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Epidermal Growth Factor Receptor Expression and Mutations as Diagnostic and Predictive Biomarkers in Lung Cancer: A Literature Review

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Abstract

Lung cancer remains a leading cause of cancer-related mortality worldwide, with diagnostic challenges due to nonspecific symptoms and limitations in tissue sampling. Molecular biomarkers, particularly Epidermal Growth Factor Receptor (EGFR), have gained attention for improving diagnostic accuracy and understanding tumor biology. EGFR plays a critical role in regulating cell proliferation, differentiation, and survival through multiple signaling pathways. This study aims to analyze the role of EGFR expression as a diagnostic biomarker in lung cancer by reviewing its biological function, molecular mechanisms, and clinical relevance. This study used a literature review approach by collecting relevant articles from databases such as PubMed, Scopus, and Google Scholar. Keywords including "EGFR," "lung cancer," and "biomarker" were used to identify studies discussing EGFR expression and its diagnostic value. EGFR overexpression and mutations are frequently found in lung cancer, especially non-small cell lung cancer. Activation of EGFR triggers signaling pathways such as MAPK, PI3K, and STAT, promoting tumor proliferation and survival. Detection methods, including immunohistochemistry, PCR, and FISH, are widely used. EGFR expression has shown potential as a diagnostic biomarker and provides important information for targeted therapy. EGFR expression plays a significant role in lung cancer diagnosis and offers potential as a diagnostic biomarker. However, variations across populations and tumor subtypes require careful interpretation in clinical applications.

Keywords

Epidermal Growth Factor Receptor, EGFR, Lung Cancer, Biomarker

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1. BACKGROUND

Lung cancer remains one of the most common malignancies worldwide and continues to be a leading cause of cancer-related mortality (Gao et al., 2007). According to global cancer

statistics, lung cancer accounts for a significant proportion of cancer deaths each year, reflecting the aggressive nature of this disease and the challenges associated with early detection. The high mortality rate is largely attributed to late diagnosis, as many patients present with advanced-stage disease when curative treatment options are limited.

Nonspecific clinical manifestations often complicate the diagnosis of lung cancer during the early stages of the disease. Symptoms such as chronic cough, dyspnea, chest pain, and weight loss frequently appear only when the tumor has already progressed. Conventional diagnostic methods, including imaging techniques and histopathological evaluation, remain essential; however, they may not always provide sufficient information about tumor biology. Consequently, there has been increasing interest in identifying molecular biomarkers to improve diagnostic accuracy and better understand tumor biology (Gao et al., 2007).

In recent decades, advances in molecular biology have provided new insights into the mechanisms underlying lung cancer development. Among the various molecular alterations identified in lung cancer, the Epidermal Growth Factor Receptor (EGFR) has received considerable attention. EGFR belongs to the ErbB family of receptor tyrosine kinases and plays a critical role in regulating cellular processes, including proliferation, differentiation, migration, and survival. Molecular biomarkers have increasingly contributed to the abnormal activation of EGFR signaling pathways, which have been implicated in the development and progression of several malignancies, including lung cancer (Paez et al., 2009; Pao et al., 2004).

EGFR mutations and overexpression are frequently observed in patients with non-small cell lung cancer (NSCLC), particularly in the adenocarcinoma subtype (Lynch et al., 2004; Marchetti et al., 2005; Soetandyo et al., 2020). These molecular alterations can lead to uncontrolled cellular proliferation and resistance to apoptosis, thereby promoting tumor growth. The discovery of EGFR mutations has also contributed to the development of targeted therapies, particularly tyrosine kinase inhibitors, which have significantly improved treatment outcomes in selected patient populations (Song et al., 2006; Tracy S et al., 2004).

Understanding the role of EGFR expression in lung cancer is therefore essential not only for improving diagnostic strategies but also for guiding therapeutic

decisions. As molecular diagnostics continue to evolve, EGFR has emerged as one of the most important biomarkers in lung cancer research. This literature review analyzes the biological mechanisms of EGFR and its potential as a diagnostic biomarker in lung cancer, summarizing current evidence on its molecular function and clinical relevance.

2. METHODS

This study used a literature review to analyze and summarize current scientific evidence on EGFR expression in lung cancer. Relevant scientific articles were identified through electronic databases, including PubMed, Scopus, and Google Scholar, using keywords such as "EGFR", "lung cancer", and "biomarker."

Inclusion criteria: (1) peer-reviewed original research, reviews, or clinical guidelines; (2) focus on EGFR expression, mutations, or diagnostic methodologies in primary lung cancer; (3) published in English. Exclusion criteria: (1) non-lung malignancies without comparative lung cancer data; (2) case reports, editorials, conference abstracts, or non-peer-reviewed sources; (3) studies lacking methodological transparency or clinical relevance.

Screening was performed based on titles and abstracts, followed by full-text evaluation against inclusion criteria. Data extraction captured study design, population characteristics, detection methodology, mutation/expression frequencies, and clinical outcomes. Due to the heterogeneity of study designs and reporting metrics, a qualitative thematic synthesis was performed. Study selection and screening processes were documented using a PRISMA-style flow diagram to ensure transparency. As per SANRA guidelines, formal risk-of-bias assessment and quantitative meta-analysis were not performed; instead, critical appraisal focused on methodological rigor, clinical relevance, and consistency of findings across studies.

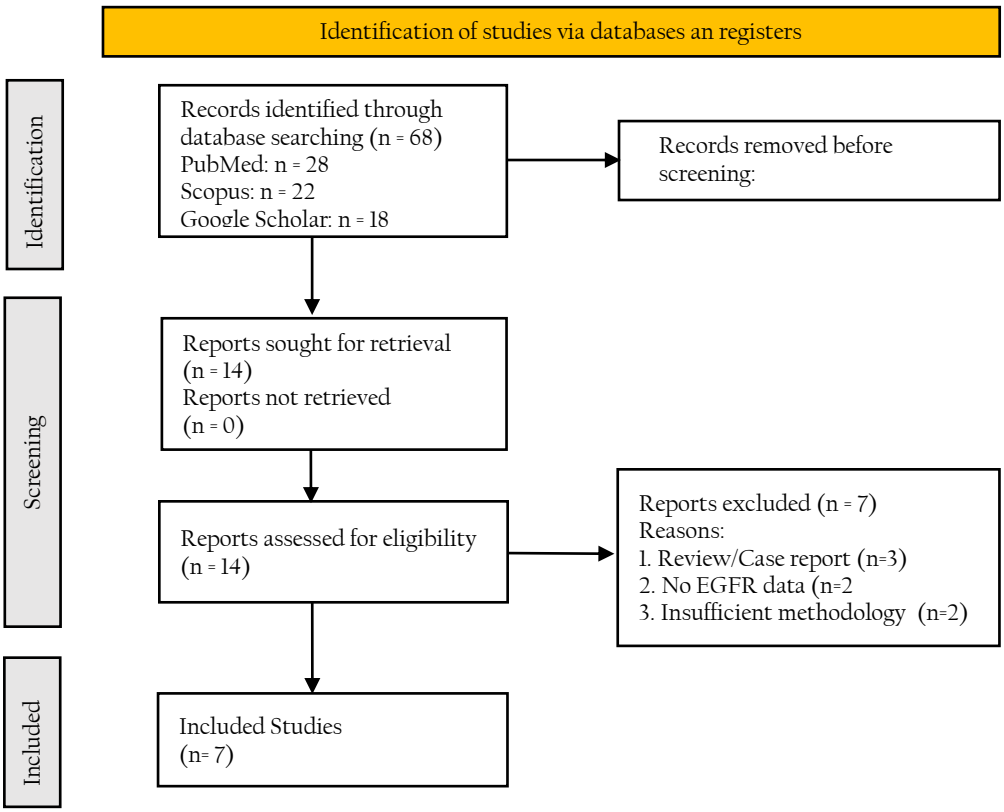

Figure 1. Flow chart of literature searches and screening results

3. RESULTS

Table 1. Articles results *(Contnue to page 152)*

No	Author	Title	Methods	Findings
1	Pao et al. (2004)	EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib.	The study utilized DNA sequencing of the EGFR tyrosine kinase (TK) domain (exons 2-28) to identify genetic alterations in lung cancer patients.	The results establish that never-smokers with adenocarcinoma represent a distinct clinical subset that achieves superior outcomes with targeted tyrosine kinase inhibitor therapy.
2	Sordella et al. (2012)	Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways.	The study utilized small interfering RNA (siRNA)-mediated knockdown to specifically silence mutant EGFR expression in non-small cell lung cancer (NSCLC) cells.	The researchers discovered that mutant EGFRs selectively activate the Akt and STAT signaling pathways, which primarily promote cell survival, rather than the ERK pathway which induces proliferatio
3	Shi et al. (2014)	A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER).	Eligible patients (aged ≥20 years) had untreated stage IIIB/IV adenocarcinoma.	The observed high mutation frequency in demographic/clinical subgroups compared with white populations suggests that mutation testing should be considered for all patients with stage IIIB/IV adenocarcinoma, even males and regular smokers, among Asian populations.

No	Author	Title	Methods	Findings
4	Bethune et al. (2010).	Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update.	The study utilized a clinical observation and molecular profiling approach to evaluate the relationship between the Epidermal Growth Factor Receptor (EGFR) structure and patient outcomes	The researchers identified that EGFR is a trans-membrane glycoprotein that regulates cellular proliferation, and its sustained activation leads to more aggressive tumor phenotypes
5	Lynch et al. (2004).	Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. s	We searched for mutations in the EGFR gene in primary tumors from patients with non-small-cell lung cancer who had a response to gefitinib, those who did not have a response, and those who had not been exposed to gefitinib.	These mutations lead to increased growth factor signaling and confer susceptibility to the inhibitor. Screening for such mutations in lung cancers may identify patients who will have a response to gefitinib.
6	Soetandyo et al. (2020)	Prognosis of advanced stage non-small-cell lung cancer patients receiving chemotherapy: Adenocarcinoma versus squamous cell carcinoma.	This study focused on a retrospective cohort consisting of 60 patients with advanced stage NSCLC and treated with chemotherap	Squamous cell carcinoma had comparable one-year mortality and disease progression rate with adenocarcinoma type in advanced stage NSCLC. However, underweight patients had a higher risk of mortality and disease progression.
7	Gainor et al. (2016).	EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: A retrospective analysis.	identified 58 patients treated with PD-1/PD-L1 inhibitors. Objective response rates (ORR) were assessed using RECIST v1.1. PD-L1 expression and CD8(+) tumor-infiltrating lymphocytes (TIL) were evaluated by IHC.	NSCLCs harboring EGFR mutations or ALK rearrangements are associated with low ORRs to PD-1/PD-L1 inhibitors. Low rates of concurrent PD-L1 expression and CD8(+) TILs within the tumor microenvironment may underlie these clinical observations.

EGFR Structure and Function

The Epidermal Growth Factor Receptor (EGFR) is a transmembrane glycoprotein that belongs to the ErbB family of receptor tyrosine kinases (Pao W et al., 2004). This family consists of four members: EGFR (ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). These receptors are involved in regulating various cellular processes including proliferation, differentiation, migration, and survival (Pao et al., 2004). Structurally, EGFR consists of three main components: an extracellular ligand-binding domain, a single hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain. The extracellular domain binds to specific ligands such as epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α). Ligand binding induces receptor dimerization, which subsequently activates the intracellular tyrosine kinase domain and triggers downstream signaling pathways (Sordella et al., 2012).

EGFR Signaling Pathway

Upon ligand binding, EGFR undergoes conformational changes that promote receptor dimerization and autophosphorylation of tyrosine residues within the intracellular domain (Sordella et al., 2012). These phosphorylated residues serve as docking sites for adaptor proteins that initiate multiple intracellular signaling cascades. Several major signaling pathways are activated following EGFR stimulation. One of the most important pathways is the mitogen-activated protein kinase (MAPK) pathway, which regulates cell proliferation and differentiation. Another important pathway is the phosphatidylinositol-3-kinase (PI3K)/Akt pathway, which promotes cell survival and inhibits apoptosis (Sordella et al., 2012). In addition, the signal transducer and activator of transcription (STAT) pathway is involved in transcriptional regulation of genes associated with tumor progression (Shi et al., 2014) (Figure 1).

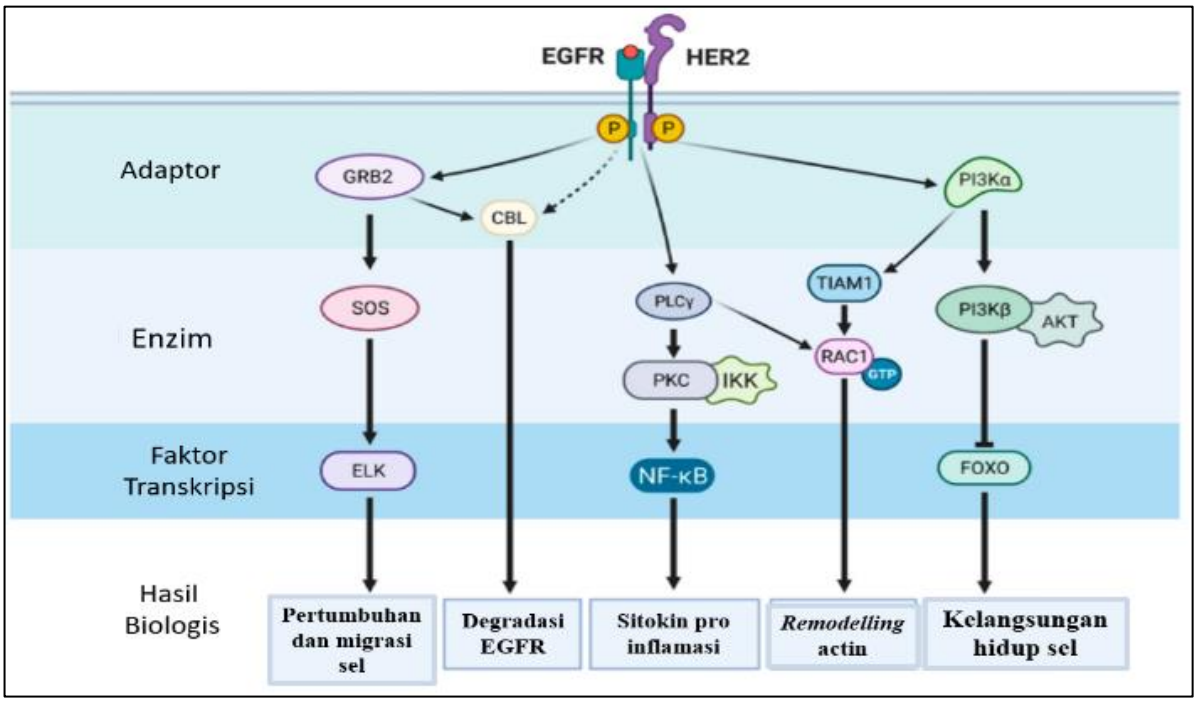

Figure 1. EGFR signal pathways

EGFR Expression in Lung Cancer

EGFR overexpression and mutation have been frequently reported in lung cancer, particularly in non-small cell lung cancer. Studies have shown that EGFR mutations occur in a substantial proportion of NSCLC patients, especially among individuals with adenocarcinoma histology, non-smokers, and Asian populations (Bethune et al., 2010). The most common EGFR mutations include deletions in exon 19 and the L858R substitution mutation in exon 21. These mutations enhance the kinase activity of

EGFR, leading to persistent activation of downstream signaling pathways that promote tumor cell proliferation and survival (Lynch et al., 2004). In addition to gene mutations, increased EGFR protein expression has also been observed in lung tumor tissues. Overexpression of EGFR is often associated with aggressive tumor behavior and poor clinical outcomes. EGFR expression has also been reported in various types of tumors, particularly malignant tumors (cancers), including colorectal, pancreatic, bladder, prostate, ovarian, glioma, breast, renal, and head and neck cancers, with varying levels of expression across tumor types, as summarized in Table 1 (Soetandyo et al., 2020).

Table 1. EGFR Expression in Various Carcinomas

Tumor Type	EGFR Expression (%)
Colorectal tumor	25–77
Pancreatic tumor	30–50
Bladder tumor	31–48
Prostate tumor	39–47
Ovarian tumor	35–70
Glioma	40–63
Breast tumor	14–91
Lung tumor	40–80
Renal tumor	50–90
Head and neck tumor	80–100

Diagnostic Role of EGFR Expression

EGFR expression has been widely investigated as a potential biomarker for lung cancer diagnosis. Detection of EGFR alterations can provide valuable information about tumor characteristics and may assist clinicians in distinguishing malignant from non-malignant lung lesions.

Several diagnostic techniques are used to evaluate EGFR expression, including immunohistochemistry (IHC), polymerase chain reaction (PCR), and fluorescence in situ hybridization (FISH). Immunohistochemistry is commonly used to assess EGFR protein expression in tumor tissue samples, while PCR-based techniques are used to detect specific gene mutations.12 Identification of EGFR alterations also has important implications for personalized medicine. Patients with EGFR-mutated tumors often respond well to EGFR-targeted therapies such as gefitinib, erlotinib, and afatinib. Therefore, evaluation of EGFR expression and mutation status has become an essential component of molecular diagnostic testing in lung cancer (Gainor et al., 2016).

4. DISCUSSION

The role of molecular biomarkers in lung cancer diagnosis has become

increasingly important in recent years, fundamentally transforming the paradigm from histology-based to molecularly-driven classification and treatment. Advances in molecular oncology have revealed that genetic and molecular alterations play a significant role in tumor development and progression, challenging the traditional view of lung cancer as a single disease entity. Among these biomarkers, EGFR has emerged as one of the most extensively studied and clinically actionable targets in lung cancer research, representing a paradigm shift toward precision oncology.

Numerous studies have demonstrated that EGFR signaling pathways are critically involved in regulating tumor cell proliferation, survival, angiogenesis, and metastasis through complex downstream signaling networks. The canonical pathways activated by EGFR include the RAS-RAF-MEK-ERK (MAPK) cascade, which primarily drives cellular proliferation and differentiation, the PI3K-AKT-mTOR axis, which promotes cell survival and metabolic reprogramming, and the JAK-STAT pathway, which modulates transcriptional programs associated with immune evasion and tumor progression (Sordella et al., 2004; Gao et al., 2007). Abnormal activation of EGFR signaling can result from gene mutations, gene amplification, protein overexpression, or autocrine ligand production, creating a self-sustaining oncogenic loop. These molecular alterations contribute to tumorigenesis by promoting uncontrolled cellular growth, resistance to programmed cell death, enhanced invasive capacity, and angiogenic switch (Suda et al., 2017).

The clinical implications of EGFR alterations extend far beyond their role in tumor biology, fundamentally reshaping diagnostic and therapeutic algorithms in lung cancer. Detection of EGFR mutations has become a standard component of molecular testing in patients with non-small cell lung cancer (NSCLC), particularly those with adenocarcinoma histology. The landmark studies by Lynch et al. (2004) and Paez et al. (2004) first established the correlation between specific EGFR mutations and dramatic clinical responses to gefitinib, ushering in the era of targeted therapy. Subsequent research has confirmed that patients harboring sensitizing EGFR mutations (exon 19 deletions and L858R substitutions) achieve objective response rates of 60-80% with first-generation tyrosine kinase inhibitors (TKIs), compared to only 10-15% with conventional chemotherapy (Pao et al., 2004; Marchetti et al., 2005).

However, the prevalence of EGFR mutations exhibits remarkable heterogeneity across different populations and tumor subtypes, reflecting complex gene-environment interactions. The PIONEER study by Shi et al. (2014) demonstrated that EGFR mutation frequency in Asian populations with adenocarcinoma histology reaches 50-60%, substantially higher than the 10-15% observed in Western populations. This disparity is particularly pronounced among never-smokers, females, and patients with adenocarcinoma histology, suggesting that EGFR-mutant lung cancer may represent a distinct molecular disease entity with unique etiologic factors. Interestingly, Shi et al. (2014) also found that even among Asian males and smokers, mutation frequencies remained sufficiently high (30-40%) to warrant universal testing, challenging earlier assumptions that certain demographic groups could be excluded from molecular screening.

The diagnostic evaluation of EGFR status presents both opportunities and challenges in clinical practice. Multiple complementary techniques are employed, each with distinct advantages and limitations. Immunohistochemistry (IHC) provides a rapid, cost-effective assessment of protein expression but suffers from subjective interpretation, antibody variability, and poor correlation with mutational status. Quantitative PCR-based methods offer high sensitivity (detecting mutations at 1-5% allele frequency) and rapid turnaround time, but are limited to predefined hotspot mutations. Next-generation sequencing (NGS) represents the gold standard, enabling comprehensive genomic profiling of multiple genes simultaneously, detection of rare variants, and identification of co-mutations that may influence therapeutic response (Bethune et al., 2010). However, NGS requires specialized infrastructure, bioinformatics expertise, and higher costs, limiting its accessibility in resource-constrained settings.

Despite significant advances in EGFR-targeted therapy, several formidable challenges remain that temper the initial enthusiasm. Primary resistance occurs in approximately 10% of patients with sensitizing mutations who fail to respond to TKIs, often due to co-occurring alterations such as KRAS mutations, PIK3CA amplifications, or epithelial-mesenchymal transition (EMT) phenotypes. More commonly, acquired resistance inevitably develops after a median of 10-14 months of TKI therapy, mediated through multiple mechanisms. The T790M gatekeeper mutation in exon

20, which increases ATP binding affinity and sterically hinders drug binding, accounts for 50-60% of cases of acquired resistance (Gainor et al., 2016). Other resistance mechanisms include MET amplification, HER2 amplification, histological transformation to small cell lung cancer, and activation of bypass signaling pathways.

The emergence of resistance has necessitated the development of sequential therapeutic strategies. Third-generation TKIs such as osimertinib were specifically designed to overcome T790M-mediated resistance while maintaining activity against sensitizing mutations, achieving response rates of 60-70% in T790M-positive patients. However, resistance to third-generation agents inevitably develops through mechanisms such as C797S mutations, further MET amplification, or neuroendocrine differentiation, creating an ongoing evolutionary arms race between therapeutic intervention and tumor adaptation (Gainor et al., 2016).

Tumor heterogeneity represents another critical challenge that complicates EGFR testing and treatment. Spatial heterogeneity refers to genetic differences between primary tumors and metastatic sites, or even within different regions of the same tumor. Temporal heterogeneity describes the evolution of clonal populations over time, particularly under selective pressure from targeted therapies. A biopsy obtained at diagnosis may not accurately reflect the molecular landscape of progressive disease, necessitating repeat biopsies or liquid biopsy approaches using circulating tumor DNA (ctDNA) to capture dynamic molecular changes (Suda et al., 2017).

The interplay between EGFR mutations and immunotherapy has emerged as a complex and clinically relevant issue. Gainor et al. (2016) demonstrated that NSCLCs harboring EGFR mutations or ALK rearrangements exhibit significantly lower response rates to PD-1/PD-L1 inhibitors compared to EGFR wild-type tumors (ORR 3-10% vs. 20-30%). This phenomenon is attributed to the immunologically "cold" tumor microenvironment characterized by low tumor mutational burden, reduced neoantigen load, low PD-L1 expression, and paucity of CD8+ tumor-infiltrating lymphocytes. These findings have important implications for treatment sequencing, suggesting that immunotherapy should not be prioritized in EGFR-mutant patients who remain candidates for TKI therapy.

Variability in diagnostic methodologies across institutions and

laboratories further complicates the clinical utility of EGFR testing. Differences in tissue processing, DNA extraction methods, assay sensitivity, and interpretation criteria can lead to discordant results. The lack of standardized thresholds for defining EGFR positivity, particularly for IHC and FISH, leads to inconsistent patient selection for targeted therapy. International efforts to harmonize testing protocols, such as the College of American Pathologists (CAP) guidelines and external quality assurance programs, are essential to ensure reliable and reproducible results across different settings.

From a health economics perspective, the high cost of EGFR testing and targeted therapies poses significant challenges for healthcare systems, particularly in low- and middle-income countries where the burden of lung cancer is increasing rapidly. While TKIs have demonstrated cost-effectiveness in mutation-positive populations compared to chemotherapy, the financial toxicity of prolonged targeted therapy, serial molecular testing for resistance monitoring, and sequential lines of therapy creates a substantial economic burden. Strategies to improve accessibility, such as generic drug development, tiered pricing models, and implementation of cost-effective diagnostic algorithms, are critical to ensure equitable access to precision medicine.

Future directions in EGFR research should prioritize several key areas. Liquid biopsy technologies using ctDNA analysis offer promising alternatives to tissue biopsy, enabling non-invasive detection of EGFR mutations, real-time monitoring of treatment response, and early identification of resistance mechanisms. However, challenges remain regarding analytical sensitivity, standardization of pre-analytical variables, and clinical validation of ctDNA-guided treatment decisions. Combination therapies targeting EGFR alongside parallel or downstream pathways (e.g., MET, HER3, PI3K, MEK) may overcome or delay resistance, though careful patient selection and toxicity management are essential.

5. CONCLUSION

EGFR plays a critical role in the molecular pathogenesis of lung cancer and has considerable potential as a diagnostic biomarker. Alterations in EGFR signaling pathways contribute to tumor proliferation, survival, and progression. Identification of EGFR expression and mutations can improve diagnostic accuracy and provide important information for targeted therapy strategies. Further

research is necessary to better understand the clinical significance of EGFR expression in lung cancer and to improve the application of molecular biomarkers in routine clinical practice.

AUTHOR CONTRIBUTIONS

Substantial contributions to conceptualization, data curation, analysis: SMM, WAH, MB, and NH. Supervision Writing - review & editing: SMM, WAH, MB. Manuscript revisions: WAH.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in this research.

DATA AVAILABILITY STATEMENT

The data are available from the corresponding author upon reasonable request.

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