]
		2-Ethoxyethyl acrylate	[157]
		2-Ethylhexyl trans-4-methoxycinnamate	[157]
		Benzaldehyde, 4-methoxy	[157]
		Dichlorodifluoromethane	[157]
		Spiro[bicyclo[2.2.1]hept-5-ene-2,1'-cyclopropane]	[157]
Pseudomonas aeruginosa	Aldehyde	Acetaldehyde	[159]
	Ketone	2-Butanone	[160]
		2-Aminoacetophenone	[161]
		2-Nonanone	[162]
		2-Heptanone	[160]
		2-Propanone	[163]
		Acetone	[159]
	Amine	Azane	[163]
		Ammonia	[159]
	Other	Dimethyl sulfide	[161]
		Hydrogen cyanide	[164]

(Continued)

Disease	Chemicals	VOC	References
		Methyl thiolacetate	[164]
		2; 3-Dimethyl-5-isopentylpyrazine	[165]
		2-Methyl-3-(2-propenyl)-pyrazine	[165]
		3-Methyl-1 H-pyrrole	[165]
		6-Tridecane	[165]
	Other	Dimethyl trisulphide	[166]
		2-Methylbutyl 2-methylbutyrate	[167]
		Amyl isovalerate	[167]
		2-Methoxy-5-methylthiophene	[167]
		2-Methylbutyl isobutyrate	[167]
		3-(Ethylthio)-propanal	[167]
		Dimethyl pyrazine	[161]
Pseudomonas aeruginosa	Ester	Methyl thiocyanate	[165]
		Thiocyanic acid methyl ester	[168]
	Aromatic	Acetophenone	[169]
		Isoprene	[160]
	Alkene	1-Undecene	[160]
		2-Pentene	[160]
	Alkane	Dodecane	[163]
		Ethanol	[159]
		2-Butanol	[168]
	Alcohol	2-Pentanol	[168]
		2-Ethylhexan-1-ol	[163]
		Methyl mercaptan	[170]
	Acid	Acetic acid	[159]
	Organosulphur	Dimethyl disulphide	[161]
		Acetaldehyde	[159]
		Benzaldehyde	[171]
	Aldehyde	Butanal	[162]
		Formaldehyde	[172]
		Acetone	[159]
		2-Nonanone	[171]
	Ketone	Heptan-2-one	[173]
		Nonan-2-one	[173]
		Pentafluoropropionamide	[174]
	Amine	Ammonia	[175]
		Indole	[160]
		Dimethyl sulfide	[159]
		2,5-Dimethylpyrazine	[171]
		2,5-Dimethyltetrahydrofuran	[171]
E. coli	Other	6-Methyl-5-hepten-2-one	[176]
		Carbon disulphide	[177]
		Dimethyl disulfide	[177]
		Carbon dioxide	[174]
		Dimethylether	[174]
		Ethyl acetate	[176]
	Ester	3-Methyl furan	[176]
		Methyl butanoate	[177]

(Continued)

Disease	Chemicals	VOC	References
E. coli	Ester	Methyl propanoate	[177]
		N-propylacetate	[160]
	Alkene	Isoprene	[160]
	Alkane	Methyl cyclohexane	[174]
	AlcoholAcid	Ethanol	[159]
		Propanol	[160]
		2-Methylbutanol	[178]
		3-Methylbutanol	[178]
		Decan-1-ol	[163]
		Octan-1-ol	[163]
		Methyl mercaptan	[172]
		Acetic acid	[159, 160]
	Organosulphur	Hydrogen sulfide	[172]
		Dimethyl trisulfide	[177]
		Carbon disulfide	[162]
	Aldehyde	Acetaldehyde	[159]
		3-Methylbutanal	[167]
		2-Methylpropanal	[167]
	Ketone	Acetone	[160]
		3-Hydroxy-2-butanone	[161]
		2-Tridecenone	[178]
	Amine	Ammonia	[159]
Staphylococcus aureus	Other	Dimethyl sulfide	[159]
		Dimethyl trisulfide	[160]
		1,1,2,2-Tetrachloroethane	[160]
		Dimethyl disulfide	[160]
	Alcohol	Ethanol	[159]
		1-Hydroxy-2-propanone	[161]
		Butanol	[179]
	Acid	Acetic acid	[167]
		Isovaleric acid	[161]
		2-Methylbutyric acid	[161]
		Isobutyric acid	[161]
Enterococcus faecalis	Amine	Ammonia	[172]
	Ketone	Acetone	[172]
Staphylococcus epidermidis	Amine	Ammonia	[172]
	Other	2-Methylbutanal	[180]
	Alcohol	3-Methyl-1-butanol	[180]
	Acid	3-Methylbutanoic acid	[180]
		2-Methylbutanoic acid	[180]
methicillin resistant staphylococcus aureus (MRSA)	Ketone	2-Heptanone	[160]
	Aromatic	1,4-Dichlorobenzene	[160]
Psychological stress	Acid	Benzoic acid	[181]
		N-decanoic acid	[181]
	Aromatic	Xylene isomer	[181]
		3-Carene	[181]
Foot odor	Acid	Acetic acid	[182]
		Isovaleric acid	[182]

(Continued)

Disease	Chemicals	VOC	References
		Propionic acid	[182]
Foot odor	Acid	Isobutyric acid	[182]
		Butyric acid	[182]
Aging	Aldehyde	2-Nonenal	[183]
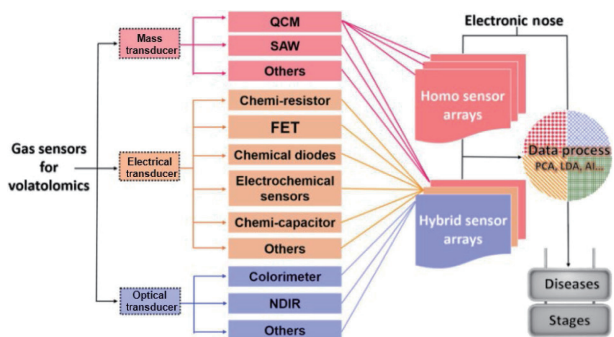
Figure 8 The category of gas sensors for volatolomics and the corresponding artificial olfaction.
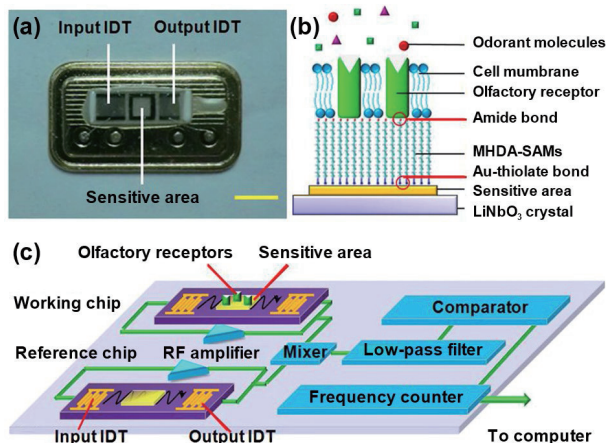
Figure 9 (a) Photograph of the real SAW sensor (scale bar is 50 mm). (b) Scheme of functional immobilization of olfactory receptors on the sensitive area of SAW chips. (c) Schematics of the SAW measurement system. Reproduced with permission from Ref. [202], © Elsevier B.V. 2011.

sensitivity and high selectivity can also be applied in E-nose in the near future.

In most cases of E-nose, studies have concentrated on a single array technology and single transduction technology, such as electric, mass, and optic. Most e-noses use cross-interactive sensor arrays that react to the VOCs on the sensitive materials' surface attaching with adsorption, desorption and/or reversible reaction, etc. Then the specific responses between the VOCs and sensors array are recorded and transformed into readable digital values which can achieve the recognition and detection based on statistical models or machine algorithm [238–242]. For the hybrid gas sensor arrays (multi-transducer arrays), different transduced techniques are used to lower correlations between the responses of the different sensor types, that greatly improve the accuracy of data analysis and pattern recognition [197, 243]. Therefore, a hybrid gas sensor array endowing with carefully selected sensing materials (receptor) and multivariable transducers is highly promising for the high-performance recognition of breath VOCs [196, 198, 244–246]. By using the same sensing materials (receptor) while distinct transducer, QCM, and chemiresistive platforms were used to investigate the selectivity of one pristine and three surface-modified single-walled carbon nanotubes

(SWCNTs) to VOCs (Fig.11(a)) [199]. As for the electrically-transduced sensor, the VOC molecules take longer to intercalate between the junctions of 2 nanotubes, thus delaying the increase in resistance (Fig. 11(b)). The signal responses of SWCNT-coated QCMs and chemiresistors to butanol and butyl acetate are shown in Figs. 11(c) and 11(d) [199].

The two cases showed the QCMs reached equilibrium faster than the chemiresistors did. Such additional mechanism involved in changes of resistance resulted in that, even with the same active materials, the response time, linearity, and relative sensitivities were all different between QCM and chemiresistor arrays. The diverse response patterns on two different sensor array transducers enable the formation of a highly selective hybrid gas sensor array.

The colorimetric sensor array, a kind of P-nose, represents a facile and visible optical-transduced detecting approach, the color patterns of which change upon exposure to VOCs [247]. The typical system of colorimetric sensing is shown in Fig. 12(a). The core parts include chamber, digital cameras, light source, gas inject controller, pump, and some sensors, which has great potential to further minimize accompanying with the development of the electronics industry [248]. Such systems, normally, achieve breath diagnosis with higher accuracy and specificity, due to the probes loaded on the sensing materials using one-lock one key strategy. Changjun Hou et al., have finished a series of works on lung cancer diagnosis-based colorimetric sensing technology [19, 248–251]. Figure 12(b) shows that the colors of the sensing matrix are changed after exposure to the breath of a lung cancer patient, in which the differences can be further magnified by the advanced algorithm. In addition, the sensor array also showed good anti-humidity properties, which avoids the common problem of humidity interference in practical applications. The main limitation of such colorimetric sensor arrays is its irreversibility.

5 Conclusions and future perspectives

In summary, the research methodology of volatolomics in healthcare is critically considered and given out, at first. Then, to our best knowledge, the sets of volatolome according to specific diseases through different body sources are systematically summarized. Thirdly, the advanced E-nose and P-nose technologies for VOCs detection are introduced. This review paper well answers the question of how to connect the clinic, volatolomics, and sensing technology together.

However, if the diagnosis based on the volatolomics would be accepted as one of the standard diagnostics methods/techniques of specific diseases, the relationship between the volatolomics (bio-/chemical markers) and special disease needs to be further clarified. Several aspects can be considered.

• The VOCs sampling and releasing method should establish a standard of operations (SOP) for ensuring the uniformity and accuracy of VOCs samples.

• Novel absorbent materials with well-tailored pore structures need to be well applied, among which crystalline porous materials might be good candidates to be studied. Till now, the widely used absorbers in volatolomics are Tanex and carbon black which lack
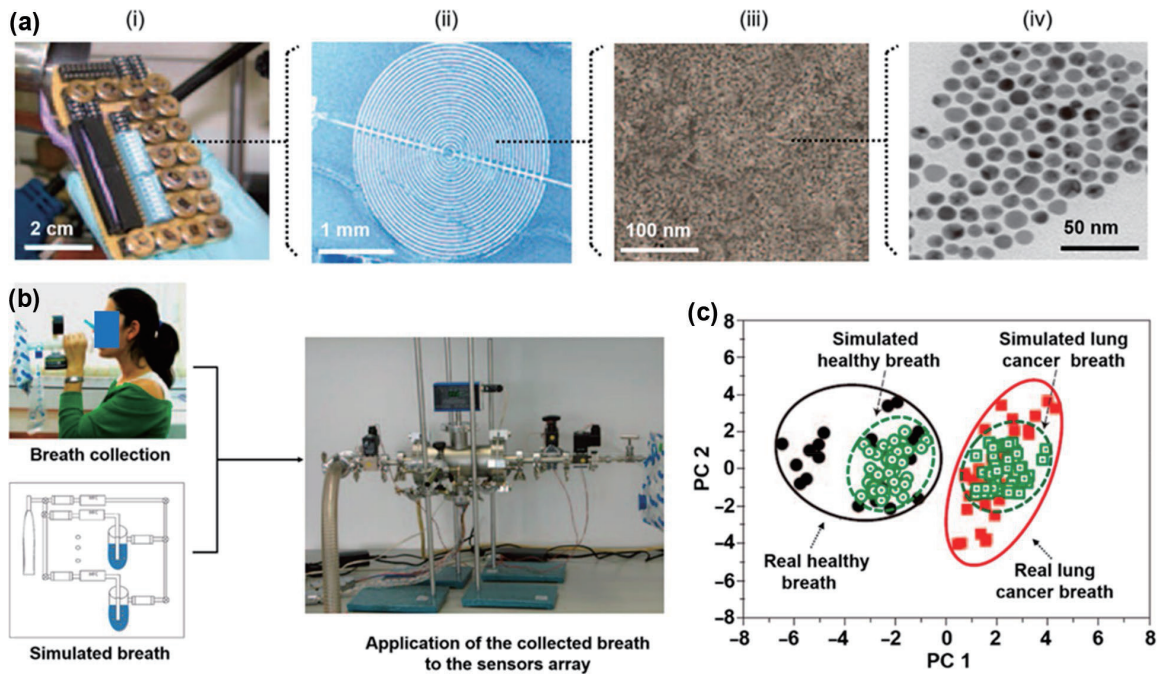
Figure 10 Chemiresistor arrays-based E-nose. (a) Photograph (i), microscopy image (ii), SEM image (iii), and TEM image (iv) of the GNP-based sensors. (b) Photo of the sensing process. (c) PCA result of healthy people and lung cancer patients. Reproduced with permission from Ref. [41], © Macmillan Publishers Limited 2009.
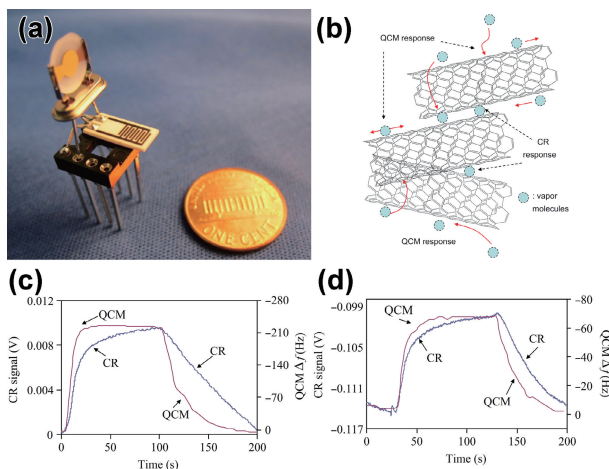

Figure 11 (a) Photograph of the sensor combination of QCM and chemiresistor based on chemically functionalized SWCNTs. (b) Scheme for the response mechanism of pristine SWCNT-coated QCMs and chemiresistors. (c) The response signals of SWCNT-coated QCMs and chemiresistors to 3,000 ppm butanol. (d) The response signals of SWCNT-coated QCMs and chemiresistors to 3,000 ppm butyl acetate. Reproduced with permission from Ref. [199], © Elsevier B.V. 2014.
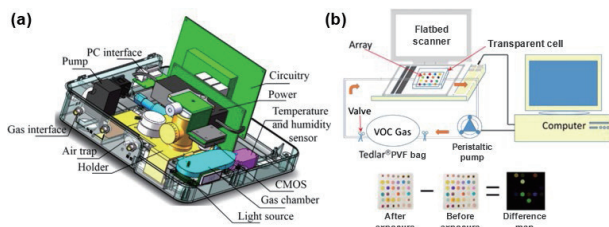
Figure 12 The typical colorimetric sensing array setup and results. (a) The structure scheme of a colorimetric sensing system. Reprinted with permission from Ref. [248], © Elsevier B.V. 2017. (b) The scheme of the colorimetric VOCs sensing experiments and their representative results. Reprinted with permission from Ref. [19], © Springer-Verlag GmbH Germany, part of Springer Nature 2018.

the ability of selective absorption. For off-line volatolomics diagnosis, absorbers, resisting humidity, CO_2, and O_2, can relief the interference towards sensors.

• Advanced algorithms should be used in identifying the principal components of confounding VOCs results via effective signal processing.

• Most advanced instruments in analytical chemistry, such as multi-dimensional GC-MS, need to be used to more precisely establish the database of volatolomics.

From the viewpoint of sensing technology, two directions along both "one-lock one-key" and "interactive semi-selective" sensors array are important and promising, even might integrate as a hybrid sensing system. Several common aspects can be considered.

• To establish the relationship between the sensing mechanism and sensing features extracted from sensing signals for more efficiently designing sensitive materials. Predictably is that the *operando* technology (the *Latin gerund*, which means working or operating) will be explosively built and utilized to *in-situ* study the hybrid sensing mechanisms under real working conditions.

• To introduce additional effects (e.g., gas separation and crystal softness) and devices (e.g., FETs) into the sensing technology for enhancing the ability to extract more effective features from sensing signals.

• To develop minimized system to precisely measure the sensing signals with low power consumption.

• To utilize advanced algorithms and ANN for promoting the ability of data mining and processing with higher precision and faster speed.

After solving the aforementioned issues, the disease diagnosis/screening through volatolomics could have greatly proceeded.

Acknowledgements

References

[1] GBD 2019 diseases and injuries collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of disease study 2019. *Lancet* **2020**, *396*, 1204–1222.

[2] Siegel, R. L.; Miller, K. D.; Fuchs, H. E.; Jemal, A. Cancer statistics, 2022. *CA: Cancer J. Clin.* **2022**, *72*, 7–33.

[3] Gould, M. K.; Huang, B. Z.; Tammemagi, M. C.; Kinar, Y.; Shiff, R. Machine learning for early lung cancer identification using routine clinical and laboratory data. *Am. J. Respir. Crit. Care Med.* **2021**, *204*, 445–453.

[4] Yang, J. S.; Xu, R. Y.; Wang, C. C.; Qiu, J. D.; Ren, B.; You, L. Early screening and diagnosis strategies of pancreatic cancer: A comprehensive review. *Cancer Commun.* **2021**, *41*, 1257–1274.

[5] Acharya, B.; Acharya, A.; Gautam, S.; Ghimire, S. P.; Mishra, G.; Parajuli, N.; Sapkota, B. Advances in diagnosis of tuberculosis: An update into molecular diagnosis of *Mycobacterium tuberculosis*. *Mol. Biol. Rep.* **2020**, *47*, 4065–4075.

[6] Vandenberg, O.; Martiny, D.; Rochas, O.; van Belkum, A.; Kozlakidis, Z. Considerations for diagnostic COVID-19 tests. *Nat. Rev. Microbiol.* **2021**, *19*, 171–183.

[7] Ito, E.; Iha, K.; Yoshimura, T.; Nakaishi, K.; Watabe, S. Early diagnosis with ultrasensitive ELISA. *Adv. Clin. Chem.* **2021**, *101*, 121–133.

[8] Afzal, A. Molecular diagnostic technologies for COVID-19: Limitations and challenges. *J. Adv. Res.* **2020**, *26*, 149–159.

[9] Pagana, K. D.; Pagana, T. J.; Pagana, T. N. *Mosby's Diagnostic and Laboratory Test Reference*, 14th ed.; Elsevier: St. Louis, 2019.

[10] Herring, W. *Learning Radiology: Recognizing the Basics*, 4th ed.; Elsevier: Philadelphia, 2019.

[11] Lamoureux, C.; Hanna, T. N.; Sprecher, D.; Weber, S.; Callaway, E. Radiologist errors by modality, anatomic region, and pathology for 1.6 million exams: What we have learned. *Emerg. Radiol.* **2021**, *28*, 1135–1141.

[12] Velusamy, P.; Su, C. H.; Ramasamy, P.; Arun, V.; Rajnish, N.; Raman, P.; Baskaralingam, V.; Senthil Kumar, S. M.; Gopinath, S. C. B. Volatile organic compounds as potential biomarkers for noninvasive disease detection by nanosensors: A comprehensive review. *Crit. Rev. Anal. Chem.*, in press, https://doi.org/10.1080/10408347.2022.2043145.

[13] Zhong, W. H.; Zhang, X. Y.; Zeng, Y. X.; Lin, D. J.; Wu, J. Recent applications and strategies in nanotechnology for lung diseases. *Nano Res.* **2021**, *14*, 2067–2089.

[14] Zhang, S.; Pang, J. B.; Li, Y. F.; Yang, F.; Gemming, T.; Wang, K.; Wang, X.; Peng, S.; Liu, X. Y.; Chang, B. et al. Emerging internet of things driven carbon nanotubes-based devices. *Nano Res.*, in press, https://doi.org/10.1007/s12274-021-3986-7.

[15] Ruddy, E. N.; Carroll, L. A. Select the best VOC control strategy. *Chem. Eng. Prog.* **1993**, *89*, 28–35.

[16] Kesselmeier, J.; Staudt, M. Biogenic volatile organic compounds (VOC): An overview on emission, physiology and ecology. *J. Atmos. Chem.* **1999**, *33*, 23–88.

[17] Kukkar, D.; Vellingiri, K.; Kaur, R.; Bhardwaj, S. K.; Deep, A.; Kim, K. H. Nanomaterials for sensing of formaldehyde in air: Principles, applications, and performance evaluation. *Nano Res.* **2019**, *12*, 225–246.

[18] Zhang, J.; Tian, Y. H.; Luo, Z. W.; Qian, C.; Li, W. W.; Duan, Y. X. Breath volatile organic compound analysis: An emerging method for gastric cancer detection. *J. Breath Res.* **2021**, *15*, 044002.

[19] Zhong, X. H.; Li, D.; Du, W.; Yan, M. Q.; Wang, Y.; Huo, D. Q.; Hou, C. J. Rapid recognition of volatile organic compounds with colorimetric sensor arrays for lung cancer screening. *Anal. Bioanal. Chem.* **2018**, *410*, 3671–3681.

[20] Buszewski, B.; Kęsy, M.; Ligor, T.; Amann, A. Human exhaled air analytics: Biomarkers of diseases. *Biomed. Chromatogr.* **2007**, *21*, 553–566.

[21] Zhu, B.; Wang, H. C. *Diagnostics of Traditional Chinese Medicine*; Singing Dragon: London, 2010.

[22] Corradi, M.; Mutti, A. News from the breath analysis summit 2011. *J. Breath Res.* **2012**, *6*, 020201.

[23] Dima, A. C.; Balaban, D. V.; Dima, A. Diagnostic application of volatile organic compounds as potential biomarkers for detecting digestive neoplasia: A systematic review. *Diagnostics* **2021**, *11*, 2317.

[24] Vishinkin, R.; Busool, R.; Mansour, E.; Fish, F.; Esmail, A.; Kumar, P.; Gharaa, A.; Cancilla, J. C.; Torrecilla, J. S.; Skenders, G. et al. Profiles of volatile biomarkers detect tuberculosis from skin. *Adv. Sci.* **2021**, *8*, 2100235.

[25] da Costa, B. R. B.; De Martinis, B. S. Analysis of urinary VOCs using mass spectrometric methods to diagnose cancer: A review. *Clin. Mass Spectrom.* **2020**, *18*, 27–37.

[26] Janssens, E.; van Meerbeeck, J. P.; Lamote, K. Volatile organic compounds in human matrices as lung cancer biomarkers: A systematic review. *Crit. Rev. Oncol. Hematol.* **2020**, *153*, 103037.

[27] Van Malderen, K.; De Winter, B. Y.; De Man, J. G.; De Schepper, H. U.; Lamote, K. Volatomics in inflammatory bowel disease and irritable bowel syndrome. *EBioMedicine* **2020**, *54*, 102725.

[28] Broza, Y. Y.; Zhou, X.; Yuan, M. M.; Qu, D. Y.; Zheng, Y. B.; Vishinkin, R.; Khatib, M.; Wu, W. W.; Haick, H. Disease detection with molecular biomarkers: From chemistry of body fluids to nature-inspired chemical sensors. *Chem. Rev.* **2019**, *119*, 11761–11817.

[29] Krilaviciute, A.; Heiss, J. A.; Leja, M.; Kupcinskas, J.; Hawick, H.; Brenner, H. Detection of cancer through exhaled breath: A systematic review. *Oncotarget* **2015**, *6*, 38643–38657.

[30] Hakim, M.; Broza, Y. Y.; Barash, O.; Peled, N.; Phillips, M.; Amann, A.; Haick, H. Volatile organic compounds of lung cancer and possible biochemical pathways. *Chem. Rev.* **2012**, *112*, 5949–5966.

[31] Broza, Y. Y.; Vishinkin, R.; Barash, O.; Nakhleh, M. K.; Haick, H. Synergy between nanomaterials and volatile organic compounds for non-invasive medical evaluation. *Chem. Soc. Rev.* **2018**, *47*, 4781–4859.

[32] Haick, H.; Broza, Y. Y.; Mochalski, P.; Ruzsanyi, V.; Amann, A. Assessment, origin, and implementation of breath volatile cancer markers. *Chem. Soc. Rev.* **2014**, *43*, 1423–1449.

[33] Van den Velde, S.; Nevens, F.; Van Hee, P.; van Steenberghe, D.; Quirynen, M. GC-MS analysis of breath odor compounds in liver patients. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci.* **2008**, *875*, 344–348.

[34] Lubes, G.; Goodarzi, M. GC-MS based metabolomics used for the identification of cancer volatile organic compounds as biomarkers. *J. Pharm. Biomed. Anal.* **2018**, *147*, 313–322.

[35] Mentana, A.; Camele, I.; Mang, S. M.; De Benedetto, G. E.; Frisullo, S.; Centonze, D. Volatolomics approach by HS-SPME-GC-MS and multivariate analysis to discriminate olive tree varieties infected by Xylella fastidiosa. *Phytochem. Anal.* **2019**, *30*, 623–634.

[36] Choi, M. J.; Oh, C. H. 2nd dimensional GC-MS analysis of sweat volatile organic compounds prepared by solid phase micro-extraction. *Technol. Health Care* **2014**, *22*, 481–488.

[37] Gruber, B.; Keller, S.; Groeger, T.; Matuschek, G.; Szymczak, W.; Zimmermann, R. Breath gas monitoring during a glucose challenge by a combined PTR-QMS/GC×GC-TOFMS approach for the verification of potential volatile biomarkers. *J. Breath Res.* **2016**, *10*, 036003.

[38] Rudnicka, J.; Kowalkowski, T.; Ligor, T.; Buszewski, B. Determination of volatile organic compounds as biomarkers of lung cancer by SPME-GC-TOF/MS and chemometrics. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci.* **2011**, *879*, 3360–3366.

[39] Stefanuto, P. H.; Zanella, D.; Vercammen, J.; Henket, M.; Schleich, F.; Louis, R.; Focant, J. F. Multimodal combination of GC × GC-HRTOFMS and SIFT-MS for asthma phenotyping using exhaled breath. *Sci. Rep.* **2020**, *10*, 16159.

[40] Yang, J.; Li, Y. J.; Liu, Q. Q.; Li, L.; Feng, A. Z.; Wang, T. Y.; Zheng, S.; Xu, A. D.; Lyu, J. Brief introduction of medical database and data mining technology in big data era. *J. Evid. Based Med.* **2020**, *13*, 57–69.

[41] Peng, G.; Tisch, U.; Adams, O.; Hakim, M.; Shehada, N.; Broza, Y.

Y.; Billan, S.; Abdah-Bortnyak, R.; Kuten, A.; Haick, H. Diagnosing lung cancer in exhaled breath using gold nanoparticles. *Nat. Nanotechnol.* **2009**, *4*, 669–673.

[42] Liu, K.; Shang, C. D.; Wang, Z. L.; Qi, Y. Y.; Miao, R.; Liu, K. Q.; Liu, T. H.; Fang, Y. Non-contact identification and differentiation of illicit drugs using fluorescent films. *Nat. Commun.* **2018**, *9*, 1695.

[43] Hu, W. W.; Wan, L. T.; Jian, Y. Y.; Ren, C.; Jin, K.; Su, X. H.; Bai, X. X.; Haick, H.; Yao, M. S.; Wu, W. W. Electronic noses: From advanced materials to sensors aided with data processing. *Adv. Mater. Technol.* **2019**, *4*, 1800488.

[44] Broza, Y. Y.; Zuri, L.; Haick, H. Combined volatolomics for monitoring of human body chemistry. *Sci. Rep.* **2014**, *4*, 4611.

[45] Xu, Z. Q.; Broza, Y. Y.; Ionsecu, R.; Tisch, U.; Ding, L.; Liu, H.; Song, Q.; Pan, Y. Y.; Xiong, F. X.; Gu, K. S. et al. A nanomaterial-based breath test for distinguishing gastric cancer from benign gastric conditions. *Br. J. Cancer* **2013**, *108*, 941–950.

[46] Amal, H.; Ding, L.; Liu, B. B.; Tisch, U.; Xu, Z. Q.; Shi, D. Y.; Zhao, Y.; Chen, J.; Sun, R. X.; Liu, H. et al. The scent fingerprint of hepatocarcinoma: *In-vitro* metastasis prediction with volatile organic compounds (VOCS). *Int. J. Nanomedicine* **2012**, *7*, 4135–4146.

[47] Xue, R. Y.; Dong, L.; Zhang, S.; Deng, C. H.; Liu, T. T.; Wang, J. Y.; Shen, X. Z. Investigation of volatile biomarkers in liver cancer blood using solid-phase microextraction and gas chromatography/mass spectrometry. *Rapid Commun. Mass Spectrom.* **2008**, *22*, 1181–1186.

[48] Hakim, M.; Billan, S.; Tisch, U.; Peng, G.; Dvrokind, I.; Marom, O.; Abdah-Bortnyak, R.; Kuten, A.; Haick, H. Diagnosis of head-and-neck cancer from exhaled breath. *Br. J. Cancer* **2011**, *104*, 1649–1655.

[49] Peng, G.; Hakim, M.; Broza, Y. Y.; Billan, S.; Abdah-Bortnyak, R.; Kuten, A.; Tisch, U.; Haick, H. Detection of lung, breast, colorectal, and prostate cancers from exhaled breath using a single array of nanosensors. *Br. J. Cancer* **2010**, *103*, 542–551.

[50] Phillips, M.; Altorki, N.; Austin, J. H. M.; Cameron, R. B.; Cataneo, R. N.; Kloss, R.; Maxfield, R. A.; Munawar, M. I.; Pass, H. I.; Rashid, A. et al. Detection of lung cancer using weighted digital analysis of breath biomarkers. *Clin. Chim. Acta* **2008**, *393*, 76–84.

[51] Phillips, M.; Cataneo, R. N.; Ditkoff, B. A.; Fisher, P.; Greenberg, J.; Gunawardena, R.; Kwon, C. S.; Rahbari-Oskoui, F.; Wong, C. Volatile markers of breast cancer in the breath. *Breast J.* **2003**, *9*, 184–191.

[52] Phillips, M.; Cataneo, R. N.; Ditkoff, B. A.; Fisher, P.; Greenberg, J.; Gunawardena, R.; Kwon, C. S.; Tietje, O.; Wong, C. Prediction of breast cancer using volatile biomarkers in the breath. *Breast Cancer Res. Treat.* **2006**, *99*, 19–21.

[53] Phillips, M.; Cataneo, R. N.; Saunders, C.; Hope, P.; Schmitt, P.; Wai, J. Volatile biomarkers in the breath of women with breast cancer. *J. Breath Res.* **2010**, *4*, 026003.

[54] Poli, D.; Carbognani, P.; Corradi, M.; Goldoni, M.; Acampa, O.; Balbi, B.; Bianchi, L.; Rusca, M.; Mutti, A. Exhaled volatile organic compounds in patients with non-small cell lung cancer: Cross sectional and nested short-term follow-up study. *Respir. Res.* **2005**, *6*, 71.

[55] Fuchs, P.; Loeseken, C.; Schubert, J. K.; Miekisch, W. Breath gas aldehydes as biomarkers of lung cancer. *Int. J. Cancer* **2010**, *126*, 2663–2670.

[56] Broza, Y. Y.; Kremer, R.; Tisch, U.; Gevorkyan, A.; Shiban, A.; Best, L. A.; Haick, H. A nanomaterial-based breath test for short-term follow-up after lung tumor resection. *Nanomedicine* **2013**, *9*, 15–21.

[57] Gaspar, E. M.; Lucena, A. F.; Duro da Costa, J.; Chaves das Neves, H. Organic metabolites in exhaled human breath—A multivariate approach for identification of biomarkers in lung disorders. *J. Chromatogr. A* **2009**, *1216*, 2749–2756.

[58] Song, G.; Qin, T.; Liu, H.; Xu, G. B.; Pan, Y. Y.; Xiong, F. X.; Gu, K. S.; Sun, G. P.; Chen, Z. D. Quantitative breath analysis of volatile organic compounds of lung cancer patients. *Lung Cancer* **2010**, *67*, 227–231.

[59] Barash, O.; Peled, N.; Hirsch, F. R.; Haick, H. Sniffing the unique

[60] "odor print" of non-small-cell lung cancer with gold nanoparticles. *Small* **2009**, *5*, 2618–2624.

Davies, M. P. A.; Barash, O.; Jeries, R.; Peled, N.; Ilouze, M.; Hyde, R.; Marcus, M. W.; Field, J. K.; Haick, H. Unique volatilomic signatures of TP53 and KRAS in lung cells. *Br. J. Cancer* **2014**, *111*, 1213–1221.

[61] Chen, X.; Xu, F. J.; Wang, Y.; Pan, Y. F.; Lu, D. J.; Wang, P.; Ying, K. J.; Chen, E. G.; Zhang, W. M. A study of the volatile organic compounds exhaled by lung cancer cells *in vitro* for breath diagnosis. *Cancer* **2007**, *110*, 835–844.

[62] Filipiak, W.; Sponring, A.; Filipiak, A.; Ager, C.; Schubert, J.; Miekisch, W.; Amann, A.; Troppmair, J. TD-GC-MS analysis of volatile metabolites of human lung cancer and normal cells *in vitro*. *Cancer Epidemiol. Biomarkers Prev.* **2010**, *19*, 182–195.

[63] Amal, H.; Leja, M.; Funka, K.; Skapars, R.; Sivins, A.; Ancans, G.; Liepniece-Karele, I.; Kikuste, I.; Lasina, I.; Haick, H. Detection of precancerous gastric lesions and gastric cancer through exhaled breath. *Gut* **2016**, *65*, 400–407.

[64] Hicks, L. C.; Huang, J. Z.; Kumar, S.; Powles, S. T.; Orchard, T. R.; Hanna, G. B.; Williams, H. R. T. Analysis of exhaled breath volatile organic compounds in inflammatory bowel disease: A pilot study. *J. Crohns Colitis* **2015**, *9*, 731–737.

[65] Karban, A.; Nakhleh, M. K.; Cancilla, J. C.; Vishinkin, R.; Rainis, T.; Koifman, E.; Jeries, R.; Ivgi, H.; Torrecilla, J. S.; Haick, H. Programmed nanoparticles for tailoring the detection of inflammatory bowel diseases and irritable bowel syndrome disease via breathprint. *Adv. Healthc. Mater.* **2016**, *5*, 2339–2344.

[66] Winlaw, D. S.; Keogh, A. M.; Schyvens, C. G.; Spratt, P. M.; Macdonald, P. S.; Smythe, G. A. Increased nitric oxide production in heart failure. *Lancet* **1994**, *344*, 373–374.

[67] Pijls, K. E.; Smolinska, A.; Jonkers, D. M. A. E.; Dallinga, J. W.; Masclee, A. A. M.; Koek, G. H.; van Schooten, F. J. A profile of volatile organic compounds in exhaled air as a potential non-invasive biomarker for liver cirrhosis. *Sci. Rep.* **2016**, *6*, 19903.

[68] Chen, S.; Zieve, L.; Mahadevan, V. Mercaptans and dimethyl sulfide in the breath of patients with cirrhosis of the liver. Effect of feeding methionine. *J. Lab. Clin. Med.* **1970**, *75*, 628–635.

[69] Kaji, H.; Hisamura, M.; Saito, N.; Murao, M. Gas chromatographic determination of volatile sulfur compounds in the expired alveolar air in hepatopathic subjects. *J. Chromatogr.* **1978**, *145*, 464–468.

[70] Cikach, F. S. Jr.; Tonelli, A. R.; Barnes, J.; Paschke, K.; Newman, J.; Grove, D.; Dababneh, L.; Wang, S. H.; Dweik, R. A. Breath analysis in pulmonary arterial hypertension. *Chest* **2014**, *145*, 551–558.

[71] Mansoor, J. K.; Schelegle, E. S.; Davis, C. E.; Walby, W. F.; Zhao, W. X.; Aksenov, A. A.; Pasamontes, A.; Figueroa, J.; Allen, R. Analysis of volatile compounds in exhaled breath condensate in patients with severe pulmonary arterial hypertension. *PLoS One* **2014**, *9*, e95331.

[72] Phillips, M.; Cataneo, R. N.; Condos, R.; Ring Erickson, G. A.; Greenberg, J.; La Bombardi, V.; Munawar, M. I.; Tietje, O. Volatile biomarkers of pulmonary tuberculosis in the breath. *Tuberculosis* **2007**, *87*, 44–52.

[73] Tangerman, A.; Winkel, E. G. Extra-oral halitosis: An overview. *J. Breath Res.* **2010**, *4*, 017003.

[74] Avincsal, M. O.; Altundag, A.; Ulusoy, S.; Dinc, M. E.; Dalgic, A.; Topak, M. Halitosis associated volatile sulphur compound levels in patients with laryngopharyngeal reflux. *Eur. Arch. Otorhinolaryngol.* **2016**, *273*, 1515–1520.

[75] Corradi, M.; Rubinstein, I.; Andreoli, R.; Manini, P.; Caglieri, A.; Poli, D.; Alinovi, R.; Mutti, A. Aldehydes in exhaled breath condensate of patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2003**, *167*, 1380–1386.

[76] Van Berkel, J. J. B. N.; Dallinga, J. W.; Möller, G. M.; Godschalk, R. W. L.; Moonen, E. J.; Wouters, E. F. M.; Van Schooten, F. J. A profile of volatile organic compounds in breath discriminates COPD patients from controls. *Respir. Med.* **2010**, *104*, 557–563.

[77] Paredi, P.; Kharitonov, S. A.; Leak, D.; Ward, S.; Cramer, D.; Barnes, P. J. Exhaled ethane, a marker of lipid peroxidation, is elevated in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2000**, *162*, 369–373.

[78] Aksenov, A. A.; Gojova, A.; Zhao, W. X.; Morgan, J. T.; Sankaran, S.; Sandrock, C. E.; Davis, C. E. Characterization of volatile organic compounds in human leukocyte antigen heterologous expression systems: A cell's "chemical odor fingerprint". *ChemBioChem* **2012**, *13*, 1053–1059.

[79] Halliwell, B.; Gutteridge, J. M.; Cross, C. E. Free radicals, antioxidants, and human disease: Where are we now? *J. Lab. Clin. Med.* **1992**, *119*, 598–620.

[80] Broza, Y. Y.; Mochalski, P.; Ruzsanyi, V.; Amann, A.; Haick, H. Hybrid volatolomics and disease detection. *Angew. Chem., Int. Ed.* **2015**, *54*, 11036–11048.

[81] Opitz, P.; Herbarth, O. The volatilome-investigation of volatile organic metabolites (VOM) as potential tumor markers in patients with head and neck squamous cell carcinoma (HNSCC). *J. Otolaryngol. Head Neck Surg.* **2018**, *47*, 42.

[82] Cauchi, M.; Weber, C. M.; Bolt, B. J.; Spratt, P. B.; Bessant, C.; Turner, D. C.; Willis, C. M.; Britton, L. E.; Turner, C.; Morgan, G. Evaluation of gas chromatography mass spectrometry and pattern recognition for the identification of bladder cancer from urine headspace. *Anal. Methods* **2016**, *8*, 4037–4046.

[83] Guadagni, R.; Miraglia, N.; Simonelli, A.; Silvestre, A.; Lamberti, M.; Feola, D.; Acampora, A.; Sannolo, N. Solid-phase microextraction-gas chromatography-mass spectrometry method validation for the determination of endogenous substances: Urinary hexanal and heptanal as lung tumor biomarkers. *Anal. Chim. Acta* **2011**, *701*, 29–36.

[84] Hanai, Y.; Shimono, K.; Matsumura, K.; Vachani, A.; Albelda, S.; Yamazaki, K.; Beauchamp, G. K.; Oka, H. Urinary volatile compounds as biomarkers for lung cancer. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 679–684.

[85] Yang, Q.; Shi, X. Z.; Wang, Y.; Wang, W. Z.; He, H. B.; Lu, X.; Xu, G. W. Urinary metabonomic study of lung cancer by a fully automatic hyphenated hydrophilic interaction/RPLC-MS system. *J. Sep. Sci.* **2010**, *33*, 1495–1503.

[86] Banday, K. M.; Pasikanti, K. K.; Chan, E. C. Y.; Singla, R.; Rao, K. V. S.; Chauhan, V. S.; Nanda, R. K. Use of urine volatile organic compounds to discriminate tuberculosis patients from healthy subjects. *Anal. Chem.* **2011**, *83*, 5526–5534.

[87] Dospinescu, V. M.; Tiele, A.; Covington, J. A. Sniffing out urinary tract infection—Diagnosis based on volatile organic compounds and smell profile. *Biosensors* **2020**, *10*, 83.

[88] Yang, H.; Kim, D.; Kim, J.; Moon, D.; Song, H. S.; Lee, M.; Hong, S.; Park, T. H. Nanodisc-based bioelectronic nose using olfactory receptor produced in *Escherichia coli* for the assessment of the death-associated odor cadaverine. *ACS Nano* **2017**, *11*, 11847–11855.

[89] Probert, C. S. J.; Ahmed, I.; Khalid, T.; Johnson, E.; Smith, S.; Ratcliffe, N. Volatile organic compounds as diagnostic biomarkers in gastrointestinal and liver diseases. *J. Gastrointestin. Liver Dis.* **2009**, *18*, 337–343.

[90] Cummings, J. H. Short chain fatty acids in the human colon. *Gut* **1981**, *22*, 763–779.

[91] Yokoyama, M. T.; Carlson, J. R. Microbial metabolites of tryptophan in the intestinal tract with special reference to skatole. *Am. J. Clin. Nutr.* **1979**, *32*, 173–178.

[92] Lee, J. H.; Karamychev, V. N.; Kozyavkin, S. A.; Mills, D.; Pavlov, A. R.; Pavlova, N. V.; Polouchine, N. N.; Richardson, P. M.; Shakhova, V. V.; Slesarev, A. I. et al. Comparative genomic analysis of the gut bacterium *Bifidobacterium longum* reveals loci susceptible to deletion during pure culture growth. *BMC Genomics* **2008**, *9*, 247.

[93] Ahmed, I.; Greenwood, R.; de Lacy Costello, B.; Ratcliffe, N. M.; Probert, C. S. An investigation of fecal volatile organic metabolites in irritable bowel syndrome. *PLoS One* **2013**, *8*, e58204.

[94] Bannaga, A. S.; Farrugia, A.; Arasaradnam, R. P. Diagnosing inflammatory bowel disease using noninvasive applications of volatile organic compounds: A systematic review. *Expert Rev. Gastroenterol. Hepatol.* **2019**, *13*, 1113–1122.

[95] Homann, N. Alcohol and upper gastrointestinal tract cancer: The role of local acetaldehyde production. *Addict. Biol.* **2001**, *6*, 309–323.

[96] Studer, S. M.; Orens, J. B.; Rosas, I.; Krishnan, J. A.; Cope, K. A.; Yang, S.; Conte, J. V.; Becker, P. B.; Risby, T. H. Patterns and significance of exhaled-breath biomarkers in lung transplant recipients with acute allograft rejection. *J. Heart Lung Transplant.* **2001**, *20*, 1158–1166.

[97] Tisch, U.; Schlesinger, I.; Ionescu, R.; Nassar, M.; Axelrod, N.; Robertman, D.; Tessler, Y.; Azar, F.; Marmur, A.; Aharon-Peretz, J. et al. Detection of Alzheimer's and Parkinson's disease from exhaled breath using nanomaterial-based sensors. *Nanomedicine* **2013**, *8*, 43–56.

[98] Paredi, P.; Kharitonov, S. A.; Barnes, P. J. Elevation of exhaled ethane concentration in asthma. *Am. J. Respir. Crit. Care Med.* **2000**, *162*, 1450–1454.

[99] Olopade, C. O.; Zakkar, M.; Swedler, W. I.; Rubinstein, I. Exhaled pentane levels in acute asthma. *Chest* **1997**, *111*, 862–865.

[100] Hunt, J. F.; Erwin, E.; Palmer, L.; Vaughan, J.; Malhotra, N.; Platts-Mills, T. A. E.; Gaston, B. Expression and activity of pH-regulatory glutaminase in the human airway epithelium. *Am. J. Respir. Crit. Care Med.* **2002**, *165*, 101–107.

[101] Ashutosh, K. Nitric oxide and asthma: A review. *Curr. Opin. Pulm. Med.* **2000**, *6*, 21–25.

[102] Kharitonov, S. A.; Yates, D.; Robbins, R. A.; Barnes, P. J.; Logan-Sinclair, R.; Shinebourne, E. A. Increased nitric oxide in exhaled air of asthmatic patients. *Lancet* **1994**, *343*, 133–135.

[103] Persson, M. G.; Gustafsson, L. E.; Zetterström, O.; Agrenius, V.; Ihre, E. Single-breath nitric oxide measurements in asthmatic patients and smokers. *Lancet* **1994**, *343*, 146–147.

[104] Montuschi, P.; Corradi, M.; Ciabattoni, G.; Nightingale, J.; Kharitonov, S. A.; Barnes, P. J. Increased 8-isoprostane, a marker of oxidative stress, in exhaled condensate of asthma patients. *Am. J. Respir. Crit. Care Med.* **1999**, *160*, 216–220.

[105] Horváth, I.; Donnelly, L. E.; Kiss, A.; Kharitonov, S. A.; Lim, S.; Chung, K. F.; Barnes, P. J. Combined use of exhaled hydrogen peroxide and nitric oxide in monitoring asthma. *Am. J. Respir. Crit. Care Med.* **1998**, *158*, 1042–1046.

[106] Marom, O.; Nakhoul, F.; Tisch, U.; Shiban, A.; Abassi, Z.; Haick, H. Gold nanoparticle sensors for detecting chronic kidney disease and disease progression. *Nanomedicine* **2012**, *7*, 639–650.

[107] Simenhoff, M. L.; Burke, J. F.; Saukkonen, J. J.; Ordinario, A. T.; Doty, R.; Dunn, S. Biochemical profile of uremic breath. *N. Engl. J. Med.* **1977**, *297*, 132–135.

[108] Altomare, D. F.; Di Lena, M.; Porcelli, F.; Trizio, L.; Travaglio, E.; Tutino, M.; Dragonieri, S.; Memeo, V.; de Gennaro, G. Exhaled volatile organic compounds identify patients with colorectal cancer. *Br. J. Surg.* **2013**, *100*, 144–150.

[109] McCurdy, M. R.; Sharafkhaneh, A.; Abdel-Monem, H.; Rojo, J.; Tittel, F. K. Exhaled nitric oxide parameters and functional capacity in chronic obstructive pulmonary disease. *J. Breath Res.* **2011**, *5*, 016003.

[110] Dekhuijzen, P. N.; Aben, K. K.; Dekker, I.; Aarts, L. P.; Wielders, P. L.; Van Herwaarden, C. L.; Bast, A. Increased exhalation of hydrogen peroxide in patients with stable and unstable chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **1996**, *154*, 813–816.

[111] Balfour-Lynn, I. M.; Laverty, A.; Dinwiddie, R. Reduced upper airway nitric oxide in cystic fibrosis. *Arch. Dis. Child.* **1996**, *75*, 319–322.

[112] Thomas, S. R.; Kharitonov, S. A.; Scott, S. F.; Hodson, M. E.; Barnes, P. J. Nasal and exhaled nitric oxide is reduced in adult patients with cystic fibrosis and does not correlate with cystic fibrosis genotype. *Chest* **2000**, *117*, 1085–1089.

[113] Kamboures, M. A.; Blake, D. R.; Cooper, D. M.; Newcomb, R. L.; Barker, M.; Larson, J. K.; Meinardi, S.; Nussbaum, E.; Rowland, F. S. Breath sulfides and pulmonary function in cystic fibrosis. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 15762–15767.

[114] Galassetti, P. R.; Novak, B.; Nemet, D.; Rose-Gottron, C.; Cooper, D. M.; Meinardi, S.; Newcomb, R.; Zaldivar, F.; Blake, D. R. Breath ethanol and acetone as indicators of serum glucose levels: An initial report. *Diabetes Technol. Ther.* **2005**, *7*, 115–123.

[115] Novak, B. J.; Blake, D. R.; Meinardi, S.; Rowland, F. S.; Pontello, A.; Cooper, D. M.; Galassetti, P. R. Exhaled methyl nitrate as a

noninvasive marker of hyperglycemia in type 1 diabetes. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 15613–15618.

[116] Pelli, M. A.; Trovarelli, G.; Capodicasa, E.; De Medio, G. E.; Bassotti, G. Breath alkanes determination in ulcerative colitis and Crohn's disease. *Dis. Colon Rectum* **1999**, *42*, 71–76.

[117] Kokoszka, J.; Nelson, R. L.; Swedler, W. I.; Skosey, J.; Abcarian, H. Determination of inflammatory bowel disease activity by breath pentane analysis. *Dis. Colon Rectum* **1993**, *36*, 597–601.

[118] Phillips, M.; Boehmer, J. P.; Cataneo, R. N.; Cheema, T.; Eisen, H. J.; Fallon, J. T.; Fisher, P. E.; Gass, A.; Greenberg, J.; Kobashigawa, J. et al. Prediction of heart transplant rejection with a breath test for markers of oxidative stress. *Am. J. Cardiol.* **2004**, *94*, 1593–1594.

[119] Hiroshi, K.; Masaya, H.; Nariyoshi, S.; Makoto, M. Evaluation of volatile sulfur compounds in the expired alveolar gas in patients with liver cirrhosis. *Clin. Chim. Acta* **1978**, *85*, 279–284.

[120] Tangerman, A.; Meuwese-Arends, M. T.; van Tongeren, J. H. M. A new sensitive assay for measuring volatile sulphur compounds in human breath by Tenax trapping and gas chromatography and its application in liver cirrhosis. *Clin. Chim. Acta* **1983**, *130*, 103–110.

[121] Hisamura, M. Quantitative analysis of methyl mercaptan and dimethyl sulfide in human expired alveolar gas and its clinical application: Study in normal subjects and patients with liver diseases. *J. Jpn. Soc. Intern. Med.* **1979**, *68*, 1284–1292.

[122] Lee, J.; Ngo, J.; Blake, D.; Meinardi, S.; Pontello, A. M.; Newcomb, R.; Galassetti, P. R. Improved predictive models for plasma glucose estimation from multi-linear regression analysis of exhaled volatile organic compounds. *J. Appl. Physiol.* **2009**, *107*, 155–160.

[123] Miekisch, W.; Schubert, J. K.; Noeldge-Schomburg, G. F. E. Diagnostic potential of breath analysis—Focus on volatile organic compounds. *Clin. Chim. Acta* **2004**, *347*, 25–39.

[124] Nakhleh, M. K.; Amal, H.; Awad, H.; Gharra, A.; Abu-Saleh, N.; Jeries, R.; Haick, H.; Abassi, Z. Sensor arrays based on nanoparticles for early detection of kidney injury by breath samples. *Nanomedicine* **2014**, *10*, 1767–1776.

[125] Ulanowska, A.; Kowalkowski, T.; Trawińska, E.; Buszewski, B. The application of statistical methods using VOCs to identify patients with lung cancer. *J. Breath Res.* **2011**, *5*, 046008.

[126] Filipiak, W.; Filipiak, A.; Sponring, A.; Schmid, T.; Zelger, B.; Ager, C.; Klodzinska, E.; Denz, H.; Pizzini, A.; Lucciarini, P. et al. Comparative analyses of volatile organic compounds (VOCs) from patients, tumors and transformed cell lines for the validation of lung cancer-derived breath markers. *J. Breath Res.* **2014**, *8*, 027111.

[127] Rudnicka, J.; Walczak, M.; Kowalkowski, T.; Jezierski, T.; Buszewski, B. Determination of volatile organic compounds as potential markers of lung cancer by gas chromatography-mass spectrometry versus trained dogs. *Sens. Actuators B: Chem.* **2014**, *202*, 615–621.

[128] Poli, D.; Goldoni, M.; Corradi, M.; Acampa, O.; Carbognani, P.; Internullo, E.; Casalini, A.; Mutti, A. Determination of aldehydes in exhaled breath of patients with lung cancer by means of on-fiber-derivatisation SPME–GC/MS. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci.* **2010**, *878*, 2643–2651.

[129] Kischkel, S.; Miekisch, W.; Sawacki, A.; Straker, E. M.; Trefz, P.; Amann, A.; Schubert, J. K. Breath biomarkers for lung cancer detection and assessment of smoking related effects—Confounding variables, influence of normalization and statistical algorithms. *Clin. Chim. Acta* **2010**, *411*, 1637–1644.

[130] Wehinger, A.; Schmid, A.; Mechtcheriakov, S.; Ledochowski, M.; Grabmer, C.; Gastl, G. A.; Amann, A. Lung cancer detection by proton transfer reaction mass-spectrometric analysis of human breath gas. *Int. J. Mass Spectrom.* **2007**, *265*, 49–59.

[131] Phillips, M.; Gleeson, K.; Hughes, J. M. B.; Greenberg, J.; Cataneo, R. N.; Baker, L.; McVay, W. P. Volatile organic compounds in breath as markers of lung cancer: A cross-sectional study. *Lancet* **1999**, *353*, 1930–1933.

[132] Callol-Sanchez, L.; Munoz-Lucas, M. A.; Gomez-Martin, O.; Maldonado-Sanz, J. A.; Civera-Tejuca, C.; Gutierrez-Ortega, C.; Rodriguez-Trigo, G.; Jareno-Esteban, J. Observation of nonanoic acid and aldehydes in exhaled breath of patients with lung cancer. *J. Breath Res.* **2017**, *11*, 026004.

[133] Phillips, M.; Cataneo, R. N.; Cummin, A. R. C.; Gagliardi, A. J.; Gleeson, K.; Greenberg, J.; Maxfield, R. A.; Rom, W. N. Detection of lung cancer with volatile markers in the breath. *Chest* **2003**, *123*, 2115–2123.

[134] Oguma, T.; Nagaoka, T.; Kurahashi, M.; Kobayashi, N.; Yamamori, S.; Tsuji, C.; Takiguchi, H.; Niimi, K.; Tomomatsu, H.; Tomomatsu, K. et al. Clinical contributions of exhaled volatile organic compounds in the diagnosis of lung cancer. *PLoS One* **2017**, *12*, e0174802.

[135] Phillips, M.; Altorki, N.; Austin, J. H. M.; Cameron, R. B.; Cataneo, R. N.; Greenberg, J.; Kloss, R.; Maxfield, R. A.; Munawar, M. I.; Pass, H. I. et al. Prediction of lung cancer using volatile biomarkers in breath. *Cancer Biomark.* **2007**, *3*, 95–109.

[136] D'Amico, A.; Pennazza, G.; Santonico, M.; Martinelli, E.; Roscioni, C.; Galluccio, G.; Paolesse, R.; Di Natale, C. An investigation on electronic nose diagnosis of lung cancer. *Lung Cancer* **2010**, *68*, 170–176.

[137] Bajtarevic, A.; Ager, C.; Pienz, M.; Klieber, M.; Schwarz, K.; Ligor, M.; Ligor, T.; Filipiak, W.; Denz, H.; Fiegl, M. et al. Noninvasive detection of lung cancer by analysis of exhaled breath. *BMC Cancer* **2009**, *9*, 348.

[138] Yu, H.; Xu, L.; Wang, P. Solid phase microextraction for analysis of alkanes and aromatic hydrocarbons in human breath. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci.* **2005**, *826*, 69–74.

[139] Fu, X. A.; Li, M. X.; Knipp, R. J.; Nantz, M. H.; Bousamra, M. Noninvasive detection of lung cancer using exhaled breath. *Cancer Med.* **2014**, *3*, 174–181.

[140] Broza, Y. Y.; Har-Shai, L.; Jeries, R.; Cancilla, J. C.; Glass-Marmor, L.; Lejbkowicz, I.; Torrecilla, J. S.; Yao, X. L.; Feng, X. L.; Narita, A. et al. Exhaled breath markers for nonimaging and noninvasive measures for detection of multiple sclerosis. *ACS Chem. Neurosci.* **2017**, *8*, 2402–2413.

[141] Ionescu, R.; Broza, Y.; Shaltieli, H.; Sadeh, D.; Zilberman, Y.; Feng, X. L.; Glass-Marmor, L.; Lejbkowicz, I.; Müllen, K.; Miller, A. et al. Detection of multiple sclerosis from exhaled breath using bilayers of polycyclic aromatic hydrocarbons and single-wall carbon nanotubes. *ACS Chem. Neurosci.* **2011**, *2*, 687–693.

[142] Tisch, U.; Aluf, Y.; Ionescu, R.; Nakhleh, M.; Bassal, R.; Axelrod, N.; Robertman, D.; Tessler, Y.; Finberg, J. P. M.; Haick, H. Detection of asymptomatic nigrostriatal dopaminergic lesion in rats by exhaled air analysis using carbon nanotube sensors. *ACS Chem. Neurosci.* **2012**, *3*, 161–166.

[143] Assady, S.; Marom, O.; Hemli, M.; Ionescu, R.; Jeries, R.; Tisch, U.; Abassi, Z.; Haick, H. Impact of hemodialysis on exhaled volatile organic compounds in end-stage renal disease: A pilot study. *Nanomedicine* **2014**, *9*, 1035–1045.

[144] Humad, S.; Zarling, E.; Clapper, M.; Skosey, J. L. Breath pentane excretion as a marker of disease activity in rheumatoid arthritis. *Free Radic. Res. Commun.* **1988**, *5*, 101–106.

[145] Phillips, M.; Sabas, M.; Greenberg, J. Increased pentane and carbon disulfide in the breath of patients with schizophrenia. *J. Clin. Pathol.* **1993**, *46*, 861–864.

[146] Wang, C. S.; Dong, R.; Wang, X. Y.; Lian, A. L.; Chi, C. J.; Ke, C. F.; Guo, L.; Liu, S. S.; Zhao, W.; Xu, G. W. et al. Exhaled volatile organic compounds as lung cancer biomarkers during one-lung ventilation. *Sci. Rep.* **2014**, *4*, 7312.

[147] Di Lena, M.; Porcelli, F.; Altomare, D. F. Volatile organic compounds as new biomarkers for colorectal cancer: A review. *Colorectal Dis.* **2016**, *18*, 654–663.

[148] Macfarlane, G. T.; Cummings, J. H.; Macfarlane, S.; Gibson, G. R. Influence of retention time on degradation of pancreatic enzymes by human colonic bacteria grown in a 3-stage continuous culture system. *J. Appl. Bacteriol.* **1989**, *67*, 521–527.

[149] Woodmansey, E. J. Intestinal bacteria and ageing. *J. Appl. Microbiol.* **2007**, *102*, 1178–1186.

[150] Navaneethan, U.; Parsi, M. A.; Lourdusamy, D.; Grove, D.; Sanaka, M. R.; Hammel, J. P.; Vargo, J. J.; Dweik, R. A. Volatile

organic compounds in urine for noninvasive diagnosis of malignant biliary strictures: A pilot study. *Dig. Dis. Sci.* **2015**, *60*, 2150–2157.

[151] Silva, C. L.; Passos, M.; Câmara, J. S. Investigation of urinary volatile organic metabolites as potential cancer biomarkers by solid-phase microextraction in combination with gas chromatography-mass spectrometry. *Br. J. Cancer* **2011**, *105*, 1894–1904.

[152] Wang, D. C.; Wang, C. S.; Pi, X.; Guo, L.; Wang, Y.; Li, M. J.; Feng, Y.; Lin, Z. W.; Hou, W.; Li, E. Y. Urinary volatile organic compounds as potential biomarkers for renal cell carcinoma. *Biomed. Rep.* **2016**, *5*, 68–72.

[153] Silva, C. L.; Passos, M.; Câmara, J. S. Solid phase microextraction, mass spectrometry and metabolomic approaches for detection of potential urinary cancer biomarkers—A powerful strategy for breast cancer diagnosis. *Talanta* **2012**, *89*, 360–368.

[154] Nam, H.; Chung, B. C.; Kim, Y.; Lee, K.; Lee, D. Combining tissue transcriptomics and urine metabolomics for breast cancer biomarker identification. *Bioinformatics* **2009**, *25*, 3151–3157.

[155] Khalid, T.; Aggio, R.; White, P.; De Lacy Costello, B.; Persad, R.; Al-Kateb, H.; Jones, P.; Probert, C. S.; Ratcliffe, N. Urinary volatile organic compounds for the detection of prostate cancer. *PLoS One* **2015**, *10*, e0143283.

[156] Wang, M. G.; Xie, R. J.; Jia, X. B.; Liu, R. C. Urinary volatile organic compounds as potential biomarkers in idiopathic membranous nephropathy. *Med Princ. Pract.* **2017**, *26*, 375–380.

[157] Abaffy, T; Möller, M.; Riemer, D. D.; Milikowski, C.; DeFazio, R. A. A case report-volatile metabolomic signature of malignant melanoma using matching skin as a control. *J. Cancer Sci. Ther.* **2011**, *3*, 140–144.

[158] Abaffy, T.; Duncan, R.; Riemer, D. D.; Tietje, O.; Elgart, G.; Milikowski, C.; Defazio, R. A. Differential volatile signatures from skin, naevi and melanoma: A novel approach to detect a pathological process. *PLoS One* **2010**, *5*, e13813.

[159] Allardyce, R. A.; Hill, A. L.; Murdoch, D. R. The rapid evaluation of bacterial growth and antibiotic susceptibility in blood cultures by selected ion flow tube mass spectrometry. *Diagn. Microbiol. Infect. Dis.* **2006**, *55*, 255–261.

[160] Boots, A. W.; Smolinska, A.; van Berkel, J. J. B. N.; Fijten, R. R. R.; Stobberingh, E. E.; Boumans, M. L. L.; Moonen, E. J.; Wouters, E. F. M.; Dallinga, J. W.; Van Schooten, F. J. Identification of microorganisms based on headspace analysis of volatile organic compounds by gas chromatography-mass spectrometry. *J. Breath Res.* **2014**, *8*, 027106.

[161] Preti, G.; Thaler, E.; Hanson, C. W.; Troy, M.; Eades, J.; Gelperin, A. Volatile compounds characteristic of sinus-related bacteria and infected sinus mucus: Analysis by solid-phase microextraction and gas chromatography-mass spectrometry. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci.* **2009**, *877*, 2011–2018.

[162] Zscheppank, C.; Wiegand, H. L.; Lenzen, C.; Wingender, J.; Telgheder, U. Investigation of volatile metabolites during growth of *Escherichia coli* and *Pseudomonas aeruginosa* by needle trap-GC-MS. *Anal. Bioanal. Chem.* **2014**, *406*, 6617–6628.

[163] Kunze, N.; Göpel, J.; Kuhns, M.; Jünger, M.; Quintel, M.; Perl, T. Detection and validation of volatile metabolic patterns over different strains of two human pathogenic bacteria during their growth in a complex medium using multi-capillary column-ion mobility spectrometry (MCC-IMS). *Appl. Microbiol. Biotechnol.* **2013**, *97*, 3665–3676.

[164] Shestivska, V.; Nemec, A.; Dřevínek, P.; Sovová, K.; Dryahina, K.; Španěl, P. Quantification of methyl thiocyanate in the headspace of *Pseudomonas aeruginosa* cultures and in the breath of cystic fibrosis patients by selected ion flow tube mass spectrometry. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 2459–2467.

[165] Neerincx, A. H.; Geurts, B. P.; Habets, M. F. J.; Booij, J. A.; van Loon, J.; Jansen, J. J.; Buydens, L. M. C.; van Ingen, J.; Mouton, J. W.; Harren, F. J. M. et al. Identification of *Pseudomonas aeruginosa* and *Aspergillus fumigatus* mono- and co-cultures based on volatile biomarker combinations. *J. Breath Res.* **2016**, *10*, 016002.

[166] Schöller, C.; Molin, S.; Wilkins, K. Volatile metabolites from some gram-negative bacteria. *Chemosphere* **1997**, *35*, 1487–1495.

[167] Filipiak, W.; Sponring, A.; Baur, M. M.; Filipiak, A.; Ager, C.; Wiesenhofer, H.; Nagl, M.; Troppmair, J.; Amann, A. Molecular analysis of volatile metabolites released specifically by staphylococcus aureus and pseudomonas aeruginosa. *BMC Microbiol.* **2012**, *12*, 113.

[168] Bean, H. D.; Dimandja, J. M. D.; Hill, J. E. Bacterial volatile discovery using solid phase microextraction and comprehensive two-dimensional gas chromatography-time-of-flight mass spectrometry. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci.* **2012**, *901*, 41–46.

[169] Shestivska, V.; Španěl, P.; Dryahina, K.; Sovová, K.; Smith, D.; Musílek, M.; Nemec, A. Variability in the concentrations of volatile metabolites emitted by genotypically different strains of *Pseudomonas aeruginosa. J. Appl. Microbiol.* **2012**, *113*, 701–713.

[170] Carroll, W.; Lenney, W.; Wang, T. S.; Španěl, P.; Alcock, A.; Smith, D. Detection of volatile compounds emitted by *Pseudomonas aeruginosa* using selected ion flow tube mass spectrometry. *Pediatr. Pulmonol.* **2005**, *39*, 452–456.

[171] Yu, K. S.; Hamilton-Kemp, T. R.; Archbold, D. D.; Collins, R. W.; Newman, M. C. Volatile compounds from *Escherichia coli* O157:H7 and their absorption by strawberry fruit. *J. Agric. Food Chem.* **2000**, *48*, 413–417.

[172] Storer, M. K.; Hibbard-Melles, K.; Davis, B.; Scotter, J. Detection of volatile compounds produced by microbial growth in urine by selected ion flow tube mass spectrometry (SIFT-MS). *J. Microbiol. Methods* **2011**, *87*, 111–113.

[173] Maddula, S.; Blank, L. M.; Schmid, A.; Baumbach, J. I. Detection of volatile metabolites of *Escherichia coli* by multi capillary column coupled ion mobility spectrometry. *Anal. Bioanal. Chem.* **2009**, *394*, 791–800.

[174] Guamán, A. V.; Carreras, A.; Calvo, D.; Agudo, I.; Navajas, D.; Pardo, A.; Marco, S.; Farré, R. Rapid detection of sepsis in rats through volatile organic compounds in breath. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci.* **2012**, *881–882*, 76–82.

[175] Chippendale, T. W. E.; Španěl, P.; Smith, D. Time-resolved selected ion flow tube mass spectrometric quantification of the volatile compounds generated by *E. coli* JM109 cultured in two different media. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 2163–2172.

[176] Bianchi, F.; Careri, M.; Mangia, A.; Mattarozzi, M.; Musci, M.; Concina, I.; Falasconi, M.; Gobbi, E.; Pardo, M.; Sberveglieri, G. Differentiation of the volatile profile of microbiologically contaminated canned tomatoes by dynamic headspace extraction followed by gas chromatography-mass spectrometry analysis. *Talanta* **2009**, *77*, 962–970.

[177] Umber, B. J.; Shin, H. W.; Meinardi, S.; Leu, S. Y.; Zaldivar, F.; Cooper, D. M.; Blake, D. R. Gas signatures from *Escherichia coli* and *Escherichia coli*-inoculated human whole blood. *Clin. Transl. Med.* **2013**, *2*, 13.

[178] Elgaali, H.; Hamilton-Kemp, T. R.; Newman, M. C.; Collins, R. W.; Yu, K. S.; Archbold, D. D. Comparison of long-chain alcohols and other volatile compounds emitted from food-borne and related gram positive and gram negative bacteria. *J. Basic Microbiol.* **2002**, *42*, 373–380.

[179] Zhu, J. J.; Bean, H. D.; Kuo, Y. M.; Hill, J. E. Fast detection of volatile organic compounds from bacterial cultures by secondary electrospray ionization-mass spectrometry. *J. Clin. Microbiol.* **2010**, *48*, 4426–4431.

[180] Saranya, R.; Aarthi, R.; Sankaran, K. Simple and specific colorimetric detection of *Staphylococcus* using its volatile 2-[3-acetoxy-4,4,14-trimethylandrost-8-en-17-yl] propanoic acid in the liquid phase and head space of cultures. *Appl. Microbiol. Biotechnol.* **2015**, *99*, 4423–4433.

[181] Martin, H. J.; Turner, M. A.; Bandelow, S.; Edwards, L.; Riazanskaia, S.; Thomas, C. L. P. Volatile organic compound markers of psychological stress in skin: A pilot study. *J. Breath Res.* **2016**, *10*, 046012.

[182] Ara, K.; Hama, M.; Akiba, S.; Koike, K.; Okisaka, K.; Hagura, T.; Kamiya, T.; Tomita, F. Foot odor due to microbial metabolism and its control. *Can. J. Microbiol.* **2006**, *52*, 357–364.

[183] Yamazaki, S.; Hoshino, K.; Kusuhara, M. Odor associated with aging. *Anti-Aging Med.* **2010**, *7*, 60–65.

[184] Gallagher, M.; Wysocki, C. J.; Leyden, J. J.; Spielman, A. I.; Sun, X.; Preti, G. Analyses of volatile organic compounds from human skin. *Br. J. Dermatol.* **2008**, *159*, 780–791.

[185] Abaffy, T.; Möller, M. G.; Riemer, D. D.; Milikowski, C.; DeFazio, R. A. Comparative analysis of volatile metabolomics signals from melanoma and benign skin: A pilot study. *Metabolomics* **2013**, *9*, 998–1008.

[186] Campbell, L. F.; Farmery, L.; George, S. M. C.; Farrant, P. B. J. Canine olfactory detection of malignant melanoma. *BMJ Case Rep.* **2013**, *2013*, bcr2013008566.

[187] D'Amico, A.; Bono, R.; Pennazza, G.; Santonico, M.; Mantini, G.; Bernabei, M.; Zarlenga, M.; Roscioni, C.; Martinelli, E.; Paolesse, R. et al. Identification of melanoma with a gas sensor array. *Skin Res. Technol.* **2008**, *14*, 226–236.

[188] Kwak, J.; Gallagher, M.; Ozdener, M. H.; Wysocki, C. J.; Goldsmith, B. R.; Isamah, A.; Faranda, A.; Fakharzadeh, S. S.; Herlyn, M.; Johnson, A. T. C. et al. Volatile biomarkers from human melanoma cells. *J. Chromatogr. B: Analyt. Technol. Biomed. Life Sci.* **2013**, *931*, 90–96.

[189] Pickel, D.; Manucy, G. P.; Walker, D. B.; Hall, S. B.; Walker, J. C. Evidence for canine olfactory detection of melanoma. *Appl. Anim. Behav. Sci.* **2004**, *89*, 107–116.

[190] Dormont, L.; Bessière, J. M.; Cohuet, A. Human skin volatiles: A review. *J. Chem. Ecol.* **2013**, *39*, 569–578.

[191] Barzantny, H.; Schröder, J.; Strotmeier, J.; Fredrich, E.; Brune, I.; Tauch, A. The transcriptional regulatory network of *Corynebacterium jeikeium* K411 and its interaction with metabolic routes contributing to human body odor formation. *J. Biotechnol.* **2012**, *159*, 235–248.

[192] Marshall, J.; Holland, K. T.; Gribbon, E. M. A comparative study of the cutaneous microflora of normal feet with low and high levels of odour. *J. Appl. Bacteriol.* **1988**, *65*, 61–68.

[193] Natsch, A.; Derrer, S.; Flachsmann, F.; Schmid, J. A broad diversity of volatile carboxylic acids, released by a bacterial aminoacylase from axilla secretions, as candidate molecules for the determination of human-body odor type. *Chem. Biodivers.* **2006**, *3*, 1–20.

[194] De Giovanni, N.; Fucci, N. The current status of sweat testing for drugs of abuse: A review. *Curr. Med. Chem.* **2013**, *20*, 545–561.

[195] Holmberg, M.; Winquist, F.; Lundström, I.; Gardner, J. W.; Hines, E. L. Identification of paper quality using a hybrid electronic nose. *Sens. Actuators B: Chem.* **1995**, *27*, 246–249.

[196] Ulmer, H.; Mitrovics, J.; Noetzel, G.; Weimar, U.; Göpel, W. Odours and flavours identified with hybrid modular sensor systems. *Sens. Actuators B: Chem.* **1997**, *43*, 24–33.

[197] Pardo, M.; Kwong, L. G.; Sberveglieri, G.; Brubaker, K.; Schneider, J. F.; Penrose, W. R.; Stetter, J. R. Data analysis for a hybrid sensor array. *Sens. Actuators B: Chem.* **2005**, *106*, 136–143.

[198] Li, C. L.; Chen, Y. F.; Liu, M. H.; Lu, C. J. Utilizing diversified properties of monolayer protected gold nano-clusters to construct a hybrid sensor array for organic vapor detection. *Sens. Actuators B: Chem.* **2012**, *169*, 349–359.

[199] Lu, H. L.; Lu, C. J.; Tian, W. C.; Sheen, H. J. A vapor response mechanism study of surface-modified single-walled carbon nanotubes coated chemiresistors and quartz crystal microbalance sensor arrays. *Talanta* **2015**, *131*, 467–474.

[200] Zetola, N. M.; Modongo, C.; Matsiri, O.; Tamuhla, T.; Mbongwe, B.; Matlhagela, K.; Sepako, E.; Catini, A.; Sirugo, G.; Martinelli, E. et al. Diagnosis of pulmonary tuberculosis and assessment of treatment response through analyses of volatile compound patterns in exhaled breath samples. *J. Infect.* **2017**, *74*, 367–376.

[201] Cho, Y. S.; Jung, S. C.; Oh, S. Diagnosis of bovine tuberculosis using a metal oxide-based electronic nose. *Lett. Appl. Microbiol.* **2015**, *60*, 513–516.

[202] Wu, C. S.; Du, L. P.; Wang, D.; Zhao, L. H.; Wang, P. A biomimetic olfactory-based biosensor with high efficiency immobilization of molecular detectors. *Biosens. Bioelectron.* **2012**, *31*, 44–48.

[203] Chen, X.; Cao, M. F.; Li, Y.; Hu, W. J.; Wang, P.; Ying, K. J.; Pan, H. M. A study of an electronic nose for detection of lung cancer based on a virtual SAW gas sensors array and imaging recognition method. *Meas. Sci. Technol.* **2005**, *16*, 1535–1546.

[204] Mazzone, P. J.; Hammel, J.; Dweik, R.; Na, J.; Czich, C.; Laskowski, D.; Mekhail, T. Diagnosis of lung cancer by the analysis of exhaled breath with a colorimetric sensor array. *Thorax* **2007**, *62*, 565–568.

[205] Janzen, M. C.; Ponder, J. B.; Bailey, D. P.; Ingison, C. K.; Suslick, K. S. Colorimetric sensor arrays for volatile organic compounds. *Anal. Chem.* **2006**, *78*, 3591–3600.

[206] Vincent, T. A.; Gardner, J. W. A low cost MEM based NDIR system for the monitoring of carbon dioxide in breath analysis at ppm levels. *Sens. Actuators B: Chem.* **2016**, *236*, 954–964.

[207] Meng, Z.; Stolz, R. M.; Mendecki, L.; Mirica, K. A. Electrically-transduced chemical sensors based on two-dimensional nanomaterials. *Chem. Rev.* **2019**, *119*, 478–598.

[208] Paolesse, R.; Nardis, S.; Monti, D.; Stefanelli, M.; Di Natale, C. Porphyrinoids for chemical sensor applications. *Chem. Rev.* **2017**, *117*, 2517–2583.

[209] Shehada, N.; Cancilla, J. C.; Torrecilla, J. S.; Pariente, E. S.; Brönstrup, G.; Christiansen, S.; Johnson, D. W.; Leja, M.; Davies, M. P. A.; Liran, O. et al. Silicon nanowire sensors enable diagnosis of patients via exhaled breath. *ACS Nano* **2016**, *10*, 7047–7057.

[210] Cao, L. A.; Yao, M. S.; Jiang, H. J.; Kitagawa, S.; Ye, X. L.; Li, W. H.; Xu, G. A highly oriented conductive MOF thin film-based Schottky diode for self-powered light and gas detection. *J. Mater. Chem. A* **2020**, *8*, 9085–9090.

[211] Yuan, H. Y.; Tao, J. F.; Li, N. X.; Karmakar, A.; Tang, C. H.; Cai, H.; Pennycook, S. J.; Singh, N.; Zhao, D. On-chip tailorability of capacitive gas sensors integrated with metal-organic framework films. *Angew. Chem., Int. Ed.* **2019**, *58*, 14089–14094.

[212] Sun, Z. B.; Yu, S. H.; Zhao, L. L.; Wang, J. F.; Li, Z. F.; Li, G. A highly stable two-dimensional copper (II) organic framework for proton conduction and ammonia impedance sensing. *Chem. Eur. J.* **2018**, *24*, 10829–10839.

[213] Yao, M. S.; Li, W. H.; Xu, G. Metal-organic frameworks and their derivatives for electrically-transduced gas sensors. *Coord. Chem. Rev.* **2021**, *426*, 213479.

[214] Pauling, L.; Robinson, A. B.; Teranishi, R.; Cary, P. Quantitative analysis of urine vapor and breath by gas–liquid partition chromatography. *Proc. Natl. Acad. Sci. USA* **1971**, *68*, 2374–2376.

[215] Amal, H.; Haick, H. Point of care breath analysis systems. In *Advanced Nanomaterials for Inexpensive Gas Microsensors*. Llobet, E., Ed.; Elsevier: Cambridge, MA, 2020; pp 315–334.

[216] Nakhleh, M. K.; Badarny, S.; Winer, R.; Jeries, R.; Finberg, J.; Haick, H. Distinguishing idiopathic Parkinson's disease from other parkinsonian syndromes by breath test. *Parkinsonism Relat. Disord.* **2015**, *21*, 150–153.

[217] Nardi-Agmon, I.; Abud-Hawa, M.; Liran, O.; Gai-Mor, N.; Ilouze, M.; Onn, A.; Bar, J.; Shlomi, D.; Haick, H.; Peled, N. Exhaled breath analysis for monitoring response to treatment in advanced lung cancer. *J. Thorac. Oncol.* **2016**, *11*, 827–837.

[218] Kim, S. J.; Choi, S. J.; Jang, J. S.; Cho, H. J.; Kim, I. D. Innovative nanosensor for disease diagnosis. *Acc. Chem. Res.* **2017**, *50*, 1587–1596.

[219] Schuermans, V. N. E.; Li, Z. Y.; Jongen, A. C. H. M.; Wu, Z. Q.; Shi, J. Y.; Ji, J. F.; Bouvy, N. D. Pilot study: Detection of gastric cancer from exhaled air analyzed with an electronic nose in Chinese patients. *Surg. Innov.* **2018**, *25*, 429–434.

[220] Hanson, C. W. 3rd; Thaler, E. R. Electronic nose prediction of a clinical pneumonia score: Biosensors and microbes. *Anesthesiology* **2005**, *102*, 63–68.

[221] Kateb, B.; Ryan, M. A.; Homer, M. L.; Lara, L. M.; Yin, Y. F.; Higa, K.; Chen, M. Y. Sniffing out cancer using the JPL electronic nose: A pilot study of a novel approach to detection and differentiation of brain cancer. *NeuroImage* **2009**, *47*, T5–T9.

[222] Wu, A. Q.; Wang, W. Q.; Zhan, H. B.; Cao, L. A.; Ye, X. L.; Zheng, J. J.; Kumar, P. N.; Chiranjeevulu, K.; Deng, W. H.; Wang, G. E. et al. Layer-by-layer assembled dual-ligand conductive MOF nano-films with modulated chemiresistive sensitivity and selectivity. *Nano Res.* **2021**, *14*, 438–443.

[223] Campbell, M. G.; Sheberla, D.; Liu, S. F.; Swager, T. M.; Dincă, M. Cu$_3$(hexaiminotriphenylene)$_2$: An electrically conductive 2D metal-organic framework for chemiresistive sensing. *Angew. Chem.* **2015**, *127*, 4423–4426.

[224] Stolz, R. M.; Mahdavi-Shakib, A.; Frederick, B. G.; Mirica, K. A. Host-guest interactions and redox activity in layered conductive metal-organic frameworks. *Chem. Mater.* **2020**, *32*, 7639–7652.

[225] Yao, M. S.; Zheng, J. J.; Wu, A. Q.; Xu, G.; Nagarkar, S. S.; Zhang, G.; Tsujimoto, M.; Sakaki, S.; Horike, S.; Otake, K. et al. A dual-ligand porous coordination polymer chemiresistor with modulated conductivity and porosity. *Angew. Chem., Int. Ed.* **2020**, *59*, 172–176.

[226] Fan, Y.; Zhang, J.; Shen, Y.; Zheng, B.; Zhang, W. N.; Huo, F. W. Emerging porous nanosheets: From fundamental synthesis to promising applications. *Nano Res.* **2021**, *14*, 1–28.

[227] Donarelli, M.; Ottaviano, L.; Giancaterini, L.; Fioravanti, G.; Perrozzi, F.; Cantalini, C. Exfoliated black phosphorus gas sensing properties at room temperature. *2D Mater.* **2016**, *3*, 025002.

[228] Cho, S. Y.; Koh, H. J.; Yoo, H. W.; Jung, H. T. Tunable chemical sensing performance of black phosphorus by controlled functionalization with noble metals. *Chem. Mater.* **2017**, *29*, 7197–7205.

[229] Yao, M. S.; Otake, K. I.; Xue, Z. Q.; Kitagawa, S. Concluding remarks: Current and next generation MOFs. *Faraday Discuss.* **2021**, *231*, 397–417.

[230] Yao, M. S.; Wang, P.; Gu, Y. F.; Koganezawa, T.; Ashitani, H.; Kubota, Y.; Wang, Z. M.; Fan, Z. Y.; Otake, K. I.; Kitagawa, S. A comparative study of honeycomb-like 2D π-conjugated metal-organic framework chemiresistors: Conductivity and channels. *Dalton Trans.* **2021**, *50*, 13236–13245.

[231] Meng, Z.; Stolz, R. M.; Mirica, K. A. Two-dimensional chemiresistive covalent organic framework with high intrinsic conductivity. *J. Am. Chem. Soc.* **2019**, *141*, 11929–11937.

[232] Zhang, H. H.; Gu, C.; Yao, M. S.; Kitagawa, S. Hybridization of emerging crystalline porous materials: Synthesis dimensionality and electrochemical energy storage application. *Adv. Energy Mater.* **2022**, *12*, 2100321.

[233] Jian, Y. Y.; Qu, D. Y.; Guo, L. H.; Zhu, Y. J.; Su, C.; Feng, H. R.; Zhang, G. J.; Zhang, J.; Wu, W. W.; Yao, M. S. The prior rules of designing Ti$_3$C$_2$T$_x$ MXene-based gas sensors. *Front. Chem. Sci. Eng.* **2021**, *15*, 505–517.

[234] Kim, S. J.; Koh, H. J.; Ren, C. E.; Kwon, O.; Maleski, K.; Cho, S. Y.; Anasori, B.; Kim, C. K.; Choi, Y. K.; Kim, J. et al. Metallic Ti$_3$C$_2$T$_x$ MXene gas sensors with ultrahigh signal-to-noise ratio. *ACS Nano* **2018**, *12*, 986–993.

[235] Lee, E.; VahidMohammadi, A.; Prorok, B. C.; Yoon, Y. S.; Beidaghi, M.; Kim, D. J. Room temperature gas sensing of two-dimensional titanium carbide (MXene). *ACS Appl. Mater. Interfaces* **2017**, *9*, 37184–37190.

[236] Yao, M. S.; Xiu, J. W.; Huang, Q. Q.; Li, W. H.; Wu, W. W.; Wu, A. Q.; Cao, L. A.; Deng, W. H.; Wang, G. E.; Xu, G. Van der Waals heterostructured MOF-on-MOF thin films: Cascading functionality to realize advanced chemiresistive sensing. *Angew. Chem., Int. Ed.* **2019**, *58*, 14915–14919.

[237] Yao, M. S.; Tang, W. X.; Wang, G. E.; Nath, B.; Xu, G. MOF thin film-coated metal oxide nanowire array: Significantly improved chemiresistor sensor performance. *Adv. Mater.* **2016**, *28*, 5229–5234.

[238] Lei, G. L.; Lou, C. M.; Liu, X. H.; Xie, J. Y.; Li, Z. S.; Zheng, W.; Zhang, J. Thin films of tungsten oxide materials for advanced gas sensors. *Sens. Actuator B: Chem.* **2021**, *341*, 129996.

[239] Liu, X. H.; Zheng, W.; Kumar, R.; Kumar, M.; Zhang, J. Conducting polymer-based nanostructures for gas sensors. *Coord. Chem. Rev.* **2022**, *462*, 214517.

[240] Lou, C. M.; Lei, G. L.; Liu, X. H.; Xie, J. Y.; Li, Z. S.; Zheng, W.; Goel, N.; Kumar, M.; Zhang, J. Design and optimization strategies of metal oxide semiconductor nanostructures for advanced formaldehyde sensors. *Coord. Chem. Rev.* **2022**, *452*, 214280.

[241] Zhang, J.; Liu, X. H.; Neri, G.; Pinna, N. Nanostructured materials for room-temperature gas sensors. *Adv. Mater.* **2016**, *28*, 795–831.

[242] Liu, X. H.; Ma, T. T.; Pinna, N.; Zhang, J. Two-dimensional nanostructured materials for gas sensing. *Adv. Funct. Mater.* **2017**, *27*, 1702168.

[243] Xu, K.; Fu, C.; Gao, Z.; Wei, F.; Ying, Y.; Xu, C.; Fu, G. Nanomaterial-based gas sensors: A review. Instrum. *Sci. Technol.* **2018**, *46*, 115–145.

[244] Jin, C. G.; Kurzawski, P.; Hierlemann, A.; Zellers, E. T. Evaluation of multitransducer arrays for the determination of organic vapor mixtures. *Anal. Chem.* **2008**, *80*, 227–236.

[245] Jin, C. G.; Zellers, E. T. Limits of recognition for binary and ternary vapor mixtures determined with multitransducer arrays. *Anal. Chem.* **2008**, *80*, 7283–7293.

[246] Gutierrez-Osuna, R.; Hierlemann, A. Adaptive microsensor systems. *Annu. Rev. Anal. Chem.* **2010**, *3*, 255–276.

[247] Li, Z.; Askim, J. R.; Suslick, K. S. The optoelectronic nose: Colorimetric and fluorometric sensor arrays. *Chem. Rev.* **2019**, *119*, 231–292.

[248] Zhao, S. X.; Lei, J. C.; Huo, D. Q; Hou, C. J.; Luo, X. G.; Wu, H. X.; Fa, H. B.; Yang, M. A colorimetric detector for lung cancer related volatile organic compounds based on cross-response mechanism. *Sens. Actuators B: Chem.* **2018**, *256*, 543–552.

[249] Lei, J. C.; Hou, C. J.; Huo, D. Q.; Luo, X. G.; Bao, M. Z.; Li, X.; Yang, M.; Fa, H. B. A novel device based on a fluorescent cross-responsive sensor array for detecting lung cancer related volatile organic compounds. *Rev. Sci. Instrum.* **2015**, *86*, 025106.

[250] Hou, C. J.; Lei, J. C.; Huo, D. Q.; Song, K.; Li, J. J.; Luo, X. G.; Yang, M.; Fa, H. B. Discrimination of lung cancer related volatile organic compounds with a colorimetric sensor array. *Anal. Lett.* **2013**, *46*, 2048–2059.

[251] Huo, D. Q.; Xu, Y. H.; Hou, C. J.; Yang, M.; Fa, H. B. A novel optical chemical sensor based AuNR-MTPP and dyes for lung cancer biomarkers in exhaled breath identification. *Sens. Actuators B: Chem.* **2014**, *199*, 446–456.