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To cite this article: Funmilayo S. Moninuola *et al* 2019 *J. Phys.: Conf. Ser.* **1378** 032010

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# A Mini Review of Trends towards Automated and Non-Invasive Techniques for Early Detection of Lung Cancer: From Radiomics through Proteogenomics to Breathomics

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## Abstract

Carcinoma of the Lung is one of the most common cancers in the world and the leading cause of tumor-related deaths. Less than 15% of patients survive 5 years post diagnosis due to its relatively poor prognosis. This has been ascribed to lack of effective diagnostic methods for early detection. Different medical imaging techniques such as chest radiography, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are used in routine clinical practice for tumor detection. These techniques are medically unsatisfactory and inconvenient for patients due to poor diagnostic accuracy. Endobronchial biopsies are the gold standard for diagnosis but have the inherent risk of full or partial invasive procedures. Thus, diagnostic technology that uses data mining algorithms with medical image analysis, generally known as radiomics emerged. Radiomics extracts complex information from conventional radiographic images and quantitatively correlates image features with diagnostic and therapeutic outcomes. In spite of the benefits, radiomics is prone to high false positives and there is no established standard for acquisition of parameters. Further efforts towards outcome improvement led to the proteomic and genomic (proteogenomic) approach to lung cancer detection. Although proteogenomic has a diagnostic edge over traditional techniques, variations in bio-specimen and heterogeneity of lung cancer still possess a major challenge. Recent findings have established that changes normally occur in the gene or protein due to tumor growth in the lungs and this often leads to peroxidation of cell membrane that releases Volatile Organic Compounds (VOCs) through the breath of Lung Cancer patients. The comprehensive analysis of breath VOCs, which is tagged Breathomics in the literature, unveils opportunities for noninvasive biomarker discovery towards early detection. Breathomics has therefore become the current pace-setter in medical diagnostics research because of its non-invasiveness and cost effectiveness. This paper presents a mini survey of trends in early lung cancer detection from radiomics, through proteogenomic to breathomics.

**Keywords:** Breathomics, CT, Early Detection, Lung Cancer, MRI, Proteogenomic, Radiomics.



## 1. Introduction

Lung Cancer (LC), also known as lung carcinoma or bronchogenic carcinoma, is a virulent lung sarcoma formed by unrestrained cell growth in the tissues of the lung. LC is the most common cause of cancer deaths worldwide and the sixth principal cause of death among all cancer types in Africa [1-3]. Therapeutic regimens were once independent of subtype but became a concern as the understanding of phenotypic differences in tumors improved over the years [4, 5]. The current 5-year survival rate for lung cancer is 15%. Furthermore, only 16% of lung cancer cases are discovered when localized while 22% and 57% are diagnosed at regional and distant stages respectively. Despite the knowledge that early detection of lung cancer would have a significant impact on survival rates, there has not been an effective screening test that yields results as obtainable for other cancer types such as breast and colorectal [6, 7]. The gold standard for the diagnosis of LC is tissue analysis acquired via some form of biopsy, typically endobronchial. This method is invasive and cannot be used in the general population.

Studies show that traditional methods for initial LC detection includes the use of medical imaging approach such as Positron Emission Tomography (PET), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Low-Dose CT (LDCT), and Chest Radiograph (CRG) scans. Most of all these methods are time consuming, expensive, potentially hazardous (in terms of radiation exposure) and are less sensitive in detecting cancerous cells at the early stage in addition to their invasiveness [1, 8-10]. Recent advances in medical image processing has led to the development of non-invasive diagnosis that leverages on these imaging techniques. For instance, *radiomic approach* involves extracting radiographic image data of the lung into mineable features with high resolution, using a large amount of robotically extracted data-characterization algorithms. Nevertheless, one of the problems with radiomics is that the radiographic images do not show the complexity of tumor morphology that affects the region of interest [11]. Several investigators have shown that gene expression of normal lung tissues can be distinguished from the cancerous ones by simultaneous profiling of the protein and gene expression of LC tumor, typically referred to the *proteogenomic approach*. The main challenge of this method is the limited training data samples of proteins and genes as they are gathered from fewer subjects while the protein and gene expressions in each sample is usually unlimited [10]. A screening procedure that can discover lung cancer at onset before it spreads is advantageous in reducing lung cancer morbidity and mortality and consequently heightens the chances of successful treatment. It has been established in the literature that human exhaled breath contains over 3,000 Volatile Organic (VOC) such as chain, alicyclic and aromatic hydrocarbons. These VOCs are likely biomarkers of several pulmonary diseases, including LC. The analysis of exhaled breath to infer the health status of a human subject is referred to as *breathomics*. Its major strengths over other approaches for early detection and screening of pulmonary diseases is that it is inexpensive and non-invasive [12]. Thus, a non-invasive breath test has immense potential as a lung cancer examination method.

## **2.0 Evolution of Existing Approaches for Early Detection of Lung Cancer**

The quest for early detection of lung cancer, has led to different novel modalities with progressive improvement in the level of sensitivity, specificity and reduction in the rate of false negatives and false positives. Each of the existing approaches have specific benefits and potential drawbacks. There is therefore a need to understand their various roles in LC screening as reported in the literature.

### **2.1 Radiomics**

The conventional screening and detection methods for lung cancer include; CRG, CT, LDCT, MRI and PET. These procedures are aimed at detecting nodules in subjects that are highly prone to lung cancer. Although they are well known methods with a large pool of experienced users, they are beset with demerits [13, 14]. Physicians and Radiologists find it difficult to identify cancerous nodules when analyzing ordinary radiographic image because the cross section is complex. This demands additional work by the radiologists in detecting the lung cancer and therefore there is a high probability of error. Radiomics is the development of processes and techniques for high-resolution extraction of quantitative features that convert images from the conventional imaging methods into datasets, which could be mined for clinical decision supports [15]. Computer Aided Diagnosis (CAD) method was developed to assist physicians and radiologists to precisely examine the radiographic scans in order to increase the accuracy of neoplasm nodule detection. Several studies [16], [17] showed that using radiomics has substantially improved the performance of automated analysis of radiological images. Thus, radiologists use the computer output to double check before making final decisions because the system is considered useful for detection of potential nodules [11]. Segmentation, feature extraction, classification and nodule detection are the main stages employed in radiomics. Original radiographic images of subjects are obtained from database of LC screening radiographic images with marked-up annotated lesions such as Lung Image Database Consortium (LIDC) [18, 19]. The performance of the procedure is not easy to determine due to variation in image utilized. Also, a lack of integration between the radiologist and CAD systems can restrain the rate of progress. In fact, most of the proposed models reported in the literature could not classify the cancer as benign or malignant. Also, lack of prior information about the region of interest for preprocessing sometimes lead to incorrect decision or errors of omission.

### **2.2 Proteomics and Genomics**

Proteomics is a detail investigation of all set of proteins found in tissue, gene, or cell. This technology profiles how disease changes the structure of protein. Protein structure changes from a healthy to cancerous cell when there is a modification or alteration in protein complement which may affect the structure and function of the cell.

Genomics and Proteomics are used for synchronized investigation of the genes and proteins

respectively, that are expressed in a specified gene, cell or tissue type and also identify new molecular targets. The simultaneous profiling of molecular expression of the gene and proteins tumor uses microarray technology. Lung cancer-associated proteins are generated by lung cancer tissues. In turn, the immune system tends to produce high-affinity auto-antibodies to these proteins. Blood biomarkers contain unique proteins and auto-antibodies to tumor-associated antigens that might be detectable 1–3 years preceding clinical diagnosis [20, 21]. Previous Studies used an algorithmic solution for binary classifications of LC biomarkers. According to Broodman [22], some widely-known and clinically utilized lung cancer protein biomarkers are carcinoembryonic antigen (CEA), CYFRA 21-1 (cytokeratine 19 fragment), Neuron-Specific Enolase (NSE), Progastrin Releasing Peptide (ProGRP), and Squamous Cell Carcinoma Antigen (SCCA). Antigen-125 (CA-125), Human Epididymis protein 4 (HE4) and surfactant form of protein B (Pro-SFTPB) are other lung cancer protein biomarkers [23, 24]. A study by Adetiba et al. [25], showed that lung cancer can be predicted using neural network ensembles with histogram of oriented gradient genomic features.

Furthermore, the acclaimed Protein Pathway Array (PPA) analysis method that allows the identification of important, but low abundance proteins and phosphoproteins in Lung Cancer has been developed [26, 27] [28, 29]. Poor sensitivity to low marker concentration is one of the downsides of this approach. The process also consumes a lot of time and money. Moreover, the available data to test the performance of these biomarkers for subsequent lung cancer cases and control discrimination is not sufficiently available [30].

### 2.3 Breathomics

Breath analysis is a state-of-the-art method for early disease detection that is also known as Breathomics. According to Smolinska *et al.* [31], the purpose of Breathomics studies is to discover patterns in Volatile Organic Compound (VOC) that underlie abnormal metabolic processes in humans.

Breath research started about fifty decades ago when Pauling used gas chromatography procedure to prove that human breath is made up of about two hundred and fifty gases [32]. The application of machine intelligence techniques (such as machine learning) to analyze the “fingerprint” (breathprint or breath signature) of VOC patterns in Breathomics is still at its infancy [31].

Anatomization of breath can be employed in medical examination and ecological assessment because it is non-invasive.

A lot of molecules are released into the atmosphere during respiration. Breath is composed a combination of inorganic gas, inert gas and small fraction of VOCs concentration in the range of parts per million (ppm) to parts per trillion (ppt) by volume. VOCs are generated through endogenous or exogenous processes and its constitution quantitatively and qualitatively are not the same in individuals.

O'Neill et. al. [33] reported that the exhaled breath of lung cancer patients contains twenty-eight biomarkers such as: lipid-peroxidation, hexane, aniline methlpentane and o-toluidine cancer [33-35].

A systematic analysis of VOCs by Phillips et. al. [36] also affirm the difference in the breath of lung cancer and healthy subjects by suggesting alkanes and benzene derivatives among twenty-two VOCs for early detection of lung cancer..

Not fewer than three thousand VOCs are found in healthy humans' breath till date, only Isoprene, Ethane, Pentane, Acetone and few are common to everyone. VOCs occurs as a result of metabolic processes and are instructive in medical prognosis [36-40].

Since lung cancer cells have unique metabolic properties, metabolic activity within the body mirrors the composition of VOCs in the exhaled breath. These metabolic by-products circulate within the blood and transfer to the lungs where they are exhaled from the body. This implies that variations in the body's metabolic procedures result in unique VOC prints or signatures. Thus, authors have suggested that disease-specific metabolism can be detected as breath signatures (breathprint) signifying the presence of lung cancer from the analysis of exhaled breath of lung cancer patients [35, 41, 42]. The exhaled breath can be examined based on two unique albeit interrelated methods: Chemical Analysis of VOCs (VOC identification) and Electronic Nose based VOC Analysis (VOC patterning). Although the chemical analysis methods are capable of early detection of lung cancer, they are not portable, they have no ease of use and cannot be used at the Point-of-Care (POC) in the clinic or homes [43, 44]. Thus, this mini review addresses the Electronic Nose based VOC Analysis as a breathomics approach.

### 2.3.1 Electronic Nose

The Electronic Nose (E-nose) approach to VOC analysis overcomes the limitations of the chemical analysis approach through qualitative and pattern-based "breathprint" systems. The contrast of the human olfactory system and E-nose is presented diagrammatically in Fig.1. As shown in the upper part of the figure, E-Nose is made up of a sensing sub-system, which is the hardware and the automated pattern recognition sub-system. The sensing system is made up of an array of sensors where each sensor detects a specific biomarker based on the chemical properties and then converts it to an electrical signal to form a signature or pattern. The signature of each biomarker is then used to build a database of labeled signatures that is used to train a pattern recognition system to form an intelligent system. The E-nose is subsequently applied to classify unknown samples to differentiate the VOC biomarkers. Principal Component Analysis (PCA) is mostly used for feature projection while the pattern recognition units currently in use are supervised pattern classification algorithms such as k-Nearest Neighbors (k-NN), Support Vector Machine (SVM) and Artificial Neural Network (ANN) [45]. E-nose as a breathomics method has huge potentials to support PoC-based early diagnosis of lung cancer. This method is inexpensive, non-invasive, has a speedy response time and has a generally portable system.

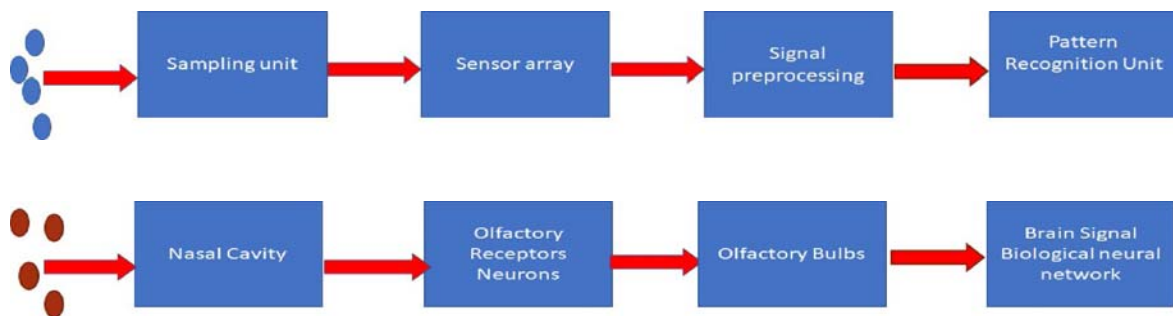


Figure 1: E-nose versus Human Nose Block Diagrams

### 3.0 Result and Discussion

Tables 1, 2 and 3 presents the literature matrices of selected existing studies that are based on radiomics, proteogenomics and breathomics respectively. In table 1, a literature matrix of some radiomics research work is shown where different database and methodologies were used for lung nodules detection and classification. Due to the sensitivity of this approach to image analysis, there is a need for standardization of the machine learning techniques involved in radiomics analysis of lung nodules images. Table 2 highlights matrix of some proteogenomics research work where different biomarkers, tumor types and groups of patients were investigated for early detection of LC. Like radiomics, there is no resolution on the type of biomarkers or composition of the biomarkers and the technology that should be focused on for early detection of LC.

Table 1: Literature Matrix of Some Radiomics Approaches

S/N	Database	Segmentation Method	Classifier	Sensitivity (%)	Reference
1	LIDC	Watershed segmentation	SVM	92	[46]
2	LIDC/IDRI	Watershed	SVM, Naïve Bayes and FLD	94.4	[19]
3	LIDC/IDRI	Clustering	Multiview Convolutional Network	90.1	[47]
4	LIDC, ELCAP	Discrete wavelet transforms	SVM	90.9	[48]
5	LIDC/IDRI	Rule based	SVM	93.6	[18]
6	LIDC/IDRI	Structural	LDA, gradient boosting (GB 10)	82	[49]
7	Private	Selective filter based (vessel)	Rule based classification (RBC)	90	[50]
8	Private	Cylindrical filter and thresholding based	Support Vector Machine	90	[51]

9	LIDC	3D block based on Entropy Analysis	Support Vector Machine	95.28	[52]
10	JSRT	clustering watershed segmentation	Support Vector Machine	85	[53]
11	LIDC, ANODE09	Stochastic, binarization and active contour model	Support Vector Machine	89	[54]
12	ELCAP	Frequency domain analysis	Support Vector Machine	96.15	[16]

Image Database Resource Initiative (IDRI), Early Lung Cancer Action Program (ELCAP) Japanese Society of Radiological Technology (JSRT), Automatic Nodule Detection 2009 (ANODE09)

Table 2: Literature Matrix of Some Proteogenomics Approaches

S/N	Biomarker	Tumor Type	Sensitivity %	Reference
1	DNA methylation	54 NSCLC	85.2	[55]
2	DNA methylation	adjacent normal tissues 138 formalin-fixed - 116 LC and 22 controls	100	[56]
3	miRNA biomarkers	Exosomes from BAL 4 Tissue samples 13 AC vs. 15 controls	NA	[57]
4	Proteomic	-BAL -139 lung cancer and 49 controls -43 SCLC and 96 NSCLC	95	[58]
5	Proteomic	- Tissue – 13 NSCLC 6 AC and. 7 SCC	NA	[59]
6	Proteomic	- BAL - 90 suspected lung cancer prospectives followed for two years - Tissue	NA	[60]
7	Liquid biopsy	-108 patients with malignant nodules and -113 patients with benign lung nodules	75	[61]
8	DNA methylation	Plasma and sputum -150 NSCLC - 60 Control	Sputum - 98 Plasma - 93	[62]
9	Proteomic	- Tissue - 14 AC vs. adjacent normal tissue	NA	[63]



<b>10</b>	miRNA	- Sputum - 30 NSCLC patients vs. 30 controls - SCC vs. AC	90	[64]
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Deoxyribonucleic acid (DNA), microribonucleic acid (miRNA) , bronchoalveolar lavage (BAL), Not Available (NA) , Non-Small Cell Lung Cancer (NSCLC), Adenocarcinoma (AC), Squamous Cell Carcinoma (SCC)

Table 3: Literature Matrix of Some Breathomics (E-nose) Approach

S/ N	Sensor Type	Classifier	Accuracy (%)	Referenc e
<b>1</b>	MOS	Multilayer Perceptron (MPL)	75	[65]
<b>2</b>	MOS	ANN	83	[43]
<b>3</b>	MOS	PCA-KNN	8.4	[66]
<b>4</b>	Cyranose 320 sensor	SVM	87.3	[67]
<b>5</b>	Silicon nanowire Field Effect Transistor (SiNW FET)	ANN	84	[68]
<b>6</b>	QMB	PLS-DA	93	[69]
<b>7</b>	Colorimetric sensor array	Logistic prediction model	81	[70]
<b>8</b>	Metalloporphyrin s-coated QCM sensors	PLS-DA	75	[71]
<b>9</b>	Organically functionalized Au nanoparticle	PCA	86	[72]

MOS - Metal Oxide Sensor, QMB-quartz microbalance

It is apparent from the mini review at hand that analyzing breathprints of a lung cancer patient (breathomics) at an early stage offers several potential advantages over the radiomics and proteogenomics approaches [25, 57, 58, 73-76], which include:

- i. Exhaled-breath analysis is highly informative and a totally non-invasive alternative to current proteogenomics and culture-based methods.
- ii. In contrast to other specimen, breath can easily be collected, as many times as required.
- iii. The measurement of gas-phase analytes is simpler in a gas matrix (breath) than in more complex biological matrices.
- iv. It is easy to obtain and painless to the individual with no undesirable side effects.
- v. Breath analysis has great potential for direct and real-time diagnosis and monitoring.

#### 4.0 Conclusion

E-nose-based breathomics approach is a very promising method for early disease detection. In addition to the afore mentioned advantages, it is noteworthy that even though the sensitivity/accuracy of this breathomics approach is generally a bit less than the two previous approaches, it yields comparable results even at its infancy stage. This suggests its potential with more research in the coming years.

#### Acknowledgement

The publication of this research paper is fully sponsored by Covenant University Centre for Research, Innovation and Development (CUCRID), Covenant University, Ota, Nigeria.

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