Review Article

Biomarkers in lung cancer screening: a narrative review

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Abstract: Although when used as a lung cancer screening tool low-dose computed tomography (LDCT) has demonstrated a significant reduction in lung cancer related mortality, it is not without pitfalls. The associated high false positive rate, inability to distinguish between benign and malignant nodules, cumulative radiation exposure, and resulting patient anxiety have all demonstrated the need for adjunctive testing in lung cancer screening. Current research focuses on developing liquid biomarkers to complement imaging as non-invasive lung cancer diagnostics. Biomarkers can be useful for both the early detection and diagnosis of disease, thereby decreasing the number of unnecessary radiologic tests performed. Biomarkers can stratify cancer risk to further enrich the screening population and augment existing risk prediction. Finally, biomarkers can be used to distinguish benign from malignant nodules in lung cancer screening. While many biomarkers require further validation studies, several, including autoantibodies and blood protein profiling, are available for clinical use. This paper describes the need for biomarkers as a lung cancer screening tool, both in terms of diagnosis and risk assessment. Additionally, this paper will discuss the goals of biomarker use, describe properties of a good biomarker, and review several of the most promising biomarkers currently being studied including autoantibodies, complement fragments, microRNA, blood proteins, circulating tumor DNA (ctDNA), and DNA methylation. Finally, we will describe future directions in the field of biomarker development.

Keywords: Biomarkers; lung cancer; screening; diagnosis; early detection

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Background

Lung cancer remains the leading cause of cancer-related death in the world. In 2018, there were 2.09 million new cases of lung cancer globally accounting for 11.6% of total cancer cases and 1.76 million deaths from lung cancer globally accounting for 18.4% of total cancer deaths (1). In the United States, there have been long-term declines in lung cancer death rates between 2008 and 2017, largely due to declines in smoking as well as improvements in early detection and treatment. However, lung cancer continued to cause more deaths in 2017 than breast, prostate, colorectal, and brain cancers combined. This low survival is reflective of the large proportion of patients diagnosed with metastatic disease (57%) as opposed to localized disease (15%) (2-4). As a consequence of asymptomatic cancer growth, most lung cancers go undiagnosed until reaching an advanced stage. Localized disease is potentially curable with resection. Therefore, a significant difference between 5-year survival of stage 1 disease (59.5%) and metastatic disease (5.2%) exists (5). Therein lies the importance of lung cancer screening with its proven stage shift, earlier

diagnosis, and curability through resection in high risk individuals (3,6).

The National Lung Screening Trial (NLST), a large multicenter randomized control trial published in 2011, evaluated low-dose computed tomography (LDCT) as a lung cancer screening tool. The study compared annual LDCT versus annual chest radiography for three years in patients aged 55 to 74 who were either current or former smokers with a ≥30 pack-year history. The NLST demonstrated LDCT was associated with a 20% reduction in lung cancer related mortality. Additionally, the absolute risk of mortality from lung cancer dropped from 1.66% to 1.33%. This corresponded with a number needed to screen of 320 (3,7).

While screening with LDCT scans has demonstrated a reduction in lung cancer related mortality, it is not without problems. The LDCT arm of the NLST identified nodules in 24.2% of patients, however only 1.1% of these patients had lung cancer (3). Across three rounds of the study, 96.4% of the positive results in the LDCT group were false positive results (7). With the increase in detection of benign pulmonary nodules there follows an increase in unnecessary, costly, and invasive procedures. According to the National Health Interview Survey (NHIS) conducted in 2015, only 3.9% of eligible smokers reported LDCT screening in the past 12 months (8). This low utilization of lung cancer screening among eligible patients may be due to fears of overdiagnosis, patient and physician anxiety regarding indeterminate pulmonary nodules, and subsequent invasive testing for benign nodules and cumulative radiation exposure.

Current research is geared towards biomarkers as non-invasive diagnostic tools in lung cancer evaluation. In order to conduct optimal lung cancer screening, it is important to target those individuals at highest risk of disease. Liquid biomarkers can serve multiple roles in lung cancer screening. First, biomarkers can be useful for both the early detection and diagnosis of disease, thereby decreasing the number of unnecessary radiologic tests performed. Second, biomarkers can stratify cancer risk to further enrich the screening population and augment existing risk prediction. At-risk individuals would represent an enriched population or an alternative population for computed tomography (CT) screening, as biomarkers have the ability to reveal those at highest risk of developing lung cancer. Finally, biomarkers can be used to distinguish benign from malignant nodules in lung cancer screening, thereby stratifying individuals with indeterminate pulmonary nodules into high and low risk groups (9,10). Kammer *et al.* recently validated a lung cancer risk prediction model combining a blood-based biomarker (CYFRA 21-1), imaging biomarker (radiomic signature), and clinical factors (Mayo Clinic Model) (11). While risk prediction models such as the Mayo Clinic Model are commonly used in clinical practice, this work demonstrated an improvement in the diagnostic accuracy of indeterminate pulmonary nodules with a combined clinical risk factor and biomarker approach. An improvement in diagnostic accuracy could bring a reduction in invasive diagnostic procedures as well as a reduction in time to diagnosis for cancer (11).

What makes a good biomarker?

In this review, we will focus on several of the most promising biomarkers in the literature. However, before we can begin this discussion, we must first describe what makes a good biomarker. The purpose of a biomarker is to aid in the early diagnosis of disease, as well as risk prediction. Therefore, a good biomarker should positively influence clinical decision-making while minimizing harm and expense. Ideally, a clinically useful biomarker ultimately leads to decreases in the number of lung cancer-related deaths (12). A strong biomarker should be easily measurable, accurate, reproducible, and inexpensive (13). Furthermore, a clinically suitable biomarker should be developed using a population it would serve. A valuable diagnostic test must be able to classify a patient as either having a disease (sensitivity) or not having a disease (specificity). Additionally, positive and negative predictive values are of equal importance; it is necessary to be able to discern those patients with a positive test who actually have the disease and those with a negative test who truly are disease-free (14). For example, when using a biomarker for risk prediction of a disease with low prevalence, a strong negative predictive value (NPV) would be particularly valuable (13).

There are several different clinical sources of biomarkers, including blood, airway epithelium, sputum, exhaled breath condensate, and urine (15). *Table 1* summarizes a current selection of blood-based biomarkers in lung cancer screening including targets, clinical purpose, and critical diagnostic measures such as sensitivity, specificity, positive predictive value (PPV), and NPV. In this review, we will discuss the different types of existing biomarkers. We will focus on the most promising in the literature based upon the general criteria set out by Mazzone and colleagues (33).

Table 1 Selected blood-based biomarkers

Reference	Specimen	Biomarker category	Target	Clinical purpose	Development phase	Training set (cases/controls)	Validation set (cases/controls)	Sensitivity (%; 95% CI)	Specificity (%; 95% CI)	PPV (%)	NPV (%)	Reported result
Boyle (16)	Serum	Autoantibodies	6 AAB: p53, NY-ESO-1, CAGE, GBU4-5, Annexin 1, and SOX2	Diagnosis	Clinical validation	241/–	255/–	37[d]	90[d]	8[k]	99[k]	Any one or more AAB signal elevated using accepted cut-off
Chapman (17)	Serum	Autoantibodies	7 AAB: p53, NY-ESO-1, CAGE, GBU4-5, SOX2, HuD, MAGE A4	Diagnosis	Clinical validation	235/266 (optimization set)	836/– (clinical population set)	47[a]	90[a]	10[l]	99[l]	Any one or more AAB signal elevated using accepted cut-off
Jett (18)	Serum	Autoantibodies	7 AAB: p53, NY-ESO-1, CAGE, GBU4-5, SOX2, HuD, MAGE A4; 6 AAB: p53, NY-ESO-1, CAGE, GBU4-5, Annexin I, SOX-2	Diagnosis	Clinical validation	NA	1,613[b] (6AAB =752) (7AAB =861)	37 [21–55][c]	91 [89–93][c]	16	97	Any one or more AAB signal elevated using accepted cut-off
Wang (19)	Plasma	Autoantibodies	5 AABs: TTC14, BRAF, KLF8, TLK1, KRT8	Diagnosis of IPN[s]	Clinical validation	40/40	97/170	30	88	NA[m]	NA[m]	Any one or more AAB signal elevated using accepted cut-off
Ajona (20)	Plasma	C4d	C4d levels	Diagnosis of IPN[s]	Analytical validation	59/79	148/92	44[d]	89[d]	54	84	Unable to assess
Sozzi (21)	Plasma	miRNA	24 miRNA signature classifier	Diagnosis and prediction	Clinical validation	NA	69/870	87	81	27	99	Risk score
Montani (22)	Serum	miRNA	13 signature miR-Test: miR-92a-3p, miR-30b-5p, miR-191-5p, miR-484, miR-328-3p, miR-30c-5p, miR-374a-5p, let-7d-5p, miR-331-3p, miR-29a-3p, miR-148a-3p, miR-223-3p, miR-140-5p	Target "high-risk" population	Clinical validation	12/12	36/1,055	78 [64–91][d]	75 [72–78][d]	10[d]	99[d]	Risk score
Doseeva (23)	Serum	Proteins and autoantibody	3 proteins and 1 AAB: CEA, CA-125, CYFRA 21-1, NY-ESO-1	Diagnosis	Clinical validation	115/115	75/75	77[d]	80[d]	7[n]	99[n]	Multiple of median
Mazzone (24)	Serum	Proteins and autoantibody	4 proteins and 1 AAB: CEA, CA-125, CYFRA 21-1, HGF, NY-ESO-1	Diagnosis	Clinical validation	268/336	155/245	49[d]	96[d]	5[o]	96[o]	Multiple of median
Silvestri (25)	Plasma	Proteins	2 proteins: LG3BP and C163A	Diagnosis of IPN[s]	Clinical validation	NA	29/149	97 [82–100]	44 [36–52]	25	98	Integrated classifier
Molina (26)	Serum	Proteins	6 proteins: CEA, CA 15.3, SCC, CYFRA 21-1, NSE, ProGRP	Diagnosis	Clinical validation	NA	1,828/1,316	89	82	87	84	Combined panel assessment
Vachani (27)	Plasma	Proteins	5 proteins: ALDOA, COIA1, FRIL, LG3BP, and TSP1	Diagnosis of IPN[s]	Clinical validation	NA	78/63	92	20	26[p]	90[p]	Multivariate classifier
Trivedi (28)	Plasma	Proteins	3 proteins: EGFR, ProSB, TIMP1	Diagnosis of IPN[s]	Clinical validation	–[r]	49/48	94	33	32[q]	94[q]	Risk score
Cohen (29)	Plasma	Proteins and ctDNA	8 proteins and ctDNA: CA-125, CEA, CA 19-9, PRL, HGF, OPN, MPO, TIMP-1	Diagnosis	Analytical validation	NA[f]	1,005/812	59[e]	99	NA[m]	NA[m]	Gene mutation or protein elevation
Hulbert (30)	Plasma and sputum	DNA methylation	SOX17, TAC1, HOXA7, CDO1, HOXA9, ZFP42 methylation	Diagnosis	Analytical validation	99/41	51/19	98[g]; 93[h]	71[g]; 62[h]	93[g]; 86[h]	89[g]; 78[h]	Methylation panel
Weiss (31)	Plasma	DNA methylation	SHOX2 and PTGER4 methylation	Diagnosis and diagnosis of IPN[s]	Clinical validation	118/212	50/122	67[i]	73[j]	NA[m]	NA[m]	Methylation panel
Ooki (32)	Lung tissue, serum, pleural effusion, and ascites	DNA methylation	CDO1, HOXA9, AJAP1, PTGDR, UNCX, and MARCH11 methylation	Diagnosis and prognosis	Clinical validation	90/–	83/42	72[d]	71[d]	82[d]	51[d]	Methylation panel

[a], derived from clinical population set; [b], total audit population; [c], based on 7 AAB panel; [d], derived from validation set; [e], derived from 104 patients with lung cancer; [f], not specified; [g], using three best performing markers (SOX17, TAC1, HOXA7) for sputum; [h], using three best performing markers (SOX17, TAC1, CDO1) for plasma; [i], at a fixed specificity of 90%; [j], at a fixed sensitivity of 90%; [k], derived from at-risk population of 20 LCs per 1,000 population; [l], derived from LC prevalence of 2.4%; [m], unable to calculate; [n], derived from LC prevalence of 2% using multiple of median model; [o], derived from LC incidence of 0.4%; [p], derived from a LC prevalence estimate of 23% for 8–30 mm IPNs, [q], derived from predicted LC prevalence of 25%; [r], training set: 121; [r], testing set: 59; [s], indeterminate pulmonary nodule.

Methods

We searched PubMed for relevant articles pertaining to biomarkers and lung cancer. Specifically, we searched the database for articles including autoantibodies, complement fragments, microRNA, blood proteins, circulating tumor DNA, or DNA methylation and lung cancer detection, diagnosis, and screening. This search was last updated in October 2020, and supplemented with outside searches of the literature based on collaborators' research experience in this field.

Autoantibodies

The immune system is made up of the innate and adaptive immune responses. The adaptive immune system consists of both T and B cell responses. In cancer, tumor-associated antigens (TAAs) elicit a T cell response, thereby directly or indirectly killing tumor cells. These TAAs can elicit a B cell response as well, generating the production of autoantibodies (34). These autoantibodies develop in some lung cancer patients, making them useful as potential blood biomarkers for the early detection and diagnosis of cancer as well as distinguishing benign from malignant nodules. For example, if an individual with a CT-identified indeterminate pulmonary nodule tested positive for cancer related serum autoantibodies, the probability of the nodule being malignant would be higher. Additionally, given the high false positive rates associated with CT imaging as a screening tool, autoantibodies have the ability to improve the PPV of screening in those at highest risk of lung cancer (34). One of the challenges in detecting useful cancer screening biomarkers is their relative low quantity in the preclinical stage, as many of the markers are secreted by cancer cells. Autoantibodies would serve as a good biomarker, as the measurement process could utilize targeted amplification of signals from tumor cell proteins (19). Currently, there are multiple autoantibodies being studied as potential lung cancer screening biomarkers. EarlyCDT Lung is commercially available as a blood test designed to identify patients at increased risk for lung cancer in order to better facilitate CT screening (35). EarlyCDT Lung test measures seven autoantibodies: p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4, and SOX2. This seven-autoantibody panel was developed after a six-autoantibody panel was modified in 2010 (36). A study conducted by Chapman *et al.* demonstrated improved sensitivity and specificity of the seven-autoantibody panel (41% and 91%, respectively) (17). Massion *et al.* conducted a registry study in patients with at least one lung nodule and discovered that a positive autoantibody test resulted in a greater than two-fold increase in the relative risk for developing lung cancer (37). A follow-up audit of the EarlyCDT Lung seven autoantibody test performed in routine clinical practice was conducted by Jett *et al.* in 2014. This audit revealed a sensitivity and specificity of 37% and 91%, respectively, as well as a PPV of 16% (18).

Additionally, work has been done to utilize autoantibodies in the detection of benign pulmonary nodules from malignant nodules. Wang *et al.* conducted a study identifying autoantibodies in patients with lung cancer, benign pulmonary nodules, and smoker controls. Comparing autoantibody responses between individuals with lung cancer and those with CT-positive pulmonary nodules demonstrated a five-autoantibody panel (TTC14, BRAF, KLF8, TLK1, and KRT8) with a sensitivity of 30% at 88% specificity (19). In summary, autoantibodies serve as a promising blood-based biomarker for both the early detection and diagnosis of lung cancer; however, their utility in identifying high-risk populations for screening was limited and may only relate to occult malignancy.

Complement fragments

In addition to the autoantibody response of the adaptive immune system against tumor antigen, lung cancer has the ability to activate the complement cascade of the innate immune system as well (38). A study by Ajona *et al.* determined lung tumors activate the classical complement cascade, generating C4d, a degradation product of the classic complement pathway. As a result, these downstream complement fragments are increased in lung cancer patients. The group showed a higher concentration of C4d in bronchoalveolar lavage fluid from patients with lung cancer compared to individuals without lung cancer [area under ROC curve of 0.726 (95% CI, 61–84.3%; P=0.002)]. Additionally, C4d levels were measured in stage I or II lung cancer patients and control individuals. Plasma samples from individuals with lung cancer revealed higher levels of C4d than those without lung cancer (area under ROC curve of 0.782, P<0.001). Furthermore, patients with stage I lung cancer had lower C4d plasma levels than those patients with stage II, and patients with higher levels of C4d had a statistically significant shorter overall survival (38). However, when C4d was tested as a biomarker in a set of plasma samples from the Multicenter Italian

Lung Detection (MILD) trial, it could not differentiate asymptomatic high-risk individuals with or without early stage lung cancer (20).

As a clinical biomarker C4d shows greater promise in managing indeterminate pulmonary nodules. Ajona *et al.* discovered higher levels of C4d in patients with lung cancer nodules than those with benign nodules with a sensitivity and specificity of 44% and 89%. In this same study, C4d plasma levels were used to identify benign versus malignant lung nodules with a PPV of 54% and a negative predicative value of 84% (25).

microRNA

microRNA are small non-coding single-stranded RNA molecules that regulate post-transcriptional gene expression, reflecting tumor-host interactions. Alterations in their expression and frequent deregulations have been linked to the pathogenesis of most human cancers. In fact, shifts in microRNA expression are considered to be characteristic of malignant transformation (39). Additionally, microRNAs are an excellent set of biomarker candidates as they are markedly stable and resistant to degradation. Therefore, they have the ability to travel in bodily fluids for extended lengths of time (21,36,39-41). Montani *et al.* conducted a validation study using high-risk individuals enrolled in the Continuing Observation of Smoking Subjects (COSMOS) lung cancer screening program, which identified a serum microRNA signature to target an optimal population for LDCT. This 13-microRNA signature, known as the miR-Test, includes miR-92a-3p, miR-30b-5p, miR-191-5p, miR-484, miR-328-3p, miR-30c-5p, miR-374a-5p, let-7d-5p, miR-331-3p, miR-29a-3p, miR-148a-3p, miR-223-3p, and miR-140-5p. The study demonstrated a sensitivity and specificity of the miR-Test to be 77.8% (95% CI, 64.2–91.4%) and 74.8% (95% CI, 72.1–77.5%) respectively (22). Sozzi *et al.* studied the clinical utility of yet another plasma-based microRNA signature classifier (MSC) in a blinded validation study. The MSC categorizes patients into low, intermediate, or high risk of lung cancer based on 24 prespecified microRNA expression ratios. Plasma samples collected from smokers within the MILD trial were analyzed for MSC. The study revealed 87% sensitivity and 81% specificity regarding the diagnostic performance of MSC for lung cancer (21). In addition, both the miRNA signature classifier (MSC) and the miR-Test studies demonstrated a reduction in the LDCT false positive rate. These blood-based biomarkers are currently undergoing validation studies (42).

Blood proteins

There have been multiple studies which have identified serum proteins as potential biomarkers to aid in the early detection, diagnosis, and diagnostic accuracy of lung cancer. Circulating proteins can originate from overexpression on cancer cells, tissue disruption from invasive cancer, increased secretion from diseased tissue, or inflammation associated with malignancy (43). However, these biomarkers also pose several biologic challenges such as low concentrations in the blood for detection and variability in sample collection (44). PAULA's test (Protein Assays Utilizing Lung Cancer Analytes) is currently available for use as a blood test for the early detection of lung cancer as well as risk stratification in high risk individuals (45). This test utilizes a panel of three proteins CEA, CA-125, and CYFRA 21-1 as well as one autoantibody, NY-ESO-1. Doseeva *et al.* performed a validation study of PAULA's test in a high-risk population which revealed a sensitivity of 71% and specificity of 88% (23). Mazzone *et al.* performed a separate clinical validation study demonstrating a sensitivity and specificity of 49% and 96%, respectively. In addition, the study demonstrated an improved diagnostic accuracy when incorporating clinical variables with the biomarker panel. The area under the ROC curve was 0.68 when using a model built on clinical variables alone. Using a combination of clinical variables and biomarkers, the area under the curve was 0.86 (24). The PANOPTIC (Pulmonary Nodule Plasma Proteomic Classifier) Trial conducted by Silvestri *et al.* measured the relative amounts of two plasma proteins, LG3BP and C163A. This two-protein ratio combined with a lung nodule clinical risk prediction model revealed a sensitivity of 97%, specificity of 44%, and NPV of 98% in distinguishing benign from malignant nodules. Of note, the population included in this study had a clinician assessed pretest probability of malignancy of 50% or less. Silvestri *et al.* determined that if this integrated classifier result was used to direct care, 40% fewer procedures would be performed for benign nodules and 3% of malignant nodules would be misidentified (25).

Circulating tumor DNA (ctDNA)

DNA enters plasma through passive (cell necrosis or apoptosis) or active (secretion from living cells) mechanisms. In patients with lung cancer, a portion of the

cell free DNA in their bloodstream comes from tumor cells undergoing apoptosis and necrosis. This comprises ctDNA which can be used as a biomarker to detect genetic mutation (36). While there have been previous studies demonstrating the role of ctDNA, otherwise known as a liquid biopsy, in identifying advanced-stage cancer as well as surveillance for molecular residual disease after treatment, there is relatively little evidence with regards to its use for the early detection of cancer (12,46,47). A recent study by Cohen *et al.* described a blood test which measures a combination of eight protein biomarkers and ctDNA to detect eight common early-stage cancers. This blood test is known as CancerSEEK. By combining protein biomarkers and ctDNA, CancerSEEK is able to both detect genetic alterations which can identify early stage cancers as well as localize the origin of disease. The combination of ctDNA and protein biomarkers demonstrated a specificity of 99% and sensitivity of 59% for lung cancer in 104 patients (12,29). Recently, Chabon *et al.* introduced improvements to cancer personalized profiling by deep sequencing (CAPP-Seq). CAPP-Seq is a method used to analyze ctDNA in order to better facilitate lung cancer screening. This study demonstrated that while ctDNA levels were very low in early-stage lung cancers, it was present before the initiation of treatment in most patients. Using these findings in conjunction with other molecular features, this group developed and prospectively validated the machine-learning method Lung Cancer Likelihood in Plasma (Lung-CLiP) to distinguish early-stage lung cancer patients from risk-matched controls with a specificity of 96% (95% CI, 89–100%) (48). Cristiano *et al.* recently developed a method to evaluate fragmentation patterns of cell-free DNA (cfDNA) present in the genomes of both healthy individuals and those with cancer. They discovered that the cfDNA patterns in healthy patients correlated closely with white blood cell nucleosomal DNA fragmentation patterns. In patients with cancer, however, there existed several genomic differences in the cfDNA with various fragment sizes in different regions. These fragmentation patterns appeared to result from the mixture of both blood and neoplastic cell nucleosomal DNA. This study demonstrated the differences in genome-wide cfDNA fragmentation profiles between healthy individuals and those with cancer. When this method was used to analyze fragmentation profiles in 236 patients with breast, colorectal, lung, ovarian, pancreatic, gastric, or bile duct cancer, and 245 healthy individuals, sensitivities of detection ranged from 57% to >99% at 98% specificity. Furthermore, these fragmentation profiles identified the cancer tissue of origin to a limited number of sites in 75% of cases. Again, this study illustrated the potential use for cfDNA in screening and early detection of cancer (49).

DNA methylation

DNA methylation is an epigenetic modification which adds a methyl group to cytosine predominantly in CpG dinucleotides. Under normal physiologic conditions, this methylation process is tightly regulated. However, alterations in this process such as global hypomethylation, focal hypermethylation of CpG promoter islands, and direct mutagenesis at methylated cytosines can contribute to chromosomal instability and tumorigenesis (50). With regards to adenocarcinoma of the lung, studies have demonstrated the occurrence of DNA methylation before the formation of atypical adenomatoid hyperplasia (51). As a result, DNA methylation has the potential to be utilized as a biomarker for the early detection of lung cancer. A recent case-control study by Hulbert *et al.* used a lung-cancer specific gene panel to detect DNA methylation in sputum and plasma samples from patients with suspicious nodules on CT imaging preoperatively. The gene panel included *SOX17*, *TAC1*, *HOXA7*, *CDO1*, *HOXA9*, and *ZFP42*. Of these genes, the best performing markers were noted to be *SOX17*, *TAC1*, and *HOXA7*. DNA methylation was detected more frequently in patients with lung cancer compared to controls. The three gene combination of the best performing markers exhibited a sensitivity and specificity of 98% and 71% using sputum, and 93% and 62% using plasma (30). While DNA methylation is a promising biomarker for the early detection of lung cancer, this class requires further validation studies.

Future directions

There continues to be an influx of new technologies and emerging biomarkers for the early detection and diagnosis of lung cancer. Several groups are currently looking at exhaled volatile organic compounds (VOCs) as non-invasive biomarkers in the diagnosis of lung cancer. Endogenous VOCs are gaseous organic molecules which are products of different metabolic pathways in the body. Since diseases such as cancer have the ability to alter some of these pathways, it holds true that the associated VOC profile would be affected as well and could serve as a diagnostic biomarker (52). Additionally, biomarkers are being explored

specifically for use in precision medicine. This so called "omic" data incorporates metabolomics, proteomics, genomics, epigenomics, radiomics, and microbiomics with the goal of further classifying disease to more precisely diagnose and treat lung cancer (53).

As we have seen, LDCT as a lung cancer screening tool has led to a significant decrease in lung cancer related mortality. However, there is a need for adjunctive testing given the suboptimal false positive rates for LDCT. Several of these biomarkers are currently available for commercial use, but many of them require further clinical validation. Specifically, there is a tremendous need for randomized trial studies in biomarker utility testing. While this is both a time and resource intensive endeavor, biomarkers in lung cancer screening have the potential to not only present an enriched population for CT imaging, but aid in the early detection and diagnosis of disease, and distinguish between benign and malignant nodules as well.

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Footnote

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