Supplementary Online Content

Hanna GB, Boshier PR, Markar SR, Romano A. Accuracy and Methodologic Challenges of Volatile Organic Compound–Based Exhaled Breath Tests for Cancer Diagnosis: A Systematic Review and Pooled Analysis. *JAMA Oncol.* Published online August 16, 2018. doi:10.1001/jamaoncol.2018.2815

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Search strategy for cancer systematic review

#	Search
1	(cancer or neoplasm* or malignancy).ab.
2	limit 1 to abstracts
3	limit 2 to cochrane library [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
4	limit 3 to english language
5	limit 4 to human
6	limit 5 to yr="2000 -Current"
7	limit 6 to humans
8	(cancer or neoplasm* or malignancy).ti.
9	limit 8 to abstracts
10	limit 9 to cochrane library [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
11	limit 10 to english language
12	limit 11 to human
13	limit 12 to yr="2000 -Current"
14	limit 13 to humans
15	7 or 14
16	(volatile organic compound* or VOC* or Breath or Exhaled).ab.
17	limit 16 to abstracts
18	limit 17 to cochrane library [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
19	limit 18 to english language
20	limit 19 to human
21	limit 20 to yr="2000 -Current"
22	limit 21 to humans
23	(volatile organic compound* or VOC* or Breath or Exhaled).ti.
24	limit 23 to abstracts
25	limit 24 to cochrane library [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
26	limit 25 to english language
27	limit 26 to human
28	limit 27 to yr="2000 -Current"
29	limit 28 to humans
30	22 or 29
31	15 and 30
32	remove duplicates from 31

Description of the modification and application of QUADAS-2

eTable 2. Modification of QUADAS-2 assessment tools

		QUADAS-2	**QUADAS-2 (modified)**	
RISK OF BIAS	**Patient selection**	Was a consecutive or random sample of patients enrolled?	Were sampled patients representative of the intended population?	**(Am)**
		Was a case-control design avoided?	Did the study include both positive (benign conditions) as well as healthy controls?	**(Am)**
		Did the study avoid inappropriate exclusions?	Did the study avoid inappropriate exclusions?	**(Un)**
	Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	Was the index test and interpretation of data performed in standardised and reproducible fashion?	**(Am)**
		If a threshold was used, was it pre-specified?	Validation of results performed (internal or external)?	**(Am)**
	Reference standard	Is the reference standard likely to correctly classify the target condition?	Is the reference standard likely to correctly classify the target condition?	**(Un)**
		Were the reference standard results interpreted without knowledge of the results of the index test?	-	**(Om)***
	Flow and timing	Was there an appropriate interval between index test and reference standard?	Was there an appropriate interval between index test and reference standard?	**(Un)**
		-	Were index test and reference standard performed prior to therapeutic intervention?	**(Ad)**
		Did all patients receive the same reference standard?	Did all patients receive the same reference standard?	**(Un)**
		Were all patients included in the analysis?	Were all patients included in the analysis?	**(Un)**
APPLICABILITY	**Patient selection**	Are there concerns that the included patients and setting do not match the review question?	Are there concerns that the included patients and setting do not match the review question?	**(Un)**
	Index test	Are there concerns that the index test, its conduct, or interpretation differs from the review question?	Are there concerns that the authors have not demonstrated suitable reproducibility and sensitivity of the chosen index test?	**(Am)**

	Reference standard	Are there concerns that the target condition as defined by the reference standard does not match the question?	Are there concerns that the target condition as defined by the reference standard does not match the question?	**(Un)**

Am = amendment. Om = omitted. Ad = addition. Un = unchanged. *Criteria omitted as not applicable in the case of phase 1 biomarker discovery studies
REVIEW QUESTION
Test population: human subLects
Index test(s): VOC analysis within exhaled breath
Reference standard: the accepted standard for diagnosis of cancer and/or benign disease in that field
Target condition: cancer
Setting: hospital, medical centre
Intended use of the index test: diagnostic
Patient presentation: routine investigation for symptoms of malignancy
Prior testing: not applicable

eTable 3. QUADAS-2 results									
			RISK OF BIAS				**APPLICABILITY CONCERNS**		
			Patient selection	**Index Test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
1	Barash 2015	B	L	L	?	H	L	L	L
2	Li 2014	B	L	L	L	H	L	L	L
3	Mangler 2012	B	H	H	?	?	?	?	?
4	Peng 2010	B	H	H	L	H	?	L	L
5	Phillips 2003	B	?	L	L	H	L	?	L
6	Phillips 2006	B	L	L	L	H	L	?	L
7	Wang 2014	B	L	L	L	?	L	?	L
8	Amal 2015	O	L	L	?	H	L	?	L
9	Peng 2010	P	H	H	L	H	?	L	L
10	Guo 2015	T	H	H	?	?	L	?	L
11	Gruber 2014	H & N	L	H	L	H	L	?	L
12	Hakim 2011	H & N	H	H	L	H	L	L	L
13	Bouza 2017	Oc	H	H	?	H	L	L	L
14	Szabó 2015	Oc	H	H	?	?	L	L	L
1	Altomar	Cr	H	L	L	?	L	?	L

15	e 2013								
16	Amal 2015	Cr	☺	H	L	H	L	L	L
17	Peng 2010	Cr	H	H	L	H	?	L	L
18	Wang 2014	Cr	H	H	L	H	L	?	L
19	Abela 2009	E & G	H	H	L	H	L	?	L
20	Kumar 2013	E & G	L	H	L	L	L	L	L
21	Kumar 2015	E & G	L	H	L	L	L	L	L
22	Amal 2013	G	L	H	L	H	L	L	L
23	Amal 2016	G	L	H	L	?	L	L	L
24	Xu 2013	G	L	H	L	H	L	L	L
25	Qin 2010	Li	L	H	L	H	L	?	L
26	Garcia 2014	La	H	H	?	?	L	L	L
27	BaLtarevic 2009	Lu	H	H	?	H	L	☺	L
28	Bousamra 2014	Lu	H	H	?	H	L	?	L
29	Buszewski 2011	Lu	H	H	L	H	L	?	L

30	Buszewski 2012	Lu	H	H	?	?	L	L	L
31	Chen 2005	Lu	?	H	?	H	L	?	L
32	Corradi 2015	Lu	H	H	L	H	L	?	L
33	Crohns 2009	Lu	H	H	L	H	L	?	L
34	Deng 2004	Lu	H	H	?	?	L	L	L
35	Feinberg 2016	Lu	H	H	L	H	L	?	L
36	Filipiak 2014	Lu	H	H	L	H	L	L	L
37	Fu 2014	Lu	?	H	?	H	L	?	L
38	Fuchs 2010	Lu	H	H	?	H	L	L	L
39	Gaspar 2009	Lu	H	H	?	?	L	?	L
40	Handa 2014	Lu	H	H	L	H	L	?	L
41	Kischkel 2010	Lu	H	H	H	?	L	L	L
42	Li 2015	Lu	?	L	L	H	L	?	L
43	Ligor 2009	Lu	H	H	?	H	L	L	L
44	Ligor 2015	Lu	H	H	L	H	L	L	L
45	Ma 2014	Lu	H	H	?	H	L	?	L
46	Ma 2015	Lu	H	H	?	?	?	?	?

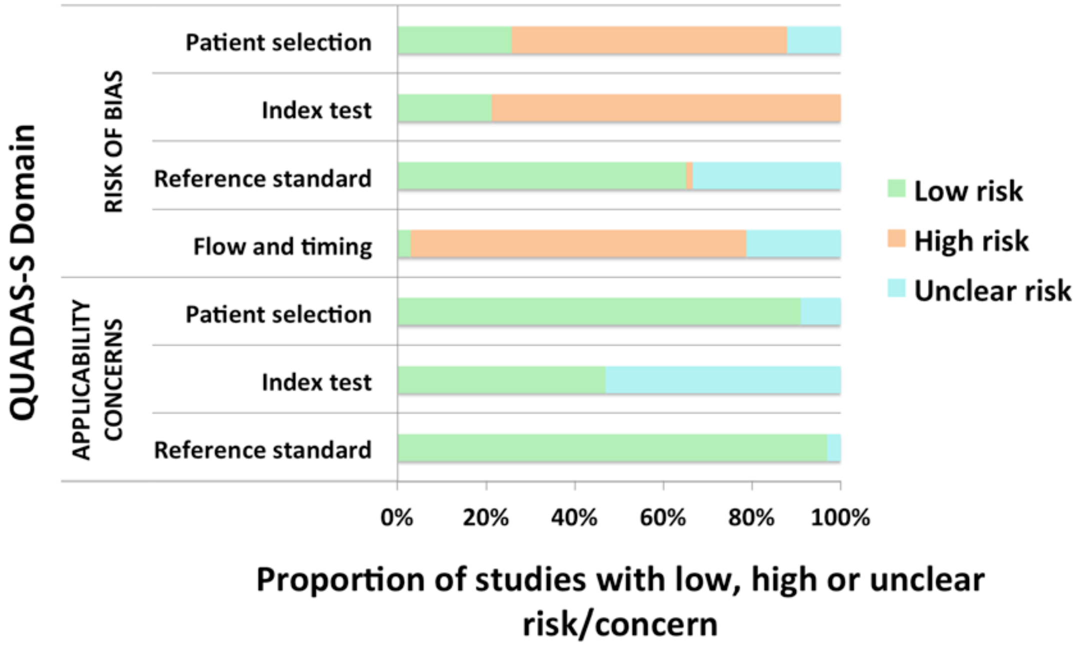
47	Peled 2012	Lu	?	H	L	H	L	?	L
48	Peng 2009	Lu	H	H	L	H	L	L	L
49	Peng 2010	Lu	H	H	L	H	?	L	L
50	Phillips 2003	Lu	L	L	L	H	L	?	L
51	Phillips 2007	Lu	H	L	L	H	L	?	L
52	Phillips 2008	Lu	H	L	L	H	L	?	L
53	Poli 2005	Lu	L	H	L	H	L	?	L
54	Poli 2010	Lu	☐	L	L	H	L	L	L
55	Rudnicka 2011	Lu	☐	H	?	H	L	L	L
56	Sakumura 2017	Lu	☐	H	?	?	L	?	L
57	Schallschmidt 2016	Lu	☐	H	?	?	L	L	L
58	Schumer 2015	Lu	?	H	L	H	L	?	L
59	Schumer 2016	Lu	H	H	L	H	L	?	L
60	Skeldon 2006	Lu	?	H	L	H	L	L	L
61	Song 2010	Lu	H	H	L	H	L	L	L
62	Ulanowska 2011	Lu	H	H	L	H	L	?	L

63	Wang 2012	Lu	?	H	L	H	L	?	L
64	Wehinger 2007	Lu	H	L	L	H	L	?	L
65	Zou 2014	Lu	L	L	L	H	L	?	L
66	de Gennaro 2010	M	L	H	L	H	L	L	L

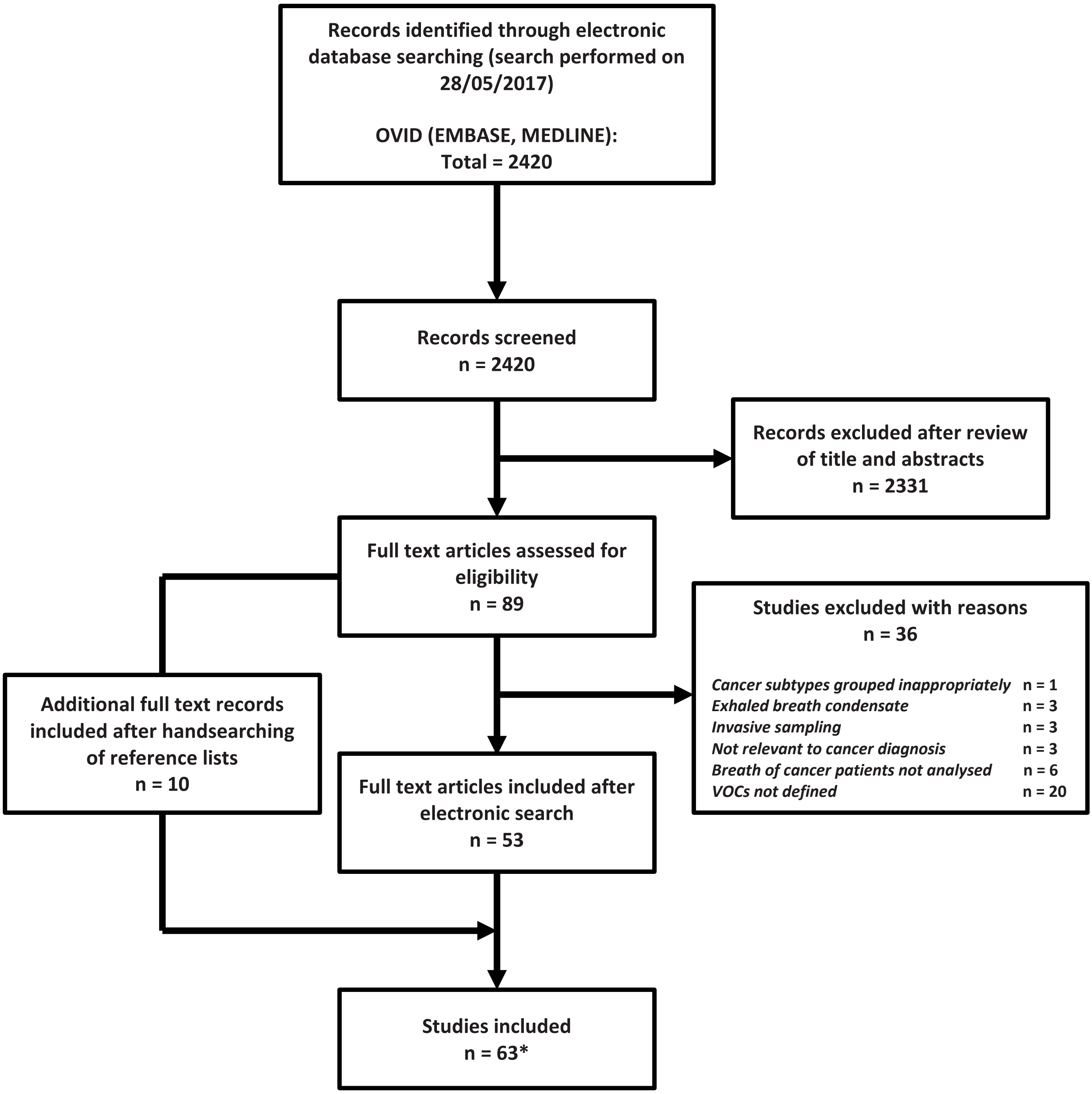
L	**Low rsk**	**H**	**High risk**	**?**	**Unclear risk**

B, breast; O, ovarian; P, prostate; Cr, colorectal; E&G, esophageal & gastric; G, gastric; Oc, oral cavity; H&N, head& neck; T, thyroid; Li, liver; La, laryngeal; Lu, lung; M, mesothelioma

eFigure 1. Risk of bias and applicability concerns using QUADAS-2



eFigure 2. PRISMA flow chart of literature search.*One study by Peng et al., 2010 presented data for four cancer types, that are considered independently for the purpose of this review.



eTable 4. Details of studies on exhaled volatile organic compounds in cancer

Author	Year	Cancer	Cancer patients (No.)	Biomarker phase	Analytical platform	Volatile organic compounds	Sensitivity	Specificity	AUC	STARD score	Ref.
Barash	2015	Breast	80	1	GC-MS	Ethanol; Heptane; 2-propenoic acid, butyl ester; 6-methyl-5-Hepten-2-one	78[a]	61[a]	0.79[a]	17	[1]
Li	2014	Breast	22	1	GC-MS	Hexanal; heptanal; octanal; nonanal	68·2[a]	91·7[a]	0.902[b]	20	[2]
Mangler	2012	Breast	10	1	GC-MS	3-methylhexane; decene[c]; caryophyllene[c]; naphthalene[c]; trichlorethylene[c]	-	-	-	12	[3]
Peng*	2010	Breast	14	1	GC-MS	3,3-dimethyl pentane; 2-amino-5-isopropyl-8-methyl-1-azulenecarbonitrile; 5-(2-methypropyl)nonane; 2,3,4-trimethyl decane; 6-ethyl-3-octyl ester 2-trifluoromethyl benzoic acid	-	-	-	14	[4]
Phillips	2003	Breast	51	1	GC-MS	Nonane; tridecane; 5-methyl undecane; 3-methyl pentadecane; 6-methyl propane; 2-methyl nonadecane, 3-methyl dodecane, 4-methyl octane, 2-methyl	88·2[a]	73·8[a]	-	18	[5]
Phillips	2006	Breast	51	1	GC-MS	2-propanol; 2,3-dihydro-1-phenyl-4(1H)-quinazolinone; 1-phenyl-ethanone; heptanal; isopropyl myristate	93·8[a]	84·6[a]	0.9[a]	13	[6]
Wang	2014	Breast	39	1	GC-MS	Cyclohexanone; 1,4-Dimethoxy-2,3-butanediol; 2,5,6-trimethyloctane	-	-	-	14	[7]

Amal	2015	Ovarian	48	1	GC-MS	Decanal; nonanal; styrene; 2-butanone; hexadecane	-	-	-	14	8
Peng*	2010	Prostate	13	1	GC-MS	Toluene; 2-amino-5-isopropyl-8-methyl-azulene carbonitrile; p-xylene; 2,2-dimethyl decane	-	-	-	14	4
Guo	2015	Thyroid	39	1	GC-MS	Cyclohexanone; 4-hydroxybutyric acid; phenol; 2,2-dimethyldecane; ethylhexanol; ethyleneglycol mono vinyl ester; cyclopropane; 1-bromo-1-(3-methyl-1-pentenylidene)-2,2,3,3-tetramethyl	100[a]	100[a]	1.0[a]	13	9
Gruber	2014	H&N	22	1	GC-MS	Ethanol; 2-propenenitrile; undecane	-	-	-	15	10
Hakim	2011	H&N	8	1	GC-MS	4,6-dimethyl-dodecane; 2,2-dimethyl-propanoic acid; 5-methyl-3-hexanone; 2,2-dimethyl-decane; limonene; 2,2,3-erimethyl-, exo- bicyclo[2·2·1]heptane	-	-	-	12	11
Bouza	2017	Oral cavity	26	1	GC-MS	Undecane; dodecane; decanal; benzaldehyde; 3,7-dimethylundecane; 4,5-dimethyl-nonane; 1-octene; hexadecane	-	-	-	11	12
Szabó	2015	Oral cavity	14	1	Portable GC	Hydrogen sulphide; Isoprene; Methyl mercaptan; Dimethyl sulphide; Acetaldehyde[d]	-	-	-	11	13
Altomare	2013	Colorectal	37	1	GC-MS	Nonanal; 4-methyl-2-pentanone; decanal; 2-methylbutane; 1,2-pentadiene; 2-methylpentane; 3-methylpentane; methylcyclohexane; 1,3-dimethylbenzene; 4-methyloctane; 1,4-dimethybenzene; 4-methylundecane; trimethyldecane	86[a]	83[a]	0.852[a]	20	14
Amal	2016	Colorectal	65	1	GC-MS	Ethanol; acetone; ethyl acetate; 4-methyl octane	-	-	-	20	15

Peng*	2010	Colorectal	22	1	GC-MS	1,1-(1-butenylidene)bis benzene; 1,3-dimethyl benzene; 1-iodo nonane; [(1,1-dimethylethylthio] acetic acid; 4-(4-propylcyclohexyl)-4-cyano[1,1'-biphenyl]-4-yl ester benzoic acid; 2-amino-5-isopropyl-8-methyl-1-azulenecarbonitrile	-	-	-	14	4
Wang	2014	Colorectal	20	1	GC-MS	Cyclohexanone; 2,2-dimethyldecane; dodecane, 4-ethyl-1-octyn-3-ol; ethylaniline; cyclooctylmethanol; trans-2-dodecen-1-ol; 3-hydroxy- 2,4,4-trimethylpentyl 2-methylpropanoate; 6-t-butyl-2,2,9,9-tetramethyl-3,5-decadien-7-yne	-	-	-	13	16
Abela	2009	OG	20	1	TDLS	Ethane[d]	-	-	-	14	17
Kumar	2013	OG	18	1	SIFT-MS	Hexanoic acid; phenol; methyl-phenol; ethyl-phenol	-	-	0.91	18	18
Kumar	2015	OG	81	1	SIFT-MS	Pentanoic acid; hexanoic acid; phenol; methyl phenol; ethyl phenol; butanal; pentanal; hexanal; heptanal; octanal; nonanal; decanal	86·7[a]	81·2[a]	0.87[a]	22	19
Amal	2013	Gastric	74[e]	1	GC-MS	2-Propenenitrile; 2-butoxy-ethanol; furfural; 6-methyl-5-hepten-2-one; isoprene; styrene; 6-methyl-5-hepten-2-one; 2-ethyl-1 hexanol; Nonanal	-	-	-	15	20
Amal	2016	Gastric	99	1	GC-MS	2-propenenitrile; furfural; 2-butoxy-ethanol; hexadecane; 4-methyl-octane; 1,2,3-tri-methyl-benzene; a-methyl-styrene; 2-butanone[f]	-	-	-	20	21
Xu	2013	Gastric	37	1	GC-MS	2-propenenitrile; furfural; 6-methyl-5-hepten-2-one	-	-	-	21	22
Qin	2010	Liver	30	1	GC-MS	3-hydroxy-2-butanone; styrene; decane	83·3[a]	91·7[a]	-	18	23
Garci	20	Laryn	10	1	GC-MS	Ethanol; 2-butanone; 2,3-butanediol; 9-tetradecen-1-ol; octene derivative; cycloheptane derivative; cyclononane derivative	-	-	-	8	24

a	14	geal									
Bajtarevic	2009	Lung	220/65	1	PTR-MS/ GC-MS[g]	2-butanone; benzaldehyde; 2,3-butanedione; 1-propanol; 3-hydroxy-2-butanone; 3-butyn-2-ol; 2-mthylbutane; 2-butene, 2-methyl; acetophenone; 1-cyclopentene; methyl propyl sulfide; Urea, tetramethyl-n-pentanal; 1-methyl-1,3 cyclopentadience; 2,3-dimethyl-2-butanol; 1,2,3,4-tetrahydro-isoquinoline; 3,7-dimethyl-undecane; cyclobutyl-benzene; butyl acetate; ethylenlmine; n-undecane; isoprene[h]; acetone[h]; methanol[h]	80[i]	100[i]	-	11	25
Bousamra	2014	Lung	107	1	FT-ICR-MS	2-butanone; 3-hydroxy-2-butanone; 2-hydroxyacetaldehyde; 4-hydroxyhexenal	28	100	0.86	13	26
Buszewski	2011	Lung	115	1	GC-MS	Ethanol; acetone; carbon disulfide; dimethyl sulfide; 2-propanol; 2-butanone; 2-pentanone; acetonitrile[j]; 1-propanol[j]	-	-	-	12	27
Buszewski	2012	Lung	29	1	GC-MS	Acetone; benzene; butanal; 2-butanone; ethyl acetate; ethylbenzene; furan; 2-pentanone; propanal; 1-propanol; 2-propanol; 2-propenal	-	-	-	5	28
Chen	2005	Lung	5	1	SAW sensor	Styrene; decane; isoprene; benzene; undecane; hexanal; 1,2,4-trimethyl benzene; heptanal	-	-	-	6	29
Corradi	2015	Lung	71	1	GC-MS	Ethyl benzene; hexane; trans-2-nonenal	-	-	-	22	30
Crohns	2009	Lung	11	1	GC-MS	Pentane	-	-	-	15	31
Deng	2004	Lung	10	1	GC-MS	Hexanal; heptanal	-	-	-	7	32

Feinberg	2016	Lung	22	1	PTR-MS	m/z 61 (proposed identity: acetic acid, isopropanol)[d]	-	-	-	15	33
Filipiak	2014	Lung	36	1	GC-MS	n-octane; n-nonane; 2,3-butanedione[k]	-	-	-	12	34
Fu	2014	Lung	97	1	FT-ICR-MS	2-butanone; 3-hydroxy-2-butanone; 2-hydroxyacetaldehyde; 4-hydroxyhexenal	89·8[l]	81·3[l]	-	10	35
Fuchs	2010	Lung	12	1	GC-MS	Pentanal; hexanal; octanal; nonanal	75[m]	95·8[m]	-	11	36
Gaspar	2009	Lung	18	1	GC-MS	2-methylundecane; 2-methyltridecane; 2-methyltetradecane; 3-methyltetradecane; *n*-C15H32; 3-methylpentadecane; branched-C16H34; 2-methylhexadecane	100[n]	100[n]	-	5	37
Handa	2014	Lung	50	1	IMS	n-dodecane; 3-methyl1-1=butanol; 2-methylbutylacetat or 2-hexanol; cyclohexanon; iso-propylamin; n-nonal or cyclohexanon; ethylbenzol; hexanal; heptanal; 3-methyl-1-butanol	76	100	-	17	38
Kischkel	2010	Lung	31	1	GC-MS	Acetonitrile; benzene; 2,5-dimethyl furan; acetone; dimethyl sulfide; dimethyl formamide; 2-methyl-1,3-butadiene; toluene; butane; propanal; butanal; hexanal; isopropanol; 1-propanol	-	-	-	8	39
Li	2015	Lung	85	1	FT-ICR-MS and GC-MS	2-butanone; 4-hydroxy-2-hexenal; 3-hydroxy-2-butanone; hydroxyacetaldehyde; hydroxy-2-nonenal; 2-pentanone / pentanal	96[o]	84[o]	0.962[p]	19	40
Ligor	2009	Lung	65	1	GC-MS	1-propanol; 2-butanone; 3-butyn-2-ol; benzyaldehyde; 2-methyl-pentane; 3-methyl-pentane; n-pentane; n-hexane	51	100	-	12	41

Ligor	2015	Lung	123	1	GC-MS	Butane; 2-methyl-butane; 4-methyl-octane; propane; 2-pentanone; propanal; 2,4-dimethyl-heptane; propene	63·5[a]	72·4[a]	0·65[a]	11	42
Ma	2014	Lung	13	1	GCxGC-FID	Acetone; isoprene; methanol; pentane; propanol	-	-	-	13	43
Ma	2015	Lung	10	1	GC-MS	Toluene; ethylbenzene; p-xylene + m-xylene; o-xylene; isopropyl benzene	-	-	-	5	44
Peled	2012	Lung	28	1	GC-MS	1-octene	-	-	-	13	45
Peng	2009	Lung	40	1	GC-MS	Hydrazine-carboxamide; methyl hydrazine; ethyl alcohol; o-xylene; 1-methyl-4-(1-methylethyl)-benzene; ethylbenzene; styrene; toluene; dimethyl ether; butylated hydroxytoluene; carbonic dihydrazide; 1-methyl-2-(1-methylethyl)-benzene; 1-methyl-3-(1-methylethyl)-benzene; 1,3,5-cycloheptatriene; 3-methyl-hexane; 3-ethyl-pentane; 1,3,5,7-cyclooctatetraene; bicyclo[4.2.0]octa-1,3,5-triene; 2,3,4-trimethyl-hexane; 2,6-bis(1,1-dimethylethyl)-4-methyl-methylcarbamate phenol; 2,4-dimethyl-heptane; 4,7-dimethyl-undecane; 2,4,6-Tris(1,1-dimethyl-ethyl)-4-methylcyclohexa-2,5-dien-1-one; 2,6,6-trimethyl octane; 2-butanone; hydrazine; 1,3-pentadiene; 3,3-dimethyl-pentane; 3,3-dimethyl-hexane; 2-methyl-hexane; 3-ethyl-hexane; 2,2,3-trimethyl-hexane; ethylidene cyclopropane; 4-methyl-octane; 2-ethyl-1-hexanol; 2-ethyl-4-methyl-1-pentanol; 2,3,4-trimethyl-pentane; 2,3-dimethyl-hexane; 3-ethyl-3-methyl-2-pentanone; 2-methyl-4,6-octadiyn-3-one; 2-propyl-1-pentanol; 6,10-dimethyl-5,9-dodecadien-2-one	-	-	-	13	46
Peng*	2010	Lung	16	1	GC-MS	1-methyl-4-(1-methylethyl)benzene; toluene; dodecane; 3,3-dimethyl pentane; 2,3,4-trimethyl hexane; 1,1'-(1-butenylidene)bis benzene	-	-	-	14	4
Phillips	2003	Lung	67	1	GC-MS	Butane; tridecane,3-methyl; tridecane, 7-methyl; octane, 4-methyl; hexane, 3-methyl; heptane; hexane; 2-methyl; pentane; decane, 5-methyl	85·1[a]	80·5[a]	-	19	47

Phillips	2007	Lung	193	1	GC-MS	1,5,9-trimethyl-1,5,9-cyclododecatriene; 2,2,4-trimethyl pentan-1,3-dioldiisobutyrate; 4-ethoxy-benzoic acid, ethyl ester; 2-methyl propanoic acid; 10,11-dihydro-5H-dibenz-(B,F)-azepine; 2,5-cyclohexadiene-1,4-dione; benzene, 1,1-oxybis; 2,5-dimethyl-furan; 2,2-diethyl-1,1-biphenyl; 2,4-dimethyl-3-pentanone; trans-caryophyllene; 2,3-dhydro-1,1,3-trimethyl-3-phenyl 1H-Indece; 1-propanol; decane, 4-methyl; diethyl ester 1,2-benzenedicarboxylic acid; 2,5-dimethyl-2,4-Hexadiene	84·6[a]	80·0[a]	0·88[a]	18	48
Phillips	2008	Lung	193	1	GC-MS	Isopropyl alcohol; 4-penten-2-ol; 1,1,2-trichloro-1,2,2-trifluoro-ethane; 2-methoxy-2-methyl-propane; 1-propene, 1-(methylthio)-, (E)-; 2,3-hexanedione; 5,5-dimethyl-1,3-hexadiene; 3-hexanone, 2-methyl-; 1H-indene, 2,3-dihydro-4-methyl-; camphor; 1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one, (1S)-; à,à4-trimethyl-3-cyclohexene-1-methanol; p-menth-1-en-8-ol; 5-isopropenyl-2-methyl-7-oxabicyclo[4.1.0]heptan-2-ol; à Isomethyl ionone; 2,2,7,7-tetramethyltricyclo[6.2.1.0(1,6)]undec-4-en-3-one; 2,2,4-trimethyl-1,3-pentanediol diisobutyrate; 4-ethoxy-benzoic acid, ethyl ester; bicyclo[3.2.2]nonane-1,5-dicarboxylic acid, 5-ethyl ester; pentanoic acid, 2,2,4-trimethyl-3-carboxyisopropyl, isobutylester propanoic acid, 2-methyl-, 1-(1,1-dimethylethyl)-2-methyl-1,3-; propanediyl ester; 3,3,6,6-tetraphenyl-1,2,4,5-tetroxane; benzophenone; 2,6-bis(1,1-dimethylethyl)-4-ethylidene-2,5-cyclohexadien-1-one; 2-[(2-ethoxy-3,4-dimethyl-2-cyclohexen-1-ylidene) methyl]-furan; 1,1-(1,2-cyclobutanediyl)bis-, cis-Benzene; 1,1-[1-(ethylthio)propylidene]bis-benzene; 1,2,3,4-tetrahydro-9-propyl-anthracene; 2-ethyl-9,10-anthracenediol; 1,1-ethylidenebis 4-ethyl-benzene	84·5	81	0·9	15	49
Poli	2005	Lung	36	1	GC-MS	2-methylpentane; pentane; ethylbenzene xylenes total; trimethylbenzene; toluene; benzene; decane; octane; pentamethylheptane	72·2	93·6	-	16	50
Poli	2010	Lung	40	1	GC-MS	Propanal; butanal; pentanal; hexana; heptanal; octanal; nonanal	90	92·1	-	16	51
Rudnicka	2011	Lung	23	1	GC-TOF/MS	Isopropyl alcohol; styrene; pentanal; carbon disulfide; 2-methyl-furan; ethylbenzene; isobutane; 2-propenal; propane; 3-methyl-furan; propanal; cyclopentane; butanal; pentane	-	-	-	5	52
Sakumura	2017	Lung	107	1	GC-MS	Hydrogen cyanide; methanol; acetonitrile; isoprene; 1-propanol	95	89	-	7	53

Schallschmidt	2016	Lung	37	1	GC-MS	Propanal; n-butanal; n-decanal; 1-butanol; 2-butanone; ethylbenzene	100[a]	100[a]	-	10	54
Schumer	2015	Lung	156	1	Silicon chip-MS	2-butanone; 3-hydroxy-2-butanone; 2-hydroxyacetaldehyde; 4-hydroxyhexenal	95·5[q]	64·4[q]	-	14	55
Schumer	2016	Lung	31	1	Silicon chip-MS	2-butanone; 2-hydroxyacetaldehyde; 4-hydroxyhexanol; 3-hydroxy-2-butanone	-	-	-	13	56
Skeldon	2006	Lung	12	1	TDLS	Ethane[d]	-	-	-	14	57
Song	2010	Lung	43	1	GC-MS	1-butanol; 3-hydroxy-2-butanone	95·3[r]	85·4[r]	0.94[r]	13	58
Ulanowska	2011	Lung	127	1	GC-MS	Pentanal; hexanal; nonane; ethanol; acetone; butane; dimethyl sulfide; isoprene, propanal; 1-propanol; 2-pentanone, furan; o-xylene; ethylbenzene; acetaldehyde; pentane; 3-methylpentane; pentane; butyrolactone; 2-methylbutane; 1-(methylthio)-propane; dimethyl sulfide; benzene; 3-methylfuran; propane; 4-methyloctane; N,N-dimethylacetamide 2,4-dimethylpentane; carbon disulfide	-	-	-	10	59
Wang	2012	Lung	88	1	GC-MS	Hexadecanal; 2,6,10,14-tetramethylpentadecane; eicosane; 5-(2-methyl-) propylnonane; 7-methylhexadecane; 8-methylheptadecane; 2,6-di-tert-butyl-,4-methylphenol; 2,6,11-trimethyldodecane; 3,7-dimethylpentadecane; nonadecane; 8-hexylpentadecane; 4-methyltetradecane; 2,6,10-trimethyl tetradecane; 5-(1-methyl-)propylnonane; 2-methylnapthalene; 2-methylhendecanal; nonadecanol; 2-pentadecanone; 3,7-dimethyldecane; tridecanone; 5-propyltridecane; 2,6-dimethylnapthalene; tridecane; 3,8-dimethylhedecane; 5-butylnonane	96·47[a]	97·47[a]	0.949[a,s]	13	60
Wehinger	2007	Lung	17	1	PTR-MS	m/z 31 (proposed identity: formaldehyde); m/z 43 (proposed identity: iso-propanol	54[t]	99[t]	0.95[u]	17	61

Zou	2014	Lung	79	1	GC-MS	5-(2-methyl-)propyl-nonane; 2,6-ditert-butyl-,4-methyl-phenol; 2,6,11,-trimethyl-dodecane; hexadecanal; 8-hexyl-pentadecane,	-	-	1.0[a,s]	22	62
de Gennaro	2010	Mesothelioma	13	1	GC-MS	Cyclopentane; cyclohexane, dodecane; xylene; toluene; decane; methyl-cyclohexane; dimethyl-nonanane; benzaldehyde; limonene; b-pinene	-	-	-	13	63

*Outcomes reported from the same study. AUC, area under the curve. STARD, Standards for Reporting of Diagnostic Accuracy Studies. H&N, head & neck; OG oesophagogastric. GC-MS, gas chromatography–mass spectrometry; portable GC, portable gas chromatography; TDLS, tunable diode laser absorption spectroscopy; SIFT-MS, selected ion flow tube mass spectrometry; PTR-MS, proton-transfer-reaction mass spectrometry; FT-ICR-MS, fourier transform ion cyclotron resonance mass spectrometry; SAW sensor, surface acoustic wave sensor; IMS, ion mobility spectrometry; GCxGC-FID, comprehensive two-dimensional gas chromatography with flame ionization detector; GC-TOF/MS, gas chromatography time-of-flight mass spectrometry; silicon chip-MS, silicon chip-mass spectrometry.

[a]Figure derived from a validated model (cancer vs. healthy control and/or benign disease). [b]Figure derived from non-validated model for all four compounds. [c]Compounds report to have a negative alveolar gradient, suggesting they are of exogenous origin. [d]Compound(s) not found to be significantly different between cancer patients and control subLects. [e]Includes patients presented in earlier publication by Xu etal., 2013. [f]The cut off for statistical significance was considered at $P<0.017$. [g]PTR-MS, n=220; GC-MS, n=65. [h]Compounds detected by PTR-MS. [i]Figures based on the 21 compounds determined by GC-MS. [j]Compounds considered to be of exogenous origin. [k]Only compounds with positive alveolar gradients are reported. [l]Sensitivity and specificity determined from patients with 2 or more of the 4 VOCs raised as diagnostic for the presence of cancer. [m]For pentanal only. [n]Two volatile organic compounds that were used in the model were not reported. [o]Figures are for cancer patients vs. all non-cancer subLects. [p]Figure is for 3-hydroxy-2-butanone only, cancer patients vs. healthy controls who are non-smokers. [q]Figure is determined for a test cut off defined by ≥1 standard deviation above the mean of the control population with ≥1 elevated cancer marker. [r]Figure is for 1-butanol only. [s]Figure is for hexadecanal only. [t]Model includes m/z 31, m/z 43 and age. [u]Figure is for iso-propanol in patients older than >50yrs.

eTable 5. Cancer VOCs in exhaled breath and their chemical class.

When multiple functional groups are present, chemical class is attributed according to IUPAC priority rules (*Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names 2013*. (2013). Cambridge: Royal Society of Chemistry. Retrieved from http://ebook.rsc.org/?DOI=10.1039/9781849733069).

Compound name	**Chemical classes**	**References**
methanol	alcohols/phenols	[27,45,56]
ethanol	alcohols/phenols	[1,11,16,26,29,48,62]
1-propanol	alcohols/phenols	[27,29,30,41,43,45,51,56]
isopropanol	alcohols/phenols	[35,41,52,55,64]
1-butanol	alcohols/phenols	[57,61]
2,3-butanediol	alcohols/phenols	[26]
3-butyn-2-ol	alcohols/phenols	[27,43]
3-methyl-1-butanol	alcohols/phenols	[40]
4-penten-2-ol	alcohols/phenols	[52]
1,4-dimethoxy-2,3-butanediol	alcohols/phenols	[7]
2-butanol,2,3-dimethyl	alcohols/phenols	[27]
2-butoxy-ethanol	alcohols/phenols	[22,23]
2-hexanol	alcohols/phenols	[40]
4-hydroxyhexanol	alcohols/phenols	[59]
phenol	alcohols/phenols	[10,20,21,48]
methyl-phenol	alcohols/phenols	[20,21]
2-ethyl-1 hexanol (all isomers)	alcohols/phenols	[10,22,48]
2-ethyl-4-methyl-1-pentanol	alcohols/phenols	[48]
2-propyl-1-pentanol	alcohols/phenols	[48]
cyclooctylmethanol	alcohols/phenols	[18]
ethyl phenol	alcohols/phenols	[20,21]
5-isopropenyl-2-methyl-7-oxabicyclo[4.1.0]heptan-2-ol	alcohols/phenols	[52]
alpha terpineol	alcohols/phenols	[52]
butylated hydroxytoluene	alcohols/phenols	[48]
trans-2-dodecen-1-ol	alcohols/phenols	[18]
9-tetradecen-1-ol	alcohols/phenols	[26]
2,6-di-tert-butyl-,4-methylphenol	alcohols/phenols	[63,65]
nonadecanol	alcohols/phenols	[63]
dodecane, 4-ethyl-1-octyn-3-ol	alcohols/phenols	[18]
formaldehyde	aldehyde	[64]
2-hydroxyacetaldehyde	aldehyde	[28,37,42,58,59]
acetaldehyde	aldehyde	[14,62]

2-propenal	aldehyde	[30,55]
propanal	aldehyde	[30,41,44,54,55,57]
butanal	aldehyde	[21,30,41,54,55,57]
furfural	aldehyde	[22,23,24]
pentanal	aldehyde	[21,27,38,42,54,55,62]
4-hydroxyhexenal (all isomers)	aldehyde	[28,37,42,58]
hexanal	aldehyde	[2,21,31,34,38,40,41,54,62]
benzaldehyde	aldehyde	[13,27,43,66]
heptanal	aldehyde	[2,6,21,31,34,40,54]
octanal	aldehyde	[2,21,38,54]
hydroxy-2-nonenal	aldehyde	[42]
nonanal	aldehyde	[2,8,15,21,22,38,40,54]
trans-2-nonenal	aldehyde	[32]
decanal	aldehyde	[8,13,15,21,57]
2-methylundecanal	aldehyde	[63]
hexadecanal	aldehyde	[63,65]
acetic acid	carboxylic acid	[35]
4-hydroxybutyric acid	carboxylic acid	[10]
propanoic acid, 2-methyl	carboxylic acid	[51]
2,2-dimethyl-propanoic acid	carboxylic acid	[12]
pentanoic acid	carboxylic acid	[21]
hexanoic acid	carboxylic acid	[20,21]
bicyclo[3.2.2]nonane-1,5-dicarboxylic acid, 5-ethyl ester	carboxylic acid	[52]
butyrolactone	ester	[62]
ethyl acetate	ester	[16,30]
2-propenoic acid, butyl ester	ester	[1]
butyl acetate	ester	[27]
ethyleneglycol mono vinyl ester	ester	[10]
2-methylbutylacetate	ester	[40]
benzoic acid, 4-ethoxy-, ethyl ester	ester	[51,52]
1,2-benzenedicarboxylic acid, diethyl ester	ester	[51]
3-hydroxy- 2,4,4-trimethylpentyl 2-methylpropanoate	ester	[18]
2,2,4-trimethyl-1,3-pentanediol diisobutyrate	ester	[52]
pentanoic acid, 2,2,4-trimethyl-3-carboxyisopropyl, isobutylester	ester	[52]
propanoic acid, 2-methyl-, 1-(1,1-dimethylethyl)-2-methyl-1,3-propanediyl ester	ester	[52]
isopropyl myristate	ester	[6]
pentan-1,3-dioldiisobutyrate, 2,2,4-trimethyl	ester	[51]
dimethyl ether	ether	[48]

propane, 2-methoxy-2-methyl-	ether	[52]
benzene, 1,1-oxybis	ether	[51]
furan	furan	[30,62]
2-methyl-furan	furan	[55]
3-methylfuran	furan	[55,62]
2,5-dimethyl furan	furan	[41,51]
ethane, 1,1,2-trichloro-1,2,2-trifluoro-	haloalkane	[52]
trichlorethylene	haloalkane	[3]
1-iodo nonane	haloalkane	[17]
1-bromo-1-(3-methyl-1-pentenylidene)-2,2,3,3-tetramethyl	haloalkane	[10]
6-ethyl-3-octyl ester 2-trifluoromethyl benzoic acid	haloalkane	[4]
ethane	hydrocarbon, aliphatic	[19,60]
cyclopropane	hydrocarbon, aliphatic	[10]
propane	hydrocarbon, aliphatic	[44,55,62]
propene	hydrocarbon, aliphatic	[44]
butane	hydrocarbon, aliphatic	[41,44,50,62]
isobutane	hydrocarbon, aliphatic	[55]
1,2-pentadiene	hydrocarbon, aliphatic	[15]
1,3-pentadiene	hydrocarbon, aliphatic	[48]
1-cyclopentene	hydrocarbon, aliphatic	[27]
2-butene, 2-methyl	hydrocarbon, aliphatic	[27]
2-methylbutane	hydrocarbon, aliphatic	[15,44,62]
butane ,2-methyl	hydrocarbon, aliphatic	[27]
cyclopentane	hydrocarbon, aliphatic	[55,66]
ethylidene cyclopropane	hydrocarbon, aliphatic	[48]
isoprene	hydrocarbon, aliphatic	[14,22,27,31,41,45,56,62]
pentane	hydrocarbon, aliphatic	[33,43,45,50,53,55,62]
1,3-cyclopentadiene,1-methyl-	hydrocarbon, aliphatic	[27]
2-methylpentane	hydrocarbon, aliphatic	[15,43,53]
3-methylpentane	hydrocarbon, aliphatic	[15,43,62]
benzene	hydrocarbon, aliphatic	[30,31,41,53,62]
cyclohexane	hydrocarbon, aliphatic	[66]
hexane	hydrocarbon, aliphatic	[32,43]
1,3,5-cycloheptatriene	hydrocarbon, aliphatic	[48]
2,4-dimethylpentane	hydrocarbon, aliphatic	[62]
2-methyl-hexane	hydrocarbon, aliphatic	[48]
3,3-dimethyl pentane	hydrocarbon, aliphatic	[4,48,49]
3-ethyl-pentane	hydrocarbon, aliphatic	[48]

3-methylhexane	hydrocarbon, aliphatic	[3,48]
heptane	hydrocarbon, aliphatic	[1,50]
hexane, 2 methyl	hydrocarbon, aliphatic	[50]
hexane, 3-methyl	hydrocarbon, aliphatic	[50]
methylcyclohexane	hydrocarbon, aliphatic	[15,66]
1,3,5,7-cyclooctatetraene	hydrocarbon, aliphatic	[48]
1-octene	hydrocarbon, aliphatic	[13,47]
2,3,4-trimethyl-pentane	hydrocarbon, aliphatic	[48]
2,3-dimethyl-hexane	hydrocarbon, aliphatic	[48]
2,4-hexadiene, 2,5-dimethyl-	hydrocarbon, aliphatic	[51]
3,3-dimethyl-hexane	hydrocarbon, aliphatic	[48]
3-ethyl-hexane	hydrocarbon, aliphatic	[48]
5,5-dimethyl-1,3-hexadiene	hydrocarbon, aliphatic	[52]
alpha methyl styrene	hydrocarbon, aliphatic	[23]
ethylbenzene	hydrocarbon, aliphatic	[30,32,40,46,48,53,55,57]
octane	hydrocarbon, aliphatic	[36,53]
2,2,3-trimethyl-hexane	hydrocarbon, aliphatic	[48]
2,3,4-trimethyl hexane	hydrocarbon, aliphatic	[48,49]
2,4-dimethyl-heptane	hydrocarbon, aliphatic	[44,48]
4-methyl octane	hydrocarbon, aliphatic	[5,15,16,23,44,48,50,62]
nonane	hydrocarbon, aliphatic	[5,36,62]
2,2,3-trimethyl-, exo- bicyclo[2.2.1]heptane	hydrocarbon, aliphatic	[12]
benzene, cyclobutyl-	hydrocarbon, aliphatic	[27]
beta-pinene	hydrocarbon, aliphatic	[66]
decane	hydrocarbon, aliphatic	[25,31,53,66]
decene	hydrocarbon, aliphatic	[3]
limonene	hydrocarbon, aliphatic	[12,66]
2,5,6-trimethyl-octane	hydrocarbon, aliphatic	[7]
2,6,6-trimethyl-octane	hydrocarbon, aliphatic	[48]
4,5-dimethyl-nonane	hydrocarbon, aliphatic	[13]
decane, 4-methyl	hydrocarbon, aliphatic	[51]
decane, 5-methyl	hydrocarbon, aliphatic	[50]
dimethyl-nonane	hydrocarbon, aliphatic	[66]
undecane	hydrocarbon, aliphatic	[11,13,27,31]
2,2-dimethyl decane	hydrocarbon, aliphatic	[9,10,12,18]
2-methylundecane	hydrocarbon, aliphatic	[39]
3,7-dimethyldecane	hydrocarbon, aliphatic	[63]
4-methylundecane	hydrocarbon, aliphatic	[15]

5-methylundecane	hydrocarbon, aliphatic	[5]
dodecane	hydrocarbon, aliphatic	[13,40,49]
pentamethylheptane	hydrocarbon, aliphatic	[53]
2,3,4-trimethyl decane	hydrocarbon, aliphatic	[4]
3,7-dimethylundecane	hydrocarbon, aliphatic	[13]
3,8-dimethylundecane	hydrocarbon, aliphatic	[63]
3-methyl dodecane	hydrocarbon, aliphatic	[5]
4,7-dimethyl-undecane	hydrocarbon, aliphatic	[48]
5-(1-methyl-)propylnonane	hydrocarbon, aliphatic	[63]
5-(2-methyl-)propylnonane	hydrocarbon, aliphatic	[4,63]
5-butylnonane	hydrocarbon, aliphatic	[63]
nonane,5-(2-methyl-)propyl-	hydrocarbon, aliphatic	[65]
tridecane	hydrocarbon, aliphatic	[5,63]
trimethyldecane	hydrocarbon, aliphatic	[15]
undecane,3,7-dimethyl-	hydrocarbon, aliphatic	[27]
2-methyltridecane	hydrocarbon, aliphatic	[39]
4,6-dimethyl-dodecane	hydrocarbon, aliphatic	[12]
tridecane, 3-methyl	hydrocarbon, aliphatic	[50]
tridecane, 7-methyl	hydrocarbon, aliphatic	[50]
1,5,9-cyclododecatriene, 1,5,9-trimethyl-	hydrocarbon, aliphatic	[51]
2,6,11-trimethyldodecane	hydrocarbon, aliphatic	[63]
2-methyltetradecane	hydrocarbon, aliphatic	[39]
3-methyltetradecane	hydrocarbon, aliphatic	[39]
4-methyltetradecane	hydrocarbon, aliphatic	[63]
caryophyllene	hydrocarbon, aliphatic	[3,51]
dodecane,2,6,11,-trimethyl-	hydrocarbon, aliphatic	[65]
3-methyl pentadecane	hydrocarbon, aliphatic	[5,39]
5-propyltridecane	hydrocarbon, aliphatic	[63]
hexadecane	hydrocarbon, aliphatic	[8,13,23]
2,6,10-trimethyl tetradecane	hydrocarbon, aliphatic	[63]
2-methylhexadecane	hydrocarbon, aliphatic	[39]
3,7-dimethylpentadecane	hydrocarbon, aliphatic	[63]
7-methylhexadecane	hydrocarbon, aliphatic	[63]
6-t-butyl-2,2,9,9-tetramethyl-3,5-decadien-7- yne	hydrocarbon, aliphatic	[18]
8-methylheptadecane	hydrocarbon, aliphatic	[63]
2,6,10,14-tetramethylpentadecane	hydrocarbon, aliphatic	[63]
nonadecane	hydrocarbon, aliphatic	[63]
2-methyl nonadecane	hydrocarbon, aliphatic	[5]

eicosane	hydrocarbon, aliphatic	63
8-hexylpentadecane	hydrocarbon, aliphatic	63,65
toluene	hydrocarbon, aromatic	9,41,46,48,49,53,66
1,3-dimethylbenzene	hydrocarbon, aromatic	15,17
1,4-dimethybenzene	hydrocarbon, aromatic	15
bicyclo[4.2.0]octa-1,3,5-triene	hydrocarbon, aromatic	48
styrene	hydrocarbon, aromatic	8,22,25,31,48,55
xylene (all isomers)	hydrocarbon, aromatic	9,46,48,53,62,66
isopropyl benzene	hydrocarbon, aromatic	46
trimethylbenzene (all isomers)	hydrocarbon, aromatic	23,31,53
1H-indene, 2,3-dihydro-4-methyl-	hydrocarbon, aromatic	52
1-methyl-2-(1-methylethyl)-benzene	hydrocarbon, aromatic	48
1-methyl-3-(1-methylethyl)-benzene	hydrocarbon, aromatic	48
1-methyl-4-(1-methylethyl)-benzene	hydrocarbon, aromatic	48,49
naphthalene	hydrocarbon, aromatic	3
2-methylnapthalene	hydrocarbon, aromatic	63
2,6-dimethylnapthalene	hydrocarbon, aromatic	63
1,1'-(1-butenylidene)bis benzene	hydrocarbon, aromatic	17,49
1,1-biphenyl,2,2-diethyl-	hydrocarbon, aromatic	51
1H-Indene, 2,3-dhydro-1,1,3-trimethyl-3-phenyl	hydrocarbon, aromatic	51
acetone	ketone	16,27,29,30,41,45,62
2,3-butanedione	ketone	27,36
2-butanone	ketone	8,23,26,27,28,29,30,37,42,43,48,57,58,59
3-hydroxy-2-butanone	ketone	25,27,28,37,42,58,59,61
2-pentanone	ketone	6,29,30,42,44,62
2,3-hexanedione	ketone	52
2,5-cyclohexadiene-1,4-dione	ketone	51
4-methyl-2-pentanone	ketone	15
cyclohexanone	ketone	7,10,18,40
3-hexanone, 2-methyl-	ketone	52
3-pentanone,2,4-dimethyl-	ketone	51
5-methyl-3-hexanone	ketone	12
3-ethyl-3-methyl-2-pentanone	ketone	48
5-hepten-2-one, 6-methyl	ketone	1,22,24
acetophenone	ketone	6,27
2-methyl-4,6-octadiyn-3-one	ketone	48
camphor	ketone	52
tridecanone	ketone	63

6,10-dimethyl-5,9-dodecadien-2-one	ketone	48
2,2,7,7-tetramethyltricyclo[6.2.1.0(1,6)]undec-4-en-3-one	ketone	52
2-pentadecanone	ketone	63
alpha isomethyl ionone	ketone	52
2,4,6-tris(1,1-dimethyl-ethyl)-4-methylcyclohexa-2,5-dien-1-one	ketone	48
hydrazine	nitrogen compound	48
carbonic dihydrazide	nitrogen compound	48
hydrazine-carboxamide	nitrogen compound	48
hydrogen cyanide	nitrogen compound	56
methyl hydrazine	nitrogen compound	48
acetonitrile	nitrogen compound	29,41,56
ethylenimine	nitrogen compound	27
dimethyl formamide	nitrogen compound	41
iso-propylamin	nitrogen compound	40
2-propenenitrile	nitrogen compound	11,22,23,24
N,N-dimethylacetamide	nitrogen compound	62
urea, tetramethyl-	nitrogen compound	27
ethylaniline	nitrogen compound	18
isoquinoline, 1,2,3,4-tetrahydro-	nitrogen compound	27
10,11-dihydro-5H-dibenz-(B,F)-azepine	nitrogen compound	51
2,3-dihydro-1-phenyl-4(1H)-quinazolinone	nitrogen compound	6
2-amino-5-isopropyl-8-methyl-1-azulenecarbonitrile	nitrogen compound	4,9,17
2,6-bis(1,1-dimethylethyl)-4-methyl-methylcarbamate	nitrogen compound	48
4-(4-propylcyclohexyl)-4-cyano[1,1'-biphenyl]-4-yl ester benzoic acid	nitrogen compound	17
hydrogen sulphide	sulfur compound	14
carbon disulfide	sulfur compound	29,55,62
methyl mercaptan	sulfur compound	14
dimethyl sulfide	sulfur compound	14,29,41,62
1-propene, 1-(methylthio)-, (E)-	sulfur compound	52
methyl propyl sulfide	sulfur compound	27,62
[(1,1-dimethylethylthio] acetic acid	sulfur compound	17

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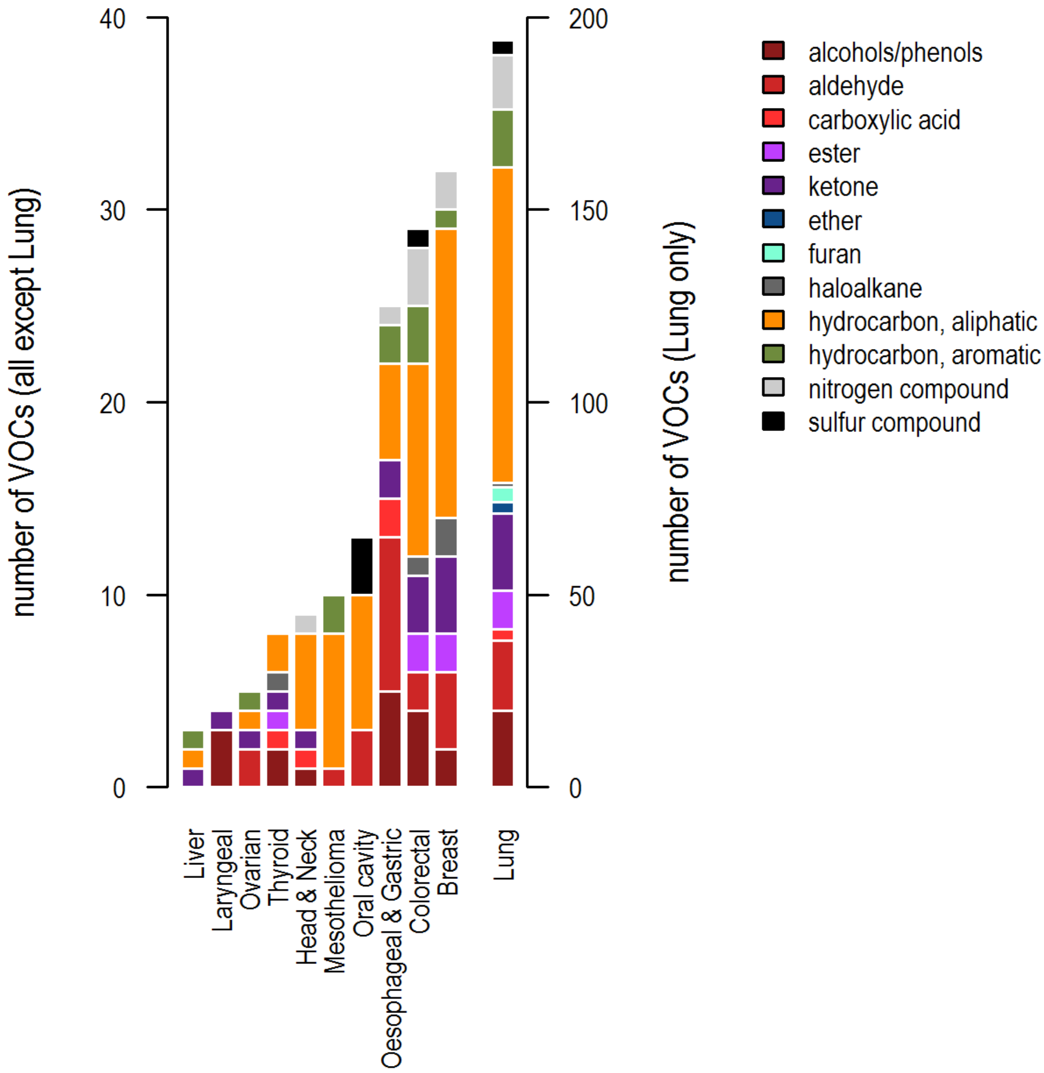
eFigure 3. Chemical classes of VOCs reported in different tumour sites.



eTable 6. STARD assessment of each study

		Barash 2015	Li 2014	Mangler 2012	Peng 2010	Phillips 2003	Phillips 2006	Wang 2014	Amal 2015	Peng 2010	Guo 2015	Gruber_2014	Hakim 2011	Bouza 2017	Szabó 2015	Altomare 2013	Amal 2016	Peng 2010	Wang 2014	Abela 2009	Kumar 2013	Kumar 2015	Amal_2013	Amal 2016	Xu 2013	Qin 2010	Garcia_2014	BaLtarevic 2009	Bousamra 2014	Buszewski 2011	Buszewski 2012	Chen_2005	Corradi 2015	Crohns 2009	Deng 2004	Feinberg 2016	Filipiak 2014	Fu 2014	Fuchs 2010
		Breast	Breast	Breast	Breast	Breast	Breast	Breast	Ovarian	Prostate	Thyroid	Head & neck	Head & neck	Oral cavity	Oral cavity	Colorectal	Colorectal	Colorectal	Colorectal	Esophageal & Gastric	Esophageal & Gastric	Esophageal & Gastric	Gastric	Gastric	Gastric	Liver	Laryngeal	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung
TITLE																																							
	1	1	1	0	0	1	1	0	1	0	0	0	0	0	0	1	1	0	0	0	1	1	0	1	1	1	0	1	1	0	0	0	1	0	0	0	0	0	0
ABSTR																																							
	2	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	0	1	0	0	1	1	1	1
INTRO																																							
	3	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	4	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	1	1	0	1	0	1	1	0	1	1	0	0	1	1	0	1	0	0	1
METH																																							
Study	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Partici	6	1	1	1	0	1	1	1	0	0	1	1	0	0	1	0	1	0	1	1	1	1	0	1	0	1	0	0	0	0	0	0	1	1	0	1	0	0	0
	7	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	1	1	0	1	1	1	1
	8	0	0	0	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	9	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Test	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	1	1	0	0	1	1	0	0	0	0	1	1	0	0	0	1	0	0	1	1	1	1	0	1	1	0	0	0	1	0	0	1	1	0	0	1	0	0
	1	1	1	0	1	1	1	1	0	1	0	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	0	1	1	0	0	1	1	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	1	1	0	1	1	1	1	0	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	0	0	1	1	0	0	1	0	0
	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Analys	1	1	1	1	0	1	1	0	0	0	1	0	0	0	0	1	0	0	0	0	1	1	0	1	1	1	0	1	1	0	0	0	1	0	0	0	0	1	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0
	1	0	1	0	1	1	0	0	1	1	1	0	0	1	0	0	1	1	0	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0
RESUL																																							
Partici	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	1
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	2	0	1	0	1	0	0	1	1	1	0	0	0	0	0	1	1	1	1	0	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Test	2	1	1	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	1	0
	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	0	0	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DISCU																																							
	2	1	1	0	0	1	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	1	1	0	1	0	0	1	1	0	0	0	1	0	0	1	0	0	1
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OTHER																																							
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1
TOTAL		**1**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**1**	**1**	**1**	**1**	**2**	**1**	**2**	**2**	**1**	**8**	**1**	**1**	**1**	**5**	**6**	**2**	**1**	**7**	**1**	**1**	**1**	**1**

eTable 6. STARD assessment of each study (continued)

		Gaspar 2009	Handa 2014	Kischkel 2010	Li 2015	Ligor 2009	Ligor 2015	Ma_2014	Ma 2015	Peled 2012	Peng 2009	Peng 2010	Phillips 2003	Phillips 2007	Phillips 2008	Poli 2005	Poli 2010	Rudnicka 2011	Sakumura 2017	Schallschmidt 2016	Schumer 2015	Schumer 2016	Skeldon 2006	Song 2010	Ulanowska 2011	Wang 2012	Wehinger_2007	Zou 2014	de Gennaro_2010
		Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Lung	Mesoth elioma
TITLE OR																													
	1	0	1	0	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1	1	1	0	0	0	0	1	1	1	0
ABSTRACT																													
	2	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1
INTRODUCTI																													
	3	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
	4	0	1	0	0	2	0	0	0	0	0	0	0	0	0	1	1	0	0	1	0	0	1	0	0	0	0	1	1
METHODS																													
Study design	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Participants	6	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	1
	7	0	1	1	1	0	0	1	0	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1
	8	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Test methods	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	0	1	0	1	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	1	1	1	0	1	1	1
	1	0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
	1	0	0	0	1	0	1	0	0	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1
	1	0	1	1	0	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Analysis	1	1	1	0	1	1	1	0	0	0	0	0	1	1	1	1	1	0	0	1	1	0	0	1	0	1	1	1	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	1	0	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	1	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RESULTS																													
Participants	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	0	0	1	1	1	0	1	1	1	1	1	1
	2	1	1	0	1	0	0	1	0	1	1	1	1	1	0	0	1	0	0	0	1	1	0	1	0	1	1	1	0
	2	0	0	0	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	2	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Test results	2	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0
	2	0	0	0	1	0	0	1	0	1	0	0	0	0	1	0	1	0	1	0	0	0	0	1	0	0	1	1	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DISCUSSION																													
	2	0	1	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	1	1	0
	2	1	0	0	1	1	0	1	0	0	1	1	1	1	1	1	0	0	0	0	1	0	1	0	0	0	0	1	1
OTHER																													
	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0
TOTAL		**5**	**17**	**8**	**19**	**12**	**11**	**13**	**5**	**13**	**13**	**14**	**19**	**18**	**15**	**16**	**16**	**5**	**7**	**10**	**14**	**13**	**14**	**13**	**10**	**13**	**17**	**22**	**13**

eTable 7. Summary of factors reported to influence levels of volatile organic compounds within exhaled breath

Classification	Factor	Example	Possible consequence	Example of mitigation or acceptance	References
Environmental	**Ambient air**	Inhalation of ambient air containing variable levels of target VOCs that is dependent on the time and location of sampling	Elevated and variable levels of target VOCs within inspiratory air diminishes confidence in the ability to accurately determine that which is produced endogenously and associated with disease processes	Concurrent analysis of ambient air is advised in order to provide a reference point for VOCs levels detected in exhaled breath samples. Exclusion of VOCs found to be in high concentrations within inspired air has been recommended. Alternatively correction of trace gas levels in ambient inhaled air through determining their specific retention coefficients has been demonstrated. Inhalation of synthetic 'clean' air another approach.	64-97
	Environmental exposure	Inhalation of exogenous contaminants within ambient air e.g. anaesthetic gases	High levels of contaminant compounds may influence the accurate detection and quantification of trace gases that are of clinical interest		84,88,98-105
SubLect	**SubLect specific**	SubLect specific factors, including: age; gender and BMI	Such factors are recognised to significantly affect the concentrations of selected VOCs within exhaled breath	These factors are typically considered to be non-modifiable. Appreciation for their potential influence is however recommended.	39,72,73,76,80,87,91,93,94,106-115
	Cardiovascular	Variation in cardiovascular parameters, including: heart rate; blood pressure and	Changes in cardiorespiratory parameters are recognised	Recording of basic cardiorespiratory parameters should be	73,74,80,88,92,116-121

		cardiac output	to alter the delivery and partition of specific VOCs between the fluid and gas phases altering their concentration detected within exhaled breath	considered at the time of breath sampling as well as a standard period of rest prior to breath testing.	
	Respiratory	Variation in respiratory parameters, including: respiratory rate and tidal volume			66,73,74,92,116-121
	Biochemical	Influence of biochemical parameters including: cholesterol; blood glucose and white bloods cell counts	A relationship between biochemical parameters and the levels of selected exhaled VOCs has been reported.	For the maLority of exhaled VOCs a link to a source of systemic origin and association with biochemical processes is yet to be established. Where such a link exists, recognition of it influence upon exhaled VOCs levels should be considered during the development of a clinical breath tests.	76,92,107,108
	Diet	Diet and oral intake	Timing of last oral intake can influence exhaled VOCs levels secondary to ingestion of exogenous contaminants and alteration of systemic metabolic pathways	Whilst the relationship between oral intake and the concentrations of specific VOCs (e.g. acetone) is well established, for many other trace gases there is inadequate evidence. Until more is known in regard to the effects of dietary intake the timing and nature of last oral intake should form part of the minimal dataset recorded at the time of breath sampling. A	80,86,87,91-95,114,122-130

				standard period of fasting prior to breath testing is also considered beneficial.	
	Exercise	Variation in activity status, and related metabolic and cardiorespiratory parameters	The effects of exercise on metabolism and cardiorespiratory function may influence the systemic synthesis of VOCs as well as their delivery and release within the lungs	Recording of basic cardiorespiratory parameters should be considered at the time of breath sampling as well as a standard period of rest prior to breath testing.	74,76,111,116-119,125,131,132
	Smoking	Active and/or passive inhalation of cigarette smoke	Altered VOCs that are observed in the breath of those exposed to cigarette smoke may originate from exogenous contaminants from the smoke itself as well as local and systemic cellular changes	Documentation of smoking status as well as timing of last exposure to cigarette smoke should form part of the minimal dataset recorded at the time of breath sampling.	67,98,99,107-110,125,133-135
	Inter-subLect variation	Inherent variation in the concentration of exhaled VOCs both within individual and groups of individuals	Knowledge of the normal variation of VOCs within the exhaled breath of healthy subLects is an essential step to determining changes brought about by disease states	An understanding of normal inter- and intra-subLect variation is important for establish normal ranges for these VOCs. Controlling for other factors listed herein is anticipated to minimise the observed inter- and intra-subLect variation	69,70,72,75,76,87,91,93-95,108,110-115,122-125,134,136
	Intra-subLect variation				67,70,71,76,86,90-92,110,115,117,136,137
Sampling	**Breathing parameters**	Parameters associated with the rate, depth and speed of exhalation	Modifiable breath manoeuvres have been associated with variation of	Where possible standard practices for breath sampling should be adhered too. The	80-82,86,89,90,104,121,138-143

			a number of exhaled VOCs	development of consensus guidelines for standardised analysis should be considered for selected VOCs.	
	Body position	Transition between different body positions	An association between body position at the time of breath sampling and the detected levels of certain VOCs is reported	Ensuring a standard period of rest in a specific position (e.g. sitting) prior to breath testing is recommended	117,120
	Sample storage	The method and duration of storage of off-line breath samples	Stored breath samples are vulnerable to the effects of decay, contamination and carryover that this typically dependent upon the method and duration of storage.	Where possible on-line breath sampling should be utilised, obviating the potentially negative effects associated with sample storage. Where off-line sampling is unavoidable a suitable method should be adopted and storage time should be kept to a minimum.	46,69,71,83,110,113,117,137,144-148
	Expiratory compartment	Sampling of mixed (whole) or alveolar breath samples and breath exhaled via either the oral or nasal cavities	The compartment from which breath is samples can serve to either enrich or contaminate VOC levels within collected samples	Where possible standard practices for breath sampling should be adhered too. The expiratory compartment which is to sampled should be Ludiciously choose to ensure optimal detection of desired VOCs whilst avoiding unwanted	75,77,113,117

				contamination	
Instrument	**Analytical technique**	Variation between different analytical techniques used for the detection of gas phase VOCs is poorly understood	Uncertainty in regard to the comparability of results determined using different analytical techniques	Cross platform validation of findings are recommended during the discovery phase of VOCs as clinical breath biomarkers	66,70,71,90,116,119,125,137,141
	Reproducibility	Intra- and inter-instrument variability and reproducibility of results	Reproducibility of findings both within individual and separate institutions has not been shown for the maLority of trials.	Standardisation of analytical techniques and reproducibility of findings within multicentre trials should be prioritised. Investigators are encouraged to report aspects relating to the reproducibility of the chosen analytical technique	
	Sensitivity **Reliability**	Intra- and inter-instrument characteristics permitting accurate detection to trace VOCs	The specification and capabilities of individual analytical techniques influence accuracy of VOCs detection.	Continued refinement and Ludicious selection of analytical method is required to ensure the accurate detection of gas phase VOCs. Investigators are encouraged to report aspects relating to the sensitivity and reliability of the chosen analytical technique.	
VOC, volatile organic compound. BMI, body mass index. PTR/-MS, proton transfer reaction - mass spectrometry. SIFT-MS, selected ion flow tube – mass spectrometry					

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