Review Article on Oncology: Lung Cancer

A narrative review of genetic biomarkers in non-small cell lung cancer: an update and future perspectives

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Background and Objective: Lung cancer has long been the leading cause of cancer deaths in the United States. Lung cancer has a poor prognosis, and our understanding of who will maximally benefit from different therapies is incomplete. This article discusses genetic biomarkers that may help in this regard.

Methods: From origin until February 25, 2022, PubMed database was searched for terms "non-small cell lung cancer", "genomics" and "biomarker", with special attention paid to literature published within the past 10 years. Search was language restricted to English. Additional literature was identified through hand searches of the references of retrieved literature.

Key Content and Findings: The most robustly described biomarkers for non-small cell lung cancer (NSCLC) are assessment of specific gene mutations. These are currently used in clinical practice for both prediction and prognostication. Abnormal mutation status of *STK11*/LKB1 and *KEAP1*-NFE2L2 are associated with poor response to radiotherapy (RT), and *STK11*/LKB1 is further associated with resistance to PD-L1 immunotherapy. Abnormal TP53 is associated with decreased benefit from cisplatin in squamous cell carcinoma (SCC). In terms of prognostication, RB1 mutations are associated with decreased overall survival (OS) in NSCLC and *KEAP1*-NFE2L2 mutations are associated with increased local recurrence (LR). Additional work has focused on gene expression levels, as well as analysis of genetic factors and signaling molecules affecting the tumor microenvironment (TME). High levels of Rad51c and NFE2L2 are associated with resistance to chemotherapy, and high Rad51c levels are further associated with resistance to RT. High nuclear expression of β-catenin has additionally been associated with poor RT response. Further, there is increasing evidence that some long non-coding RNAs (lncRNAs) may play a crucial role in regulation of tumor radiosensitivity. Much of this work has had promising early results but will require further validation before routine clinical use. Finally, there is evidence that quantification of some signaling molecules and microRNAs (miRNAs) may have clinical utility in predicting adverse outcomes in RT.

Conclusions: An improved understanding of tumor genetics in NSCLC has led to the development of targeted therapies and improved prognostication. As more work is done in this field, more and more genetic biomarkers will become candidates for clinical use. Much work will be required to validate these findings in the clinical setting.

Keywords: Non-small cell lung cancer (NSCLC); biomarkers; prognostication

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Background

Primary tumors of the lung have traditionally been classified into two groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Approximately 80–85% of lung cancer cases are NSCLC whereas 15–20% are SCLC (1). The World Health Organization (WHO) 2021 classification of lung tumors provides a slightly different paradigm, in which cancers previously classified NSCLC are specified to be adenocarcinoma (ADC), squamous cell carcinoma (SCC), large cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, or other NSCLC (2). SCLC is now considered a subset of neuroendocrine tumors. This classification still largely relies on histological examination, but there is an increasing role for the use of genetic testing in classification of these tumors (2). Accurate classification is important as different subtypes are associated with differing prognoses, as well as choice and responsiveness to treatment. As an example, it has been shown that pemetrexed is efficacious in the treatment of non-squamous histological subtypes of NSCLC, but less so for squamous tumors (3). For the purposes of this review, we will primarily be using the traditional classification system while utilizing more specificity when possible.

Lung cancer has long been the leading cause of cancer deaths in the United States. The American Cancer Society projects in 2022 that 350 people will die each day from lung cancer, which is more than twice the number of deaths predicted for colorectal cancer which is the second leading cause of cancer death (4). Historically, survival in lung cancer has been stagnant when compared to other cancers for several reasons including higher rates of metastatic disease at diagnosis and difficulty finding effective therapeutic agents for advanced disease. However, since the turn of the century we have made advances in our abilities to both diagnose and treat lung cancer. The increasing number of available targeted agents and immunotherapies has provided a great benefit to patients with advanced disease; however, with increasing treatment options comes the need for more effective tailoring of treatments to individual patients. An improved understanding of biomarkers in lung cancer will be essential to this effort.

The Food and Drug Administration (FDA) defines a biomarker as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure of intervention". This broad definition can include molecular, histologic, radiographic, or physiologic characteristics. Biomarkers can further be subdivided according to their applications. There are biomarkers with diagnostic, monitoring, pharmacodynamic/response, predictive, prognostic, safety, and susceptibility/risk applications (5). It is important to note that there can be significant overlap between these categories.

A better understanding of tumor genetics, and subsequent targeting of these alterations in the clinical setting has significantly improved outcomes in NSCLC. However, there is room for improvement in both diagnostics and treatment. While these improvements are welcomed, an estimated 27% of NSCLC cancers do not have an identified driver mutation (6), though do have other genetic abnormalities, the significance of which are not yet known. Given the rapid improvements over the past decade, it is likely many of these could be targeted in the future, but for now we must use this information in other ways to understand their significance. Thus, in this review we will provide a thorough discussion of biomarkers in NSCLC, in order to give an overview for clinicians in how these might be useful in diagnosis and management of disease. We present the following article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-2022-01/rc).

Methods

From origin until February 25, 2022, a literature search was conducted through the PubMed database. Search was language restricted to papers in English. Terms including "lung cancer", "non-small cell lung cancer", "genomics" and "biomarker" were utilized. Papers were included based on subject matter relevance as determined by consensus of authors. Special attention was paid to primary literature and systematic reviews. The search was prioritized for papers published within the past 10 years, although older papers were considered on an individual basis. Additional literature was identified through review of the reference section of retrieved literature. A total of 130 articles were screened and 79 were ultimately included. *Table 1* provides an overview of the search methodology.

Available biomarkers in NSCLC

The number of biomarkers associated with NSCLC has rapidly expanded over the past decade. However, most of these have not yet been utilized in routine clinical practice. The biomarkers that are currently available for routine

Table 1 A summary of search methodology

Items	Specification
Date of search	Jan 1, 2022–Feb 25, 2022
Databases and other sources searched	PubMed
Search terms used	"(Lung Cancer) AND (Biomarker)", "(Lung Cancer) AND (Genomics)", "Non-Small Cell Lung Cancer"
Inclusion criteria	Article languages: English
	Publication date: after Jan 1, 2000 (papers published after 2010 prioritized)
	Article types: primary literature, systematic reviews. Secondary literature considered on an individual basis
Selection process	Individual authors conducted PubMed searches and identified possible papers for inclusion. Papers were ultimately included based on consensus of all authors

clinical use include assessments of specific gene mutation status through reverse transcriptase polymerase chain reaction (7), next-generation sequencing (NGS) of solid tumor specimens to assess mutation status of several different genes along with tumor mutational burden (TMB) (8), and IHC to assess presence or absence of clinically relevant proteins. Clinically, these biomarkers are most often evaluated through use of companion diagnostics (CDx) assays. The FDA defines CDx assays as *in vitro* diagnostic devices that provide information essential to the safe and effective use of corresponding therapeutic product (9). These diagnostic tests are increasingly becoming a routine part of care for patients with NSCLC. A 2020 survey of practicing oncologists found that 99.6% of patients were tested for at least one biomarker through FDA approved testing (10). These panels largely depend on having a solid tissue sample available for testing, but tests utilizing liquid biopsy are increasingly available (11). Liquid biopsy has the potential to analyze circulating tumor DNA (ctDNA), along with circulating RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). CtDNA is the subset of cell free DNA (cfDNA) that came from tumor cells. In the detection of driver mutations, cfDNA analysis has a reported sensitivity of 75%. Additionally, it was found that the ability of cfDNA analysis to identify these driver mutations was correlated with increasing cfDNA levels (12).

Analysis of tumor genetics in liquid biopsy can also be done through analysis of circulating tumor cells (CTCs). One potential advantage of CTC analysis, and liquid biopsy overall, when compared to analysis of solid tumor samples is that it more easily allows analysis of tumor genetics at different points in time. As an example, some studies suggest that CTC analysis finds higher rates of PD-LI positivity than tumor biopsy in NSCLC patients (13). PD-L1 expression is a dynamic process, whereas analysis of PD-L1 expression from biopsy samples yields information about a specific time point. The dynamic nature of PD-L1 expression could be an explanation as to why only about 50% of PD-L1 positive patients respond to PD-L1 inhibitor treatment. Thus, isolation of CTCs is a non-invasive procedure that could improve our ability to monitor treatment response.

Prognostic biomarkers

Studies have identified several biomarkers that have prognostic and/or predictive value in NSCLC. These include expression levels and mutational status of intrinsic genes of the tumor, as well as expression levels and mutational status of genes related to the tumor microenvironment (TME). The majority of these biomarkers are not used in routine clinical practice, and studies assessing prognostic and/or predictive value often have conflicting results. The combination of biomarkers into prognostic or predictive panels has had greater success than individual biomarkers alone, as exhibited by the CDx panels previously discussed. However, even with prognostic signatures comprised of several independent biomarkers, clinical validation is a concern. A 2017 meta-analysis found that of the 42 published messenger RNA (mRNA) prognostic signatures identified, 25 were prognostic for survival after adjustment for clinical risk factors and 18 performed better than random signatures. Seventeen prognostic signatures were identified for ADC

Table 2 A summary of mutational biomarkers discussed in this review along with their potential clinical relevance

Gene	Status	Relevance
TP53	Abnormal mutation status	Controversial in prognostication, some studies suggest decreased survival (15,16)
		In SCC, decreased benefit from ACT compared to WT TP53 (15)
STK11/LKB1	Abnormal mutation status	Worse outcome after definitive RT (17,18)
		Resistance to PD-L1 targeting immunotherapies (19,20)
RB1	Abnormal mutation status	Decreased OS compared to WT in NSCLC (21)
		Increased OS compared to WT in SCLC (22,23)
BRCA1/2	Pathogenic germline mutations	Patients significantly more likely to develop NSCLC before age 50 (24)
		Better response to EGFR-TKI in patients with somatic EGFR mutations (24)
Rad51c	High expression	Shorter OS and DFS (25)
		Induction of cell resistance to cisplatin and radiation (26)
ERCC1	High expression	Decreased objective RR (27)
		Higher risk of treatment failure in chemoradiation (28)
KEAP1-NFE2L2	Abnormal mutation status	Increased LR (29)
		Clinical resistance to RT (30)
	High *NFE2L2* expression	Low treatment response to platinum-based chemotherapy (31)
		Poor PFS (31)
SETD1A	High expression	Poor OS and FPS (32,33)
β-catenin	Increased nuclear expression	Negative correlation with radiation response (34)
KNSTRN	Increased expression	Associated with progression of ADC: poor OS, PFS, and DSS (35)
TMB	Increased burden	Greater clinical benefit for immunotherapy (36)
		In WT-EGFR: predictive of increased RFS benefit from pemetrexed/cisplatin *vs.* vinorelbine/cisplatin (37)

TMB, tumor mutational burden; SCC, squamous cell carcinoma; ACT, adjuvant cisplatin therapy; WT, wild type; RT, radiotherapy; OS, overall survival; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; DFS, disease-free survival; RR, response rate; LR, local recurrence; PFS, progression-free survival; FPS, functional performance status; ADC, adenocarcinoma; DSS, disease-specific survival; RFS, relapse-free survival.

and 8 identified for SCC (14). With these considerations, we provide an overview of potential biomarkers in the context of relations to genes and/or genetic pathways that have been implicated in oncogenesis (*Table 2*).

Tumor suppressors

TP53

TP53, located on chromosome 17p13.1, encodes the tumor suppressor protein p53. p53 plays important roles in cell cycle regulation, apoptosis, autophagy, and DNA repair. *TP53* mutations are the most commonly identified mutations NSCLC, with incidence greater in SCC than ADC (38,39). Additionally, *TP53* mutations have been closely linked to smoking status (40). The use of *TP53* abnormalities in prognostication has historically been controversial. A systemic review from 2001 found abnormal p53 status to be associated with poor survival in all subsets of NSCLC, however, a 2016 pooled analysis of four randomized trials found no prognostic value in the presence of *TP53* mutations in exons 5–8 (15,16).

Interest in the downstream effects of TP53 mutations has led to identification of differentially expressed genes (DEGs). DEG analysis of SCC patients with *TP53* mutations found three genes with significant prognostic value in SCC: *KLK6*, *MUC22*, and *CSN1S1*. These three

genes were combined into a prognostic signature which was shown to have greater prognostication for overall survival (OS) than TNM stage or T stage alone (41).

Although the previously mentioned 2016 pooled analysis found no prognostic value for TP53 mutations, they did find a marginal predictive effect for benefit of adjuvant cisplatin therapy (ACT) for OS in those with *TP53* mutation (15). Wild type (WT) *TP53* patients treated with ACT had better OS when compared to observation, but this effect was not observed for mutant *TP53* patients. This effect was only significant in SCC, and the authors note that it was restricted to mutations predicted to disrupt the DNA-binding domain of the p53 protein. Further validation of such findings is still needed.

STK11/LKB1

LKB1 protein, encoded by *STK11* gene, is the second most commonly altered tumor suppressor in NSCLC (42,43). These alterations are typically loss of function and co-occur frequently with activating *KRAS* mutations (44). Tumors with these concurrent mutations are associated with aggressive clinical course, poor survival, and immunosuppressed phenotype and *STK11*/LKB1 mutation has been associated with worse outcome after definitive RT in patients with stage III NSCLC (17,18). When compared to *STK11*/LKB1 WT tumors, *STK11*/LKB1 mutated tumors were associated with significantly higher cumulative rates of locoregional failure and shorter disease-free survival (DFS) and OS following RT, and this radioresistance is believed to occur via activation of the *KEAP1*/NRF2 pathway. In addition to its radioresistant phenotype, lung tumors with co-mutations in *STK11* and *KRAS* also demonstrate resistance to PD-L1 targeting immunotherapies (19,20). Assessment of *STK11*/LKB1 mutational status has promising clinical utility, especially as a predictive biomarker for RT and immunotherapy.

RB1

Retinoblastoma protein is a tumor suppressor protein that is dysfunctional in several human cancers. There is evidence that mutations to *RB1* confer negative prognostic value in NSCLC. In a study of stage III and IV NSCLC patients, *RB1* mutation was noted in 8.2% of patients. The median OS for WT *RB1* was 28.3 *vs.* 8.3 months for mutant *RB1*. It was additionally found that the presence of mutant *RB1* correlated with lack of response to immunotherapy (21). Interestingly the rate of RB1 mutations appears higher in SCLC with a rate as high as 75% and WT RB1 was associated with a significantly shorter OS (22,23). This difference in outcomes between lung cancer subtypes suggest a more complex mechanism than simple regulation of the cell cycle or response to chemotherapy. In EGFR-mutant NSCLC, concurrent *RB1* and *TP53* mutations were associated with worse outcomes and defined the population at risk for SCLC transformation (45). RB1 mutational status has potential clinical utility in assessment of prognosis.

Double stranded DNA (dsDNA) break repair genes

Genes involved in repair of dsDNA breaks have been implicated in a wide number of cancers. Perhaps most widely appreciated is the relationship between *BRCA1* and *BRCA2* mutations and breast cancer (46,47). *BRCA1* expression in solid lung tumor samples has been assessed through immunohistochemistry (IHC) as a binary value. In the 51.4% of patients identified as *BRCA1* WT, there was no statistically significant difference in RR, median PFS, or OS when compared to *BRCA1* loss patients (27). Genetic analysis of tumor cells suggests that *BRCA1/2* mutations occur in only about 2.1% of NSCLC patients with advanced disease and these are mainly somatic, as opposed to germline, mutations (48). In a study of Chinese patients with late-stage NSCLC, researchers found an incidence of pathogenic germline *BRCA1/2* mutations to be 1.03%, with 76.6% of these being mutations in *BRCA2*. They found no association between these mutations and prognosis but did find that patients with these mutations were significantly more likely to develop NSCLC before the age of 50 (24). Additionally, there is potential predictive value in these mutations—in patients with somatic *EGFR* mutations being treated with EGFR-TKI, presence of germline BRCA mutations (gBRCAm) conferred better response to this therapy (24).

Other genes integral to the process of dsDNA repair have been identified as more significant predictors of prognosis. Rad51c, is a component of protein complexes that play critical roles in both initial and late stages of homologous recombination (HR). Rad51 has been shown to be an independent prognostic factor for NSCLC, with elevated levels of this protein correlating with shorter OS and DFS in NSCLC patients (25). Additionally, *in vitro* experiments found high levels of Rad51c induced cell resistance to cisplatin and radiation (26). Further, Rad51c has been implicated in the development of gemcitabine resistance (49). Assessment of Rad51c expression levels

has promising clinical utility as a predictive biomarker for several treatment modalities.

Non-dsDNA break repair

ERCC1 plays an important role in nucleotide excision repair. In a study of 110 NSCLC tumor samples, patients were divided into *ERCC1* expressing or *ERCC1* loss based on IHC analysis. It was found that 54.7% of patients expressed *ERCC1*, and there was a decreased objective response rate (RR) compared to *ERCC1* loss patients (27). Similar findings were noted in a cohort NSCLC undergoing chemoradiation where ERCC1 overexpression was associated with higher risk of treatment failure (28).

Free-radical defense

KEAP1-NFE2L2 pathway activation leads to expression of free radical defense genes, which could protect against radiation-induced DNA damage. Mutations in either *KEAP1* or *NFE2L2* occur in approximately 20% of NSCLC and lead to constitutive pathway activation (42,50). Tumor genotyping of a cohort of 232 patients found that mutations in *KEAP1* and *NFE2L2* were significantly associated with local recurrence (LR), and that these mutations were present in almost half of tumors that had LR (29). Functional evaluation of these mutations enabled the classification of mutations as pathologic [loss-of-function (LOF) for *KEAP1 vs.* gain-of-function (GOF) for *NFEL2*] or passenger (i.e., neutral), and this classification further improved the association with LR. Pathogenic *KEAP1/NFE2L2* mutations result in overexpression of *NFE2L2* target genes, but analysis of gene expression did not find an association with LR or OS. This suggests that gene expression studies are not a suitable surrogate for genotyping in assessing this effect. Conversely, a recent systematic review found that high *NFE2L2* expression is predictive for poor OS (hazard ratio =1.86; P<0.001) (31). Additionally, this systematic review found that high *NFE2L2* expression was associated with low treatment response in platinum-based chemotherapy [hazard ratio =0.11; 95% confidence interval (CI): 0.02–0.51; P=0.005] and poor progression-free survival (PFS) (hazard ratio =2.27; 95% CI: 1.26–4.09; P=0.006) (31).

Mutations in *KEAP1/NFE2L2* also strongly predict clinical resistance to RT in patients with NSCLC (30). This is most likely due to enhanced expression of reactive oxygen species (ROS) scavengers and detoxification pathways. In tumor cells with KEAP1 mutations, glutaminase inhibition increased radiosensitivity (29). If these results are validated in the clinical setting, mutational assessment of *KEAP1* could provide significant benefit to patients who are being evaluated for RT.

WNT pathway

The WNT signaling pathways are a complex group of signal transduction pathways. The WNT/β-catenin pathway has been shown to be a critical signaling pathway in maintenance of cancer stem cell properties (51).

SETD1A is a member of SET1/MLL family H3K4 methyltransferases which is involved in pluripotency and malignant transformations of stem cells (52,53). High expression of SETD1A has been associated with poor outcomes in lung cancer (32). In NSCLC cells, SETD1A regulates cancer stem cell property and sensitivity to cisplatin through activation of the WNT/β-catenin pathway (33). *SETD1A* is itself a downstream target of the WNT/β-catenin pathway, creating a positive feedback loop of SETD1A/WNT/β-catenin in NSCLC cells. *SETD1A* has been found to be significantly increased in NSCLC, with overexpression predictive of poor prognosis (33). RNA sequencing data from The Cancer Genome Atlas (TCGA) database showed increased *SETD1A* levels in NSCLC tissues compared to normal lung tissues, and this result was supported by IHC staining of clinical specimens as well (33). In IHC analysis, high SETD1A expression was significantly associated with poor OS and functional performance status (FPS). Additionally, *SETD1A* knockdown was found to increase sensitivity of NSCLC cells to cisplatin treatment (33). IHC analysis found β-catenin nuclear expression to be negatively correlated with radiation response (34).

Cell cycle pathway

Cell cycle pathway mutations appear important in NSCLC. In 2013, Wistuba *et al.* provided validation of a cell-cycle progression genes (CCP score) based model from mRNA expression levels of 31 proliferation genes in stage I and II tumor samples from ADC patients (54). In this model, the CCP score was shown to be a significant predictor of lung cancer death in early-stage ADC treated surgically. Such a model could have value in clinical practice in determining the relative need for adjuvant therapy in these patients. Further evidence of the importance of the CCP score was

demonstrated in 2016 by Eguchi *et al.* which showed that combining the CCP score with pathologic stage could yield a molecular prognostic score (mPS) that had greater prognostic value than CCP score alone (55).

Additionally, increased expression level of *KNSTRN*, which is an essential component of the mitotic spindle, was found to be associated with progression of ADC (35). High *KNSTRN* was associated with poor OS, PFS, and disease-specific survival (DSS) in these patients. Functional and biological pathways that were associated with either high or low *KNSTRN* expression were identified, and it was shown that with high *KNSTRN* expression was primarily related to cell cycle checkpoints, DNA replication, cell cycle mitotic spindle checkpoint, G2-M checkpoint 9, and M phase. *KNSTRN* expression appeared to have a positive association with some number of immune cell types including T helper 2 cells, gamma delta T cells, and CD56 natural killer cells. Overall, this adds to the evidence that quantification of both genes related to intrinsic behavior of the tumor, as well as the behavior of the TME, could have value as biomarkers.

TME

There is increasing evidence that the tumor progression is affected by both intrinsic features of tumor cells, as well as features of the TME, and the importance of the immune system in cancer initiation and progression is now well established (56,57). To this end, quantification of gene expression in immune-related genes (IRGs) can have prognostic value. Li *et al.* developed a prognostic signature based on 25 IRGs in non-squamous NSCLC (58). Their prognostic signature was validated against a quantitative-PCR-based 14-gene assay that had previously been shown to reliably identify patients with early stage non-squamous NSCLC at high risk for mortality after surgical resection (59). The majority of the genes utilized by the 14-gene assay are known elements of classical oncogenic pathways, including *BAG1*, *BRCA1*, *CDC6*, *ERBB3*, and *WNT3A*. Five genes utilized in this assay were also utilized in previously published prognostic gene signatures for non-squamous NSCLC: *CDC6*, *ERBB3*, *FUT3*, *LCK*, and *RND3* (59). This was additionally the first gene expression panel for non-squamous NSCLC to undergo large-scale, independent validation.

Infiltrating stromal and immune cells comprise the majority of normal cells found in tumor tissue. Quantification of these cell types has historically been dependent on IHC of biopsy specimens. 'Estimation of STromal and Immune cells in MAlignant Tumors using Expression data' (ESTIMATE) now allows inference of the fraction of stromal and immune cells in tumor samples based on gene expression signatures with higher scores representing a greater proportion of the respective cell type (60). In ADC, higher immune scores were associated with earlier clinical stage and T stage whereas high stromal scores were associated with earlier M stage (60). Additionally, higher immune scores were associated with better OS. In contrast to ADC, in SCC cases neither immune nor stromal scores had significant associations with clinical characteristics or prognosis. There are several DEGs that are significant to OS in NSCLC, one study identified 23 immune-related prognostic genes in ADC and seven in SCC (61). IHC analysis found high density of FOXP3-positive in stroma to be significantly associated with recurrence. In these patients with high FOXP3, concurrent high stromal CD3 had shorter recurrence-free probability (RFP) compared to concurrent low stromal CD3. Creation of a FOXP3 risk index based off concurrent CD3 expression was found to be a strong predictor of recurrence. Low risk patients had 5-year RFP of 85% *vs.* 77% in high-risk patients. No other immune cells had prognostic value (62).

Signaling molecules such as cytokines and interleukins are also important in regulation of the TME, and have been studied for potential prognostic or predictive value (63). Increased expression of IL-12R2 associated with reduced risk of recurrence while increased expression of IL-7R associated with increased risk of recurrence (62). Significant associations not found between expression levels and recurrence for cytokines CCR7, CXCL12, or CXCR4 (62).

Other important immune related biomarkers include PD-1 and its ligands PD-L1 and PD-L2. PD-1 directed immune checkpoint blockade has been shown to have durable antitumor activity in many advanced malignancies (64,65). PD-L1 surface expression on tumor cells has been identified as an important predictor of tumor response (66). IFN-γ has been shown to be a critical driver of PD-L1 expression in both cancer and host cells (67,68). An 18-gene T cell inflamed gene expression profile predicted response to pembrolizumab across multiple solid tumors (69). Further, gene expression analysis of the stimulator of interferon genes (STING) pathway has also been explored for predictive value in immunotherapy. STING pathway is activated by detection of cytosolic DNA fragments by cyclic GMP-AMP synthase,

leading to a type I IFN response (70). NSCLCs with high STING pathway activation have higher levels of targetable immune checkpoints and markers of an active immune microenvironment that are associated with clinical responses to immunotherapy (69,71). STING activation as measured by expression data of targetable immune genes could be a potential biomarker for novel immunotherapy and immunotherapy-based combination in NSCLC. In ADC tumors with STING activation, *STK11* mutant tumors had lower expression of immune genes when compared to other ADC tumors (71). Interestingly, patients with concomitant mutations in *STK11* and *TP53* were found to have high STING activation and immune expression, suggesting a novel subset of STK11-mutant ADC patients that may benefit from immunotherapy (71).

TMB

TMB is another potential biomarker in NSCLC. A 2019 meta-analysis found that a higher TMB appeared to be associated with greater clinical benefit in patients receiving immunotherapy for NSCLC (36). Utilizing TMB may complement PD-L1 and deficient mismatch repair/microsatellite instability testing in identifying good candidates for immunotherapy among NSCLC patients (36). Additionally, other complex interactions of TMB exist—for example in the subset of NSCLC patients found to have WT-EGFR, it has been suggested that high TMB is predictive of increased relapse-free survival (RFS) benefit when treated with pemetrexed/cisplatin *vs.* vinorelbine/cisplatin (37). The constellation of WT-EGFR with high TMB can be taken as a surrogate of impaired DNA repair ability, leading to increased sensitivity to pemetrexed/cisplatin.

Non-mRNA biomarkers

In addition to quantification of serum protein levels and the utilization of mRNA to determine protein expression levels, various other RNAs have been identified as having prognostic or predictive value.

LncRNAs have emerged as important regulators of different disease processes, including cancer. Iyer *et al.* found that in a consensus human transcriptome of 91,013 expressed genes, over 68% (58,648) were classified as lncRNAs, 79% of which were previously unannotated (72). Further, they identified 7,942 lineage- or cancer-associated lncRNA genes. In investigating the transcriptional dynamics across different tissue samples, they found the top 1% of cancer-associated lncRNAs demonstrated highly specific signatures for each cancer type; with the exception of lung and kidney cancers. SCC and ADC were found to share numerous transcripts associated with cancer.

There is increasing evidence that some lncRNAs may be related to radioresistance and play a crucial role in regulation of tumor radiosensitivity. Two such examples are lncRNA KCNQ1OT1 (73) and lncRNA SBF2-AS1 (74). SBF2-AS1 has been linked to poor prognosis and advanced tumor progress of NSCLC. One mechanistic explanation for this effect is a competitive endogenous RNA (ceRNA) effect in sequestration of miR-302a, therefore affecting expression levels. Inhibition of SBF2-AS1, or increased expression of miR-302a enhanced radiosensitivity and promotes apoptosis of NSCLC cells (74).

Song *et al.* found four radioresistance-related lncRNAs that were remarkably well correlated with OS in NSCLC (75). These are CASC19 and LINC01977 as potential risky indicators, while LINC02471 and MAGI2-AS3 as potential protective indicators. Their 4 lncRNA signature offered a reliable reference for prognostic forecast. While this work is promising for future prognostication, more evidence is needed within this area at this time.

Normal tissue biomarkers

RT plays an important role in all stages of NSCLC. However, not all patients respond in the same way when receiving RT. Both tumor recurrence and tolerance to radiation are frequently encountered. Reports suggest that the local failure rate of RT alone in NSCLC is 24–40%, while 30–50% with radical chemotherapy (75). This heterogeneity in response is the subject of much investigation, including efforts to predict tumor response using biomarkers. RT may result in long-term toxicities such as pneumonitis or possible cardiac injury, both risks increase with increasing incidental radiation dose to these organs. These concerns must be balanced with the potential benefits from RT. A better understanding of individual predispositions through use of biomarkers could better inform clinical decision making.

Pulmonary

Although advances in RT technology have improved our ability to avoid irradiating healthy lung tissue, radiation induced pneumonitis is still a source of significant

morbidity. In a group of 836 patients treated between 1993 and 2010, a meta-analysis found the overall rate of symptomatic pneumonitis to be 29.8% (76). This meta-analysis found that increasing mean lung dose (MLD), carboplatin/paclitaxel chemotherapy, and increased age were predictive of symptomatic pneumonitis. Measurement of 30 cytokines in 142 patients with stage I-III NSCLC treated with definitive RT found plasma levels of IL-8 and TGF-1 to be predictive of grade 2 radiation induced lung toxicity (RILT2) (77). Low levels of IL-8 before initiation of treatment were associated with higher risk of RILT2. They calculated the ratio of TGF-1 to IL-8 at 2 weeks of treatment compared to levels before treatment, and found that the higher the ratio, the greater the risk of RILT2. That is to say that the greater the increase in measured TGF-1 during the first 2 weeks of treatment, the greater the risk of RILT2. The link between MLD and RILT has been well established, and the authors show that a model incorporating IL-8, TGF-1, and MLD to better predict risk of RILT2 than MLD alone.

Cardiac

There is also concern for possible damage to the heart in treating NSCLC with RT. Radiation-induced cardiac toxicity (RICT) can be a source of morbidity and mortality for patients, and it can be difficult to predict who will be affected. As the benefits of dose escalation in NSCLC continue to be investigated with some suggesting decrement to higher heart dose (78,79). A better understanding of who will experience adverse effects would be clinically valuable. Historically, prediction of RICT has relied on the combination of dosimetric parameters such as mean heart dose (MHD) with clinical factors such as pre-existing cardiac disease (PCD). In 2017, a meta-analysis of 125 patients from four different prospective RT trials the 24-month cumulative incidence of grade 3 cardiac event was 11% (95% CI: 5% to 16%). The authors found that PCD conferred a hazard ration of 2.96 (95% CI: 1.07 to 8.21; P=0.04) and that mean heart dose conferred a hazard ratio of 1.07/Gy; (95% CI: 1.02 to 1.13/Gy; P=0.01) (80). Hawkins *et al.* built upon this work to develop a predictive model for RICT that incorporates levels of circulating miRNAs (c-miRNAs) along with MHD and PCD (81). It was found that a model comprised of 14 c-miRNA species performed similarly to a model based solely on clinical data, but that combining the two models did not improve prognostication. Additionally, they observed a higher prevalence of PCD in patients with high-risk c-miRNA profiles, suggesting an association between some c-miRNAs and PCD. The authors note that there are numerous reports of various miRNA species being utilized as biomarkers of various cardiac diseases, including several of the same miRNA species they investigated.

Conclusions

Large amounts of information continue to be discovered regarding the role of genetics and molecular tumor environment in the initiation and progression of NSCLC. This information has thus far successfully been leveraged into advances in novel therapeutics targeting alterations such as EGFR, and ALK. However, at this time, much of these alterations, such as *TP53* and WNT, are not readily targetable, but could provide prognostic information and insight into a patient's treatment course. As we gain further insight into the pathophysiology of cancer, and build greater datasets of genomic data, substantial future work will be required to best inform clinically relevant decision making.

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Footnote

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