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Mapping the landscape of lung cancer breath analysis: A scoping review (ELCABA)

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ABSTRACT

Lung cancer is the leading cause of cancer death worldwide due to its late-stage detection. Lung cancer screening, including low-dose computed tomography (low-dose CT), provides an initial clinical solution. Nevertheless, further innovations and refinements would help to alleviate remaining limitations. The non-invasive, gentle, and fast nature of breath analysis (BA) makes this technology highly attractive to supplement low-dose CT for an improved screening algorithm. However, BA has not taken hold in everyday clinical practice. One reason might be the heterogeneity and variety of BA methods. This scoping review is a comprehensive summary of study designs, breath analytical methods, and suggested biomarkers in lung cancer. Furthermore, this synthesis provides a framework with core outcomes for future studies in lung cancer BA. This work supports future research for evidence synthesis, meta-analysis, and translation into clinical routine workflows.

1. Introduction

Lung cancer develops over a long period and results in a diverse and complex tumor biological environment. Continuous carcinogenesis leads to gradual changes in metabolism and genome. To date, thousands of markers related to lung cancer have been studied, identified, and applied. Current promising diagnostic biomarkers include microRNA signatures measured in serum or plasma. Biomarkers useful for treatment decisions, like oncogenic driver mutations, enable an efficient and targeted therapy for specific lung cancer patient populations [1,2]. Metabolic biomarkers including volatile organic compounds (VOCs), non-VOCs, proteins, and genes can reflect cellular, biochemical, and molecular (e.g., proteomic, genetic, and epigenetic) alterations and aid recognition and monitoring of normal or abnormal biological processes. Thus, metabolomic analysis can be applied in the screening, diagnosis, treatment evaluation, and recurrence monitoring of lung cancer [3]. Examples for such metabolic biomarkers are metabolites involved in glycolysis, citric acid cycle, amino acid metabolism, or cell membrane synthesis [4]. Urinary compounds, e.g., creatine riboside and *N*-acetyl neuraminic acid, have been associated with lung cancer risk prior to clinically detectable disease [5,6]. There is great need to improve this and provide smart techniques for simple, routine clinical lung cancer detection and monitoring. Patient-oriented and cost-effective approaches such as exhaled breath analysis are promising options to enlarge the screening portfolio.

Hippocrates suggested that exhaled breath could be used as an indicator of disease [7]. Years ago, dogs were trained to identify patients with a particular disease [8]. Evidence from several studies in lung cancer patients highlights the presence of VOCs, semi-VOCs, and non-VOCs in exhaled breath [9–11]. VOCs are associated with a multitude of clinical conditions [12], and originate from endogenous metabolic processes [13]. The advantage of exhaled breath is the ease with which breath can be collected for analysis by simple exhalation into a device or container. The exhaled compounds can be analyzed in the breath gas matrix itself or in a liquid phase as exhaled breath condensate (EBC). It is important to note that breath gas and EBC comprise a different spectrum of exhaled compounds. Recent technological advances have enabled real-time analysis that make results immediately available. These make

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this technology promising for supplementing low-dose CT screening.

Despite the many advantages of exhaled breath testing, its use in clinical practice is still limited, due to the lack of thoroughly validated techniques. The fast development of diverse breath analysis techniques helps to overcome these challenges, but the field is very heterogeneous with various methods at different development stages, including EBC analysis, gas chromatography (GC), proton-transfer-reaction (PTR), secondary electrospray ionization (SESI), selected ion flow tube mass spectrometry (SIFT-MS), eNose technologies and other sensors. About 109 heterogeneous reviews focus on breath analysis in oncological indications and lung cancer. These literature syntheses focus mainly on broad aspects like the breath analysis potential in global oncology or on technical advancements and possibilities. Many are more narrative in nature, and few use modern professional search strings to exhaustively screen all available literature archives [14–18]. For the first time, this work offers a comprehensive overview of identified breath compounds in lung cancer and their frequency in different reported studies and evaluates their translational value for clinical use. This review applies modern systematic search strings and uses the dynamic and innovative scoping review methodology to generate a synthesis of this heterogeneous field.

The main goal of this scoping review is to identify and map all efforts in the field of lung cancer breath analysis methods and to report identified breath biomarkers. Additionally, this study draws conclusions regarding the potential clinical value for early lung cancer detection or monitoring and suggests a framework for future research.

2. Methods

2.1. Protocol and registration

We conducted a scoping review that is reported in accordance with the Preferred Reporting Items for Systematic Reviews and meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) [19]. The protocol for this review is registered with the Open Science Framework Registry (Registration https://doi.org/10.17605/OSF.IO/GFZ2H).

2.2. Eligibility criteria

We included all studies that addressed breath analysis in lung cancer subjects, covered a human study population, and provided information on the analytical method and on identified biomarkers. Original research articles, case reports, and grey literature (e.g., dissertations) published in English or German were eligible. Conference abstracts were excluded due to limited information on methods and biomarkers.

2.3. Information sources

A medical librarian (SDK) designed a systematic literature search strategy with keywords comprising lung cancer, breath analysis, and volatile organic compound as well as corresponding index terms where available (see Supplementary Tables 1-5 for full search strings for all databases). One reviewer (FS) searched the databases Medline (Ovid), Embase (embase.com), Cochrane Library, Web of Science (Core Collection), and Scopus from inception to 30/06/2022, when the records were downloaded for screening. In addition, we searched for grey literature using Google Scholar, university library databases, and the websites of commercial breath analytics companies. All references from included studies were hand searched for additional studies, ensuring literature saturation.

In accordance with the Peer Review of Electronic Search Strategies (PRESS) guidelines [20], we applied a two-step process to validate our literature search code. In stage one, one reviewer (FS) performed an initial Embase search testing our query code and identifying all necessary keywords and synonyms out of the first 25 publications identified. Based on these findings, the query code was discussed among three reviewers and amended. Secondly, we verified that the final query code with all defined index terms and keywords identified five pre-defined eligible studies in an Embase search. Following this verification phase, the final search code (see Supplementary Table 1) was translated to all dedicated databases (see Supplementary Table 2-5).

The study selection process is reported in accordance with the PRISMA-ScR guidelines [19]. Two reviewers (FS and DK) screened all studies independently. The results were compared and discrepancies discussed until agreement. Screening of titles and abstracts, if available, was followed by full text screening and decisions on inclusion or exclusion.

2.4. Data charting process

We used data tables for data extraction. These were purpose-designed and conclusively discussed and amended among all team members. Data extracted covered publication details (e.g., authors, year of publication), details on study design and scope (e.g., technique used, lung cancer type), and details on the biomarkers identified. The full data extraction can be found in the Supplementary Material. Two authors (FS and SM) independently extracted the data and discussed any discrepancy until agreement.

The synthesis of this work covers quantitative and qualitative methods. We report on quantitative data with frequency analysis and graphical presentation. All quantitative analyses were performed using R 4.1.2 on Windows (R Core Team 2021. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

2.5. Critical appraisal

To assess the development stage of the reported breath analytical technique, we categorized the reported study methodology into study phases according to Leeflang et al. [21] and EU regulations EU2017/745 and EU2017/746. We developed a simple classification tool to rate the clinical relevance and significance of each reported breath analytical technology. References were rated as “high” valuable for potential translation into the clinical setting, if a diagnostic performance was reported according to the principles of Standards for Reporting Diagnostic accuracy studies (STARD) statement and as “low” valuable for potential translation into the clinical setting, if it was not reported according to the principles of STARD [22].

3. Results

3.1. Selection of sources of evidence

After duplicates were removed, a total of 2635 citations were identified from searches of electronic databases. Four additional citations were identified through grey literature and reference search. Based on the title and the abstract screening, 1870 citations were excluded due to absence of information about cancer, breath sampling methods, biomarkers, and human subjects or lack of criteria-matching research designs. 765 citations were sought for retrieval. Full texts of 64 studies could not be retrieved; thus, 701 were assessed for eligibility. Of these, 562 were excluded (Fig. 1). Finally, we included 138 original articles (Supplementary Table 6) which transparently report breath analysis in lung cancer subjects, address a human population, and provide information on the analytical method and on identified biomarkers.

3.2. Characteristics of sources of evidence

All included studies were published in the last 40 years from 104 different first authors and originated predominantly from Europe, Asia, and North America. These publications reported a total of 490 breath biomarkers in lung cancer (Supplementary Table 7). Ninety percent of

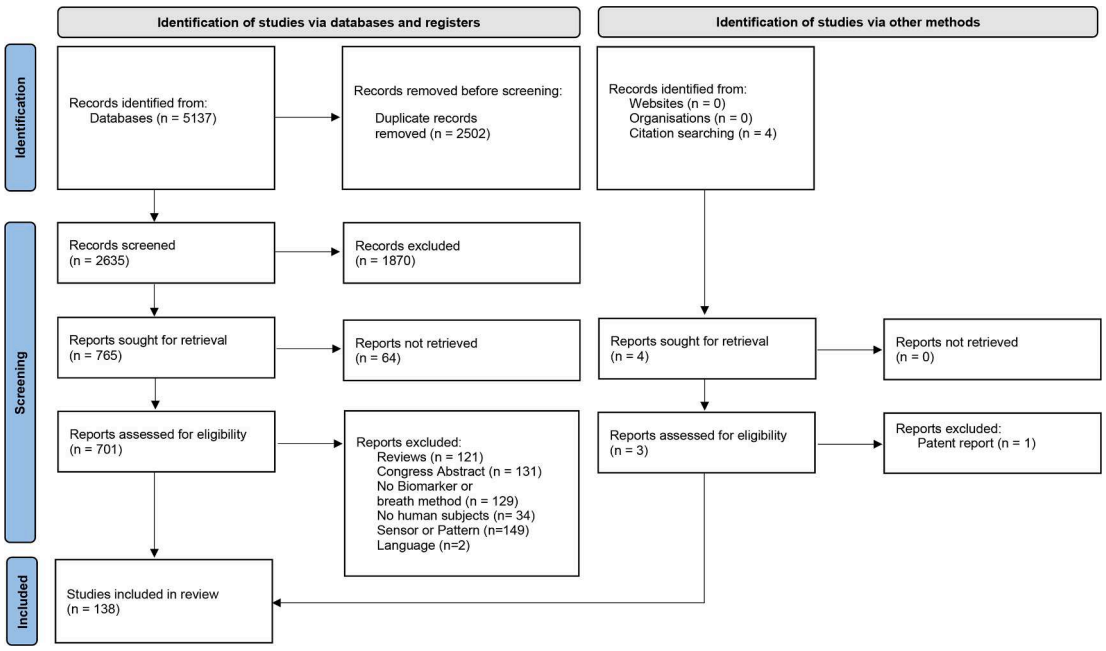

Fig. 1. PRISMA Flow Diagram.

the listed studies had a case-control design. The study design distribution is presented in Supplementary Fig. 1. The median number of lung cancer patients included in the reported studies was 38 [min = 5; max = 456]. The total sample size of study participants (patients and controls) ranges around a median of 72 [min = 5; max = 740]. Lung cancer breath analysis studies report a median count of VOCs of 8 [min = 0; max = 386]. Details about the records are listed in Supplement Table 6.

3.3. Critical appraisal within sources of lung cancer biomarker identification by breath analysis

A categorization according to development stages and a classification into higher or lower value for translation into the clinical setting was used to critically appraise the original articles. The different study phases and translational value classifications are reported in Supplementary Fig. 1 and Supplementary Table 6. Table 1 presents an overview of the 29 high-valued breath analysis studies to screen/detect lung cancer.

3.4. Results of individual sources of evidence

The characteristics of all extracted study information can be found in the Supplementary material. Supplementary Table 6 presents all information about study characteristics. We present in detail the year of publication, first author, location of the research group, study design, value of potential translation into clinical setting, study phase, number of lung cancer patients for analysis, total number of enrolled study patients, characteristics of the control group, information about the confounding factor smoking, histological lung cancer type, analytical platform, number of VOCs, and whether diagnostics accuracy is reported. Supplementary Table 7 lists all identified lung cancer breath biomarkers, corresponding references, the count (how many references report this compound), sum formula, concentration changes comparing to a control group, CAS number, chemical class, mass of the molecule, medium where the compound was identified, and the analytical technology for compound identification.

3.5. Synthesis of results

One hundred thirty-eight research papers were eligible for our analysis. In total 26 different methods were identified (Fig. 2). In most cases, mass spectrometric methods with pre-separation technologies were used. Nearly all breath-sampling approaches were off-line sampling. Only four references report online sampling and thus no influence of probe storing and logistics. EBC compounds were identified with different technologies, but mostly with specific protein assays.

Fig. 3 shows all identified lung cancer breath biomarkers which were detected in more than two different studies. Chemical classes like aliphatic hydrocarbons, aldehydes, aromatic hydrocarbons, and alcoholic compounds were frequently reported. Additionally, Table 2 presents all biomarkers that are presented in more than five different studies.

To evaluate the potential clinical significance and performance of the specific lung cancer screening methods, we extracted the study design, a classification into translational value/potential, histological lung cancer type, and sample size. All details are listed in Supplementary Table 6. Main categories are presented in Supplementary Fig. 1. Most studies have cross-sectional case-control designs. Most studies characterized breath biomarkers in an overall lung cancer group and do not stratify for histological subtypes.

4. Discussion

4.1. The landscape of lung cancer breath research

This comprehensive scoping review provides an overview of identified breath biomarkers and breath analytical methods and builds a basis for future research. In total, more references than expected were identified and analyzed. This reflects the research effort and persistence in the field of lung cancer breath research. Today Hippocrates ideas are more relevant than ever before and many researchers try to analyze the human breath.

In total 138 publications, reporting 26 different methods and 490 different potential biomarkers are presented in the results section. However, the whole landscape of lung cancer breath research also includes methods which only work with a pattern recognition principle and do not identify breath compounds. Therefore, the whole landscape of breath research includes more than 138 publications. During the screening phase a total of 293 publications were identified which report lung-cancer-specific breath analysis studies. However, 155 of 293

Table 1
Main Information from 29 high-valued breath analysis studies to screen or detect lung cancer. The whole list of all included studies is presented in Supplementary Table 6.

Year	First Author	Study Design	Trans-lational value	Study phase	Total # Patients	Lung Cancer Type	Analytical Platform	Biomarker Identification Platform	Measurement type	No VOCs	Ref
2015	Ashmawi et al	cross-sectional case-control	high	phase 1	80	NSCLC	EBC device	NA	off-line	0	[23]
2009	Bajtarevic et al	cross-sectional case-control	high	phase 2	96	All type	GC–MS	MS	off-line	21	[24]
2009	Bajtarevic et al	cross-sectional case-control	high	phase 1	661	All type	PTR-MS	MS	off-line	3	[24]
2011	Baumbach et al	cross-sectional cohort	high	phase 2	19	NSCLC	IMS	MS	on-line	4	[25]
2014	Bousamra et al	cross-sectional case-control	high	phase 2	235	All type	FT-ICR-MS	MS	off-line	4	[26]
2014	Fu et al	cross-sectional case-control	high	phase 3	217	All type	FT-ICR-MS	MS	off-line	4	[27]
2022	Wang et al	cross-sectional case-control	high	phase 3	609	All type	HPPI-MS	MS	off-line	16	[28]
2018	Butcher et al	cross-sectional case-control	high	phase 2	40	All type	SIFT-MS	MS	off-line	15	[29]
2017	Cai et al	cross-sectional case-control	high	phase 1	129	All type	eNOSE-GC	GC	off-line	23	[30]
2019	Chen et al	cross-sectional case-control	high	phase 1	333	NSCLC	EBC device	ELISA	off-line	0	[31]
2020	Chen et al	cross-sectional case-control	high	phase 1	60	NSCLC	EBC device	qPCR	off-line	0	[32]
2016	Chen et al	cross-sectional case-control	high	phase 1	60	NSCLC	EBC device	rtPCR	off-line	0	[33]
2021	Chen et al	cross-sectional case-control	high	phase 1	352	All type	TD-GC–MS	MS	off-line	19	[34]
2017	Gessner et al	cross-sectional case-control	high	phase 2	300	All type	EBC device	MBBI	off-line	0	[35]
2019	Kordiak et al	cross-sectional cohort	high	phase 2	51	All type	EBC device	PCR	off-line	0	[36]
2021	Monedeiro et al	cross-sectional case-control	high	phase 2	56	ADENO	NTD-GC–MS	MS	off-line	112	[37]
2016	Peralbo-Molina et al	cross-sectional case-control	high	phase 1	239	All type	EBC device	MS	off-line	44	[38]
2016	Peralbo-Molina et al	cross-sectional case-control	high	phase 2	256	All type	EBC device	MS	off-line	6	[39]
1999	Phillips et al	cross-sectional case-control	high	phase 2	108	All type	GC–MS	MS	off-line	22	[40]
2003	Phillips et al	cross-sectional case-control	high	phase 2	219	All type	GC–MS	MS	off-line	9	[41]
2019	Phillips et al	cross-sectional case-control	high	phase 2	462	All type	GC–MS	MS	off-line	8	[42]
2019	Rudnicka et al	cross-sectional case-control	high	phase 2	229	All type	SPME-GC–MS	MS	off-line	84	[43]
2016	Schallschmid et al	cross-sectional case-control	high	phase 2	60	All type	SPME-GC–MS	MS	off-line	24	[44]
2010	Song et al		high	phase 2	84	NSCLC	SPME-GC–MS	MS	off-line	2	[45]

(*continued on next page*)

Table 1 (*continued*)

Year	First Author	Study Design	Translational value	Study phase	Total # Patients	Lung Cancer Type	Analytical Platform	Biomarker Identification Platform	Measurement type	No VOCs	Ref
		cross-sectional case-control									
2012	Wang et al	cross-sectional case-control	high	phase 2	243	All type	SPME-GC–MS	MS	off-line	23	[46]
2018	Wang et al	cross-sectional case-control	high	phase 2	344	All type	TD-GCMS & SPME-GCMS	MS	off-line	20	[47]
2020	Xie et al	cross-sectional case-control	high	phase 2	122	NSCLC	EBC device	rtPCR	off-line	0	[48]
2020	Zhang et al	cross-sectional case-control	high	phase 2	141	NSCLC	EBC device	rtPCR	off-line	0	[49]
2013	Zou et al	cross-sectional case-control	high	phase 1	56	All type	EBC device	CLI	off-line	3	[50]

NSCLC – Non-small cell lung cancer; ADENO – Adenocarcinoma; All type – All types of lung cancer subjects were included; EBC device– Device to collect exhaled breath condensate (e.g. Turbo-DECCS, EcoScreen, R-Tube condenser); GC–MS – Gas chromatography–mass spectrometry; PTR-MS - Proton transfer reaction-mass spectrometry; IMS - Ion mobility spectrometry–mass spectrometry; FT-ICR-MS - Fourier-transform ion cyclotron resonance-mass spectrometry; HPPI-MS - High-pressure photon ionization time-of-flight-mass spectrometry, SIFT-MS - Selected-ion flow-tube mass -spectrometry, eNOSE-GC – Electronic nose–gas chromatography; TD-GC–MS - Thermal desorption–gas chromatography–mass spectrometry; NTD-GC–MS – Needle-trap device gas chromatography-mass spectrometry; SPME-GC–MS – Solid phase micro extraction gas chromatography-mass spectrometry. CLI - chemiluminescence immunoassay; rtPCR – Reverse-transkriptase polymerase chain reaction; qPCR – quantitative polymerase chain reaction; ELISA – Enzyme-Linked Immunosorbet Assay; MBBI – Multiplex bead based immunoassay; NA – Not applicable.

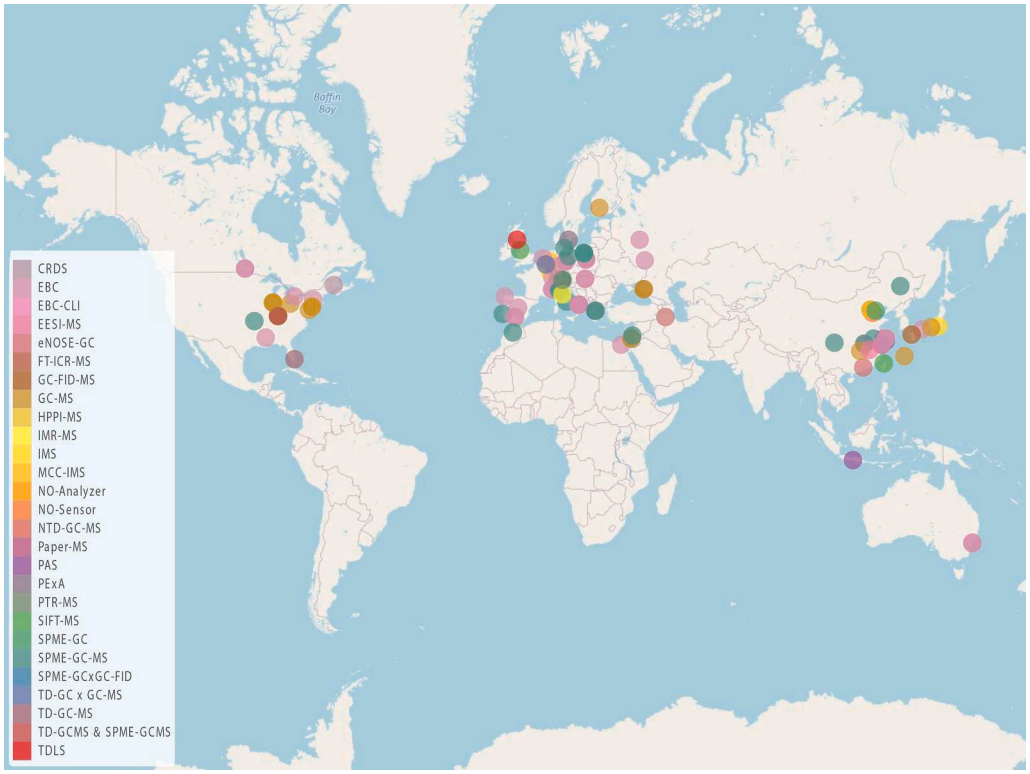

Fig. 2. Evidence atlas of different analytical lung cancer breath detection methods across all over the world. Strikingly breath research is clustered in highly developed technical and innovation-orientated hot spots in Europe, but also North America and Asia.

publications report breath technologies like sensor or eNose approaches (n = 133) or scent detection by animals (n = 22), which do not identify breath biomarkers or report which biomarker were used for recognition (Supplementary Fig. 2). Publications without biomarker identification or breath biomarker listing were not within the objective of this scoping review, and thus 155 records of pattern recognition methods were not eligible for data charting. Although the literature shows that dogs are indeed capable of reliably identifying lung cancer in breath samples, this method does not provide information on the biomarkers involved [51,52]. The field of breath sensor development is quite lively. Current reviews present a comprehensive overview [3,53–55]. The most clinically relevant pattern recognition method is the eNose approach. This

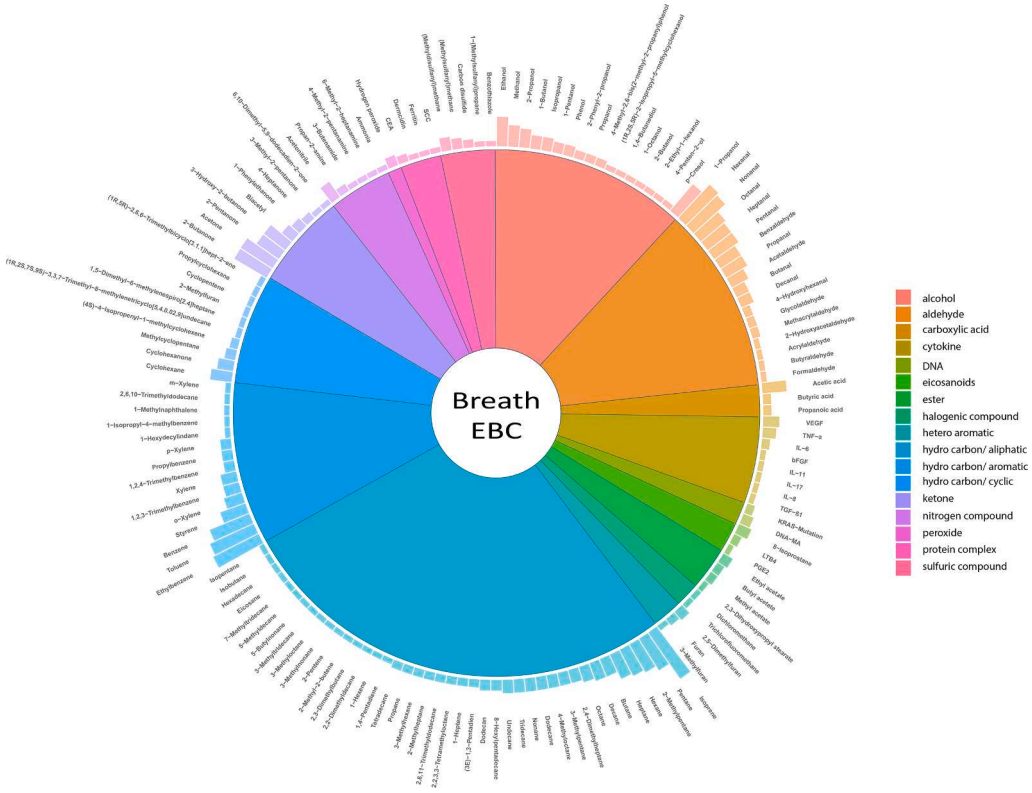

Fig. 3. Identified biomarker in different lung cancer breath detection studies. Only biomarkers are presented in this graphic, which are listed in more than two studies.

relatively new, emerging technology is based on the binding of VOCs to different sensors or sensor arrays within mostly handheld devices, often temperature modulated. The binding of VOCs to these sensors generates an electrical signal which can be measured and interpreted. Examples of such technologies are commercially available Noses like Cyranose®, Aeonose®, PEN3e-nose®, but mostly custom-made eNoses [18,56]. A recently published eNose multicenter validation study shows promising sensitivity, specificity, negative predictive value, and receiver operating characteristics (95 %; 49 %; 94 %; 0.86) [57]. eNoses are portable, inexpensive, and easy to handle in clinical routines, and produce rapid results. However, although most eNose and other sensor technologies are built on markers reported by breath biomarker identification technologies like MS or EBC assays, there is no consensus on which breath biomarkers are relevant or should act as core outcome. Thus, this review focuses on identifying breath analysis methods for lung cancer detection because such identification is key for understanding and improving different breath analysis technologies.

The most common and studied biomarker identifying methods are SPME-GC–MS, GC–MS, PTR-MS, and EBC. These have widespread use in other fields over time. Experience with GC–MS measurements in lung cancer breath research began in 1984. Newer methods like HPPI-MS [28] or SESI-HRMS [58], reported in single proof of concept designs or in ongoing studies, show even more advantages than GC–MS, such as higher sensitivity, easier measurement procedures, and simpler biomarker identification. SESI-HRMS has the advantage of possible online measurements in clinical routine [59]. However, mass spectrometry methods always need trained personnel and highly developed technical infrastructure. Thus research into biomarkers for identifying lung cancer by breath analysis are primarily located in innovation-orientated research facilities worldwide (Fig. 2).

The identification of breath biomarkers focuses on two media: directly exhaled breath gas and condensate breath gas (EBC). Both media enable detection of a broad spectrum of molecular classes, e.g., VOCs, semi-VOCs, or non-VOCs. Compounds proposed to be associated with lung cancer include not only small volatile molecules like alcohols, aldehydes, carboxylic acids, and aromatic hydrocarbons, but also complex non-volatile molecules like DNA with its alterations, cytokines, and protein structures; these are detectable in EBC (Fig. 3). To sum up, breath analysis in lung cancer not only offers opportunities for early detection and disease monitoring, but furthers understanding of metabolic and molecular pathophysiology. Some studies report specific breath molecules associated with histologic lung tumor types, tumor staging, tumor resection success, or the probability of tumor relapse [27,28,34,60]. However, these suggestions are in early research and need further validation for clinical disease monitoring.

4.2. Translation of lung cancer breath biomarkers into physiological and clinical context

The physiological origin of lung cancer breath biomarkers is diverse. Compounds described in Fig. 3 can be assigned to five main biochemical categories: oxidative stress or lipid peroxidation, inflammation, energy metabolism or cell proliferation (glycolysis, lipid degradation), genetic or epigenetic, and unknown origin.

4.2.1. Oxidative stress and lipid peroxidation

Lungs are exposed over many years to endogenously or exogenously oxidants like mitochondrial leakage products, air pollutants, and cigarette smoke. Elevated levels of reactive oxygen species are one factor for lung carcinogenesis and apoptosis. The imbalances in the redox equilibrium of lung cells results in oxidative cleavage of lung tissue lipids [61,62]. These lipids are processed in various pathways and exhaled as alkanes, aldehydes, and eicosanoids (listed in Supplementary Table 7). Cancer cells promote random lipid peroxidation, which leads to a variety of reactions in the cancer cells and an excretion of molecules like aldehydes, such as benzaldehyde and nonanal. Benzaldehyde is also involved in several metabolic pathways, such as glycolysis or gluconeogenesis, tryptophan metabolism, and fatty acid metabolism [63].

Table 2
Lung cancer breath biomarkers, which are reported in greater than 5 different studies. All reported biomarkers and references can be found in Supplement Table 7.

Compound name	Formula	CAS No	Dalton	Identified Medium	Analytical Technology
Isoprene	C_5H_8	78–79-5	68.117	Breath	PTR-MS, GC–MS, eNOSE-GC, GC-FID-MS, SPME-GC–MS, SPME-GCxGC-FID
Ethylbenzene*	C_8H_{10}	100–41-4	106.165	Breath	GC–MS, eNOSE-GC, TD-GC–MS, PTR-MS, IMS, SPME-GC–MS, GC-FID-MS, SIFT-MS
Toluene*	C_7H_8	108–88-3	92.138	Breath	SPME-GC–MS, GC-FID-MS, SIFT-MS, HPPI-MS, GC–MS
Hexanal	$C_6H_{12}O$	66–25-1	100.159	Breath/EBC	TD-GC–MS, SPME-GC–MS, GC–MS, IMS, Paper-MS, HPPI-MS, EBC device
Benzene*	C_6H_6	71–43-2	78.112	Breath	GC–MS, SPME-GC–MS, GC-FID-MS, SIFT-MS, eNOSE-GC, TD-GC–MS
Nonanal	$C_9H_{18}O$	124–19-6	142.239	Breath/EBC	IMS, MCC-IMS, SPME-GC–MS, GC–MS, Paper-MS, SIFT-MS, TD-GCMS & SPME-, HPPI-MS, EBC device
2-Butanone	C_4H_8O	78–93-3	72.106	Breath/EBC	GC–MS, FT-ICR-MS, EBC, GC-FID-MS, SPME-GC–MS, NTD-GC–MS
Aceton	C_3H_6O	67–64-1	58.079	Breath/EBC	EBC, PTR-MS, GC–MS, SPME-GC–MS, SIFT-MS, SPME-GCxGC-FID, PAS, SIFT-MS
Pentane	C_5H_{12}	109–66-0	72.149	Breath	SPME-GCxGC-FID, GC–MS, SPME-GC–MS, IMR-MS
1-Propanol	C_3H_8O	71–23-8	60.095	Breath	GC–MS, SPME-GC–MS, NTD-GC–MS, SIFT-MS
2-Methylpentane	C_6H_{14}	107–83-5	86.175	Breath	TD-GC–MS, SPME-GC–MS, NTD-GC–MS, GC–MS
Octanal	$C_8H_{16}O$	124–13-0	128.212	Breath/EBC	SPME-GC–MS, GC–MS, Paper-MS, SIFT-MS, TD-GCMS & SPME-GCMS, HPPI-MS, EBC device, SPME-GC
Ethanol	C_2H_6O	64–17-5	46.068	Breath/EBC	EBC, SPME-GC–MS, SIFT-MS, eNOSE-GC, GC–MS, SPME-GC–MS
Heptanal	$C_7H_{14}O$	111–71-7	114.186	Breath/EBC	SPME-GC–MS, IMS, Paper-MS, GC–MS, TD-GC–MS, HPPI-MS, EBC, SPME-GC
Hexane	C_6H_{14}	21666–38-6	86.175	Breath	TD-GC–MS, SPME-GC–MS, eNOSE-GC, GC-FID-MS, GC–MS, SIFT-MS
Pentanal	$C_5H_{10}O$	110–62-3	86.132	Breath/EBC	SPME-GC–MS, GC-FID-MS, GC–MS, Paper-MS, HPPI-MS, EBC device
2-Pentanone	$C_5H_{10}O$	107–87-9	86.132	Breath	GC–MS, SPME-GC–MS, FT-ICR-MS, TD-GC–MS
2-Hydroxy-2-butanone	$C_4H_8O_2$	513–86-0	88.105	Breath/EBC	EBC device, GC–MS, FT-ICR-MS, TD-GC–MS, SPME-GC–MS, SIFT-MS
Heptane	C_7H_{16}	142–82-5	100.202	Breath	eNOSE-GC, TD-GC–MS, GC–MS, SPME-GC–MS
Styrene	C_8H_8	100–42-5	104.149	Breath	SPME-GC–MS, NTD-GC–MS
Acetic acid	$C_2H_4O_2$	64–19-7	60.052	Breath/EBC	EBC device, SIFT-MS, PTR-MS, GC–MS, SPME-GC–MS, IMR-MS
Benzaldehyde	C_7H_6O	100–52-7	106.122	Breath	GC–MS, PTR-MS, Paper-MS, SPME-GC–MS, SIFT-MS
Propanal	C_3H_6O	123–38-6	58.079	Breath	GC–MS, TD-GC–MS, SPME-GC–MS, Paper-MS
Cyclohexane	C_6H_{12}	110–82-7	84.16	Breath	SPME-GC–MS, GC-FID-MS, GC–MS, SIFT-MS
Methanol	CH_4O	67–56-6	25.042	Breath/EBC	EBC, PTR-MS, GC–MS, SPME-GCxGC-FID, SPME-GC–MS, SIFT-MS
Propanaol	C_3H_8O	67–63-0	60.095	Breath	GC–MS, SPME-GC–MS, NTD-GC–MS, SIFT-MS
Acetaldehyde	C_2H_4O	75–07-0	44.053	Breath	SPME-GC–MS, SIFT-MS, TD-GC–MS, Paper-MS, IMR-MS, HPPI-MS
Acetonitrile	C_2H_3N	75–05-8	41.052	Breath	SPME-GC–MS, GC-FID-MS, GC–MS, SIFT-MS
Butane	C_4H_{10}	106–97-8	58.122	Breath	SPME-GC–MS, GC–MS, SIFT-MS
Decane	$C_{10}H_{22}$	124–18-5	142.282	Breath	TD-GC × GC–MS, GC–MS, SPME-GC–MS
o-Xylene*	C_8H_{10}	95–47-6	106.165	Breath	TD-GC–MS, SPME-GC–MS, GC–MS
1,2,3-Trimethylbenzene	C_9H_{12}	526–73-8	120.192	Breath	TD-GC–MS, SPME-GC–MS, GC–MS
Cyclohexanone	$C_6H_{10}O$	108–94-1	98.143	Breath/EBC	EBC, IMS, SPME-GC–MS, SIFT-MS, HPPI-MS
Octane	C_8H_{18}	111–65-9	114.229	Breath	eNOSE-GC, SPME-GC–MS, SIFT-MS
VEGF	NA	NA	NA	EBC	EBC device

*associated with smoking and environmental gas contaminates; EBC – exhaled breath condensate; EBC device– Device to collect exhaled breath condensate (e.g. Turbo-DECCS, EcoScreen, R-Tube condenser); GC–MS – Gas chromatography–mass spectrometry; PTR-MS - Proton transfer reaction-mass spectrometry; IMS - Ion mobility spectrometry–mass spectrometry; FT-ICR-MS - Fourier-transform ion cyclotron resonance-mass spectrometry; HPPI-MS - High-pressure photon ionization time-of-flight-mass spectrometry, SIFT-MS - Selected-ion flow-tube mass-spectrometry, eNOSE-GC – Electronic nose gas chromatography; TD-GC–MS - Thermal desorption–gas chromatography–mass spectrometry; NTD-GC–MS – Needle-trap device gas chromatography-mass spectrometry; SPME-GC–MS – Solid phase micro extraction gas chromatography-mass spectrometry; GC-FID-MS – Gas chromatography flame ionization detector-mass spectrometry; TD-GC × GC–MS – Thermal desorption gas chromatography-mass spectrometry; Paper-MS – Paper-mass spectrometry; IMR-MS - Ion molecule reaction-mass spectroscopy; SPME-GCxGC-FID - Solid phase micro extraction gas chromatography flame ionization detector-mass spectrometry.

Moreover, some aldehydes like nonanal have been considered biomarkers of apoptosis. It has been demonstrated that the levels of nonanal, 1,3-bis(1,1-dimethylethyl)-benzene, and 2,6-bis(1,1-dimethylethyl)-2,5-cyclohexadiene-1,4-dione significantly increase during apoptosis [64].

4.2.2. Inflammation

Processes like oxidative stress and apoptosis are associated with chronic inflammation. Inflammation as one hallmark of cancer is linked to lung cancer [65]. A set of cytokines is reported in different EBC studies and indicates that specific inflammatory markers can describe cancerous lung processes. IL-6 and TNF-alpha show increased levels in lung cancer patients, but are very unspecific by themselves (Fig. 3 and Supplementary Table 7).

4.2.3. Energy metabolism and cell proliferation

High proliferation is a characteristic of cancer cells. The reduction of available oxygen and hypoxia are likely a consequence of fast cell replication [66]. Therefore, another possible source of VOCs is the Warburg effect, which corresponds to increased anaerobic energy metabolism. The Warburg effect indicates an activated glycolysis over oxidative phosphorylation in lung cancer cells [67]. This reaction produces an excess of lactic acid that causes pH reduction and with that the breakage of the basement cell membranes [68]. This membrane breakage results in the release of membrane components like fatty acids. These fatty acids are further processed via lipid peroxidation and exhaled as aldehydes as shown in Fig. 3. Another indication of the Warburg effect is the occurrence of ketones in exhaled breath. Cancer cells shift their energy production from the Krebs cycle to glycolysis. This means that acetyl-CoA, the main product of mitochondrial beta-oxidation of long chain fatty acids, is used as a substrate for ketogenesis. Therefore, acetone and other ketone bodies (acetoacetate and beta-hydroxybutyrate) are produced by the hepatocytes from excess acetyl-CoA, which in turn results in increased levels of acetone in the body [69]. Production of ketones is also closely related to the increased oxidation rate of fatty acids which is observed in several cancers, implying that beta-oxidation of branched fatty acids results in the formation of heavier ketones like 3-heptanone [70]. In addition, the breath

of lung cancer patients contains more downstream products of glycolysis like acetate, acetaldehyde, and ethanol [71]. Multiple reports of the same VOCs, even nonspecific ethanol, across different studies increase the confidence that these volatiles are truly associated with lung cancer.

4.2.4. Genetic and epigenetic breath markers

EBC analysis provides insights into more complex molecular structures. This technology enables detection of genetic alterations such as microsatellite DNA alterations, and KRAS, EGFR, p16, and TP53 mutations. The determination of these oncogenic drivers is important to design an efficient lung cancer treatment strategy. Nowadays highly invasive diagnostic approaches like endobronchial needle aspiration or transthoracic fine-needle aspiration are implemented in clinical routine. Some specialized centers provide liquid biopsy, but EBC analysis has more advantages and is more patient orientated. Additionally, epigenetically potential biomarkers such as DNA methylation, histone modifications, and micro-RNA are detectable with EBC analysis (Supplementary Table 7).

4.2.5. Breath biomarker with unknown endogenous origin or environmental confounder

Overall, to translate VOCs in a context with endogenous physiological processes is difficult and needs caution. Some compounds may be confounders rather than actual biomarkers. For example, the detection of acetonitrile, toluene, and some benzene derivatives in exhaled breath may be mainly associated with smoking or arise from other environmental exposures such as gas pollutants or passive smoking [72]. Additionally, the origin of aromatic compounds like p-xylene, benzene, and 2,5-dimethylfuran is still unknown, and they have been considered possible environmental contaminants (e.g., cigarette smoke) in previous reports. Thus, one must be cautious before suggesting benzene derivatives solely as lung cancer markers [72].

4.3. Future directions and proposed core outcomes/framework

So far, only low-dose CT shows robust clinical effectiveness as a screening tool for lung cancer; it has been implemented in clinical practice in some countries [73,74]. Studies on liquid biopsies pursue the same goal as breath analysis: to simplify disease detection [75]. Circulating blood biomarkers are an interesting possibility for supplementing low-dose CT. However, this is still invasive, and analysis of specimens are more time-consuming than breath sampling. Breath analysis methods offer, in theory, more advantages for clinical routine disease detection and monitoring: better patient acceptance, rapid results, a nearly unlimited amount of sampling material, and cost effectiveness. Despite expensive acquisition cost for a mass spectrometer, amortization may be rapid if used for broad screening of high burden diseases like lung cancer. EBC or eNose equipment is rather inexpensive. The advantages of lung cancer breath analysis can position this approach before low-dose CT in future clinical workflows. For example, breath analysis combined with PLCOm2012 or USPSTF2013 [76] can pre-select individuals for low-dose CT screening. This would be cost effective, overcome other low-dose CT challenges [77], and avoid patient exposure to cumulative radiation. However, for integration into clinical workflows or guidelines there must first be a consent on relevant biomarker panels and breath technologies.

At this moment, the very broad spectrum of biomarkers and methods used across the literature prevents the conduct of meta-analyses and consent definition. Our work shows that across all included studies, 490 biomarkers were identified. The establishment of robust evidence, allowing translation of the research into clinical decision-making, would require (i) high diagnostic accuracy in case-control designs, (ii) large phase III diagnostics studies, and (iii) meta-analytic work. Furthermore, the breath analysis must be implemented in a clinical algorithm and tested within such processes. This is not yet possible due to heterogeneity in the study outcomes. Moving towards a more homogenous use of biomarkers in studies on lung cancer diagnosis using breath analysis, we propose to work on a core outcome set for the field. Core outcome sets define the most appropriate outcomes and measurements regarding a clinical research question [78]. Our work provides a basis towards this effort. Future meta-analysis studies should be designed according to a standardized framework and report their results in a comparable manner. To achieve this comparability, we propose a framework for lung cancer breath studies for clinical decision-making (Table 3).

Table 3
Lung cancer breath analysis study design framework for future research projects.

General
Patient population
-selection of subjects among the target population (patients with need for screening)
-stratification of histological tumor types
-inclusion of a clinically relevant control group in early case-control designs
Design
-longitudinal measurements
-case-control design (matching for confounding factors)
-reference standard diagnostic test as comparator
Core outcomes
-report diagnostic performance according to compounds in Table 2
-outcomes should include molecules from following functional groups (Guidance):
(a) panel of aldehydes*
(b) multiple hydrocarbons
(c) aromatic and cyclic compounds
(d) ketones; specifically, acetone
(e) alcohols such as ethanol or methanol (isopropanol and propanol are common in cancer subjects)
(f) other relevant functional groups
Standardization of breath sampling
Patient-related factors
-patient physiological conditions (e.g., smoking, activity, and fasting period)
-clinical confounding factors (patient characteristics, comorbidities, medication)
-route for breath collection (Mouth/Nose)
Environmental consideration
-location/laboratory baseline air measurement
-identification of potential contaminants (e.g., VOCs from analytical equipment, offline bags, filter, masks, …)
Breath sampling methodology
-definition of sampled breath fraction (alveolar/mixed exhaled breath)
-reliability of collection method (online, off-line)
-sampling characteristics (volume, flow rate, CO_2 threshold, MS-source setting)
-assessed storing stability of offline bags
-operator training
-standard measurements
-quality control-measures and appropriate calibration of analytical instruments
-reproducibility of VOC measurements among same analytical platforms and multicenter
Clinical- and performance evaluation of the diagnostic method
According to regulatory guidance [79–81]
Determination of the valid clinical association/scientific validity
-perform projects according to state-of-the-art technical standards
-use guidance of systematic scientific literature synthesis
Technical Performance/Analytical Performance
-availability, confidentiality, integrity, reliability, accuracy (resulting from trueness and precision), analytical sensitivity, limit of detection, limit of quantitation, analytical specificity, linearity, cut-off value(s), measuring interval (range), generalizability
Clinical Performance
-clinical/ diagnostic sensitivity, clinical/ diagnostic specificity, positive predictive value, negative predictive value, number needed to treat, number needed to harm, positive likelihood ratio, negative likelihood ratio, odds ratio, confidence interval (s), usability of the method.
Reporting of diagnostic accuracy
-according STARD statement [82]

* The excess ROS react with unsaturated lipids to form aldehyde metabolites via LPO. On considering the principal unsaturated fatty acids present in lung tissue and lung surfactant, it is reasonable to expect a panel of LPO-derived aldehydes consisting of saturated C3–C10 aldehydes, hydroxyaldehydes, and alpha,beta-unsaturated aldehydes.

4.4. Limitations

We applied an exhaustive search strategy, aiming to detect all publications on the topic. In addition, we extracted a comprehensive amount of information from the included studies. We consider these points strengths of our work. However, our work has inherent limitations. First, the search could have been extended to published study protocols or to trial registration platforms to screen for ongoing or upcoming studies as well. This would have enabled conclusions on possible shifts regarding outcomes in upcoming studies. However, the robustness from our findings does not suggest that there might be a paradigm shift without the interference of guidelines such as core outcome sets. Second, expanding the team of investigators could have led to a slightly larger number of included trials. The authors are fluent in multiple languages other than English. However, to include studies in other languages, all authors contributing to screening and data extraction would have to be fluent in the same languages, which was not the case.

5. Conclusion

This is the first scoping review describing the lung cancer breath research landscape, considering biomarker identification methods and potential biomarkers. Although translation of this diagnostic approach to the clinical setting is not yet possible, we propose a framework to guide future breath analysis studies and to create homogenous outcome sets.

Author contributions

FS designed the project and SDK designed the search string. FS did the database research. FS, DK, and SM screened the records and extracted the data. FS synthesized and charted the data. FS, DK, and SM wrote the manuscript. SDK, MK, and MAP contributed further to the writing and editing of the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MK is cofounder of Deep Breath Intelligence AG (Switzerland), which develops breath-based diagnostic tools. FS is consultants for Deep Breath Intelligence AG (Switzerland). All authors submitted the ICMJE disclosure form.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.12.003.

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